Perinatal outcome after selective termination in dichorionic twins discordant for congenital anomalies

Mar Bennasar\(^1\)\(^2\) | Júlia Ponce\(^1\) | Ximena Torres\(^1\) | Olga Gómez\(^1\)\(^2\) | Joan Sabrià\(^1\) | Eduard Gratacós\(^1\)\(^2\) | Antoni Borrell\(^1\)\(^2\) | Josep M. Martínez\(^1\)\(^2\)

\(^1\)BCNatal, Barcelona Center for Maternal-Fetal and Neonatal Medicine, Hospital Clinic and Hospital Sant Joan de Déu, Barcelona, Spain
\(^2\)August Pi i Sunyer Biomedical Research Institute (IDIBAPS), Barcelona, Spain

Correspondence
Mar Bennasar, BCNatal, Barcelona Centre de Medicina Materno-fetal Neonatal, Hospital Clinic i Hospital Sant Joan de Déu, Sabino de Arana 1, 08028 Barcelona, Spain.
Email: bennasar@clinic.cat

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Abstract

Introduction: Our objective was to evaluate the perinatal outcome of selective termination of dichorionic twin pregnancies with discordant anomalies, according to gestational age at time of procedure.

Material and methods: Retrospective review of 147 dichorionic twin pregnancies referred to our Fetal Medicine Unit between 2003 and 2018 for selective termination. Gestational age at delivery, fetal loss, and overall and 28-day post-delivery survival rates were evaluated according to gestational age at time of procedure. Selective termination procedure was defined as early, intermediate, and late when performed before 18 weeks, between 18 and 23 weeks, and after 23 weeks, respectively. Kruskal–Wallis and chi-squared test were used to compare groups.

Results: Overall survival at 28 days post-delivery, pregnancy loss, and preterm delivery before 32 weeks of gestation rates were 93.4%, 6.9%, and 15.5%, respectively. When stratified by gestational age at procedure, intermediate selective termination was associated with a lower survival rate than early and late procedures (86% vs. 96.9% and 100%, respectively; \(p = 0.035\)), and a nonsignificant trend for higher pregnancy loss (12% vs. 3.1%). Preterm delivery before 32 weeks of gestation occurred in 27% of late procedures, which was significantly higher than in early (9.5%) and intermediate (18.2%) procedures.

Conclusions: Selective termination in dichorionic twin pregnancies with discordant fetal anomaly is associated with low pregnancy loss and preterm delivery rate, primarily when performed before 18 weeks. When legally possible, late procedures can be a good alternative, particularly in those cases diagnosed beyond the 18th week of gestation.

KEYWORDS
chromosome disorders, dichorionic twin pregnancy, fetal malformation, fetal ultrasound, multiple pregnancy, pregnancy complications, selective termination
1 | INTRODUCTION

Multiple pregnancies are at increased risk of adverse perinatal outcome when compared with singletons. Although fetal complications are mainly related to preterm delivery and pregnancy loss, there is an increased incidence of structural and chromosomal anomalies in twin pregnancies. The incidence of structural malformations is increased in monochorionic pregnancies, but chromosomal anomalies are higher in dichorionic (DC) pregnancies, because each fetus has an independent risk. Fetal anomalies are frequently discordant in twin pregnancies, affecting both fetuses in less than 2% of DC and about 10%–15% of monochorionic cases. Whenever a discordant fetal abnormality is detected, the prognosis of both the affected fetus and the whole pregnancy should be discussed with parents. Hence, management options, including expectant management, termination of pregnancy or selective termination (ST) of the affected fetus, should be offered according to the local legislation. If ST is requested, chorionicity will determine the approach. Percutaneous intravascular potassium chloride administration under ultrasound guidance is a safe method for ST in DC twins, but it should be avoided in monochorionic twins because it could reach the normal fetus through vascular anastomoses leading to double fetal loss.

The initial number of fetuses and the number of fetuses terminated are known risk factors for adverse perinatal outcome. Mid-term procedures have also been related to adverse perinatal outcome, with higher fetal loss and preterm delivery rate, although results are not consistent in the literature. Late procedures have been proposed as an option in countries where local policies allow late termination, especially in cases diagnosed at the second trimester anomaly scan or later. However, data on the perinatal outcome of late ST are scarce.

Therefore, our study aims to evaluate the perinatal outcome after ST performed in DC twin pregnancies with discordant chromosomal or structural anomalies according to gestational age (GA) at the time of the procedure, in a single experienced center. To our knowledge, this is the most extensive single-center study stratifying by GA, including late procedures.

2 | MATERIAL AND METHODS

This retrospective review includes all DC twin pregnancies referred to our Fetal Medicine Unit in BCNatal between 2003 and 2018 for ST with a diagnosis of a discordant congenital abnormality. Inclusion of cases is displayed in a flowchart (Figure 1). Our standard ST protocol includes a detailed fetal anomaly assessment and chorionicity determination before the procedure. GA is evaluated by ultrasound, mainly by the first trimester crown–rump length of the largest fetus. Biparietal diameter is used for GA estimation in those patients evaluated after 14 weeks. Fetal malformation and previous genetic results from chorionic villous sampling or amniocentesis are carefully evaluated. The prognosis and risks of complete pregnancy loss and very preterm birth of both expectant management and ST are discussed with parents. Dichorionicity confirmation is performed either by differences in fetal gender, the presence of two separated placentas, or the presence of lambda sign during the first-trimester scan. Cases in which chorionicity cannot be ascertained by previous data or ultrasound examination are considered and treated as monochorionic pregnancies. When chromosomal anomaly is the only indication for ST, previously documented fetal sex, sonographic markers, and placental location are considered for fetal identification. Only if necessary, when identifying the affected fetus is not possible, confirmation with a second invasive test performed before the procedure. Maternal HIV, hepatitis B surface antigen, and hepatitis C virus serologies and informed consent are obtained before the procedure. Experienced fetal medicine specialists perform the ST, under prophylactic antibiotic administration, using a transabdominal ultrasound-guided intravascular injection of potassium chloride 2 M through a 20G needle. Relative rest is recommended for 24–48 hours. Anti-D Rhesus immunoglobulin is prescribed in Rhesus-negative patients.

Spanish legislation permits termination of pregnancy until 22+6 weeks whenever a fetal anomaly is detected and confirmed by two specialists. After a change in termination of pregnancy legislation in 2010, late termination after 23 weeks is permitted in extremely severe or lethal conditions when an external committee confirms the severity of the diagnosis. Since then, late ST scheduled at around 30–32 weeks has been offered as an option in such cases, in order to avoid the fetal loss risk associated with the procedure. These women undergo strict follow up with cervical length evaluation every 2 weeks. Two doses of betamethasone are given for pulmonary maturation before the procedure when it is performed after 24 weeks.

Data were obtained from the medical records of the patients or from a direct interview with the patient or their referring physician. Data regarding maternal age, chorionicity, previous invasive procedures, GA at diagnosis, ST reason, cervical length at procedure, GA at procedure, pregnancy complications, GA at delivery, overall survival, and neonatal survival and follow up until 28 days of life or at discharge were recorded. Preterm prelabor rupture of membranes was considered when the rupture of membranes occurred before 36 weeks. Pregnancy loss before 24 weeks was established when one of the following conditions was present: (a) delivery after active labor not responding to tocolytics, (b) clinical chorioamnionitis, and (c) spontaneous intrauterine death. Complications were considered likely related to the procedure when they appeared during the 2 weeks following the procedure. STs were divided into three gestational groups for comparison: early (<18 weeks), intermediate

Key Message

Selective termination before 18 weeks of gestation is associated with better perinatal outcome, higher neonatal survival, lower fetal loss, and lower preterm delivery rates, when compared with procedures between 18 and 23 weeks. If legally possible, third-trimester procedures are a good option.
The three pregnancies delivered at term with normal outcome (18\textsuperscript{0} to 23\textsuperscript{6} weeks), and late (≥24 weeks). These three groups were established according to previously published data\textsuperscript{11,12} and current prenatal guidelines in twin pregnancies, which recommend first-trimester screening for chromosomal anomalies, an anatomic scan at 18–22 weeks, and the statement as a “Good Practice Point” that, when the diagnosis is made in the second trimester, women might opt for late ST in the third trimester, if the law permits.\textsuperscript{7}

Survival at delivery and survival at 28 days of life or at discharge were considered as primary outcomes and were stratified by GA at time of procedure. Fetal loss, complications related to the procedure, and GA at delivery were considered secondary outcomes.

2.2 | Statistical analyses

The Kruskal–Wallis test was used to compare continuous variables between the three groups, whereas the chi-squared test was used to compare categorical variables. Differences were considered statistically significant when \( p \) values were less than 0.05. Statistical analysis was performed using \textit{Stata} version 15.1 software (StataCorp).

2.3 | Ethical approval

Ethical approval for the study was obtained from our local ethics board on July 29, 2020 (Hospital Clinic HCB/2020/0894), and all participants provided informed consent.

3 | RESULTS

The overall survival rate was 93.4\% (128/137). The rate was significantly lower in the intermediate ST group (86\%) compared with the early (96.9\%) and late (100\%) ST groups. A total of 139 ST procedures were performed. Chromosomal abnormalities were the main indication (60.6\%) in the early group, whereas structural malformations predominated in the intermediate and late groups. Overall, ST of the presenting fetus was performed in 64/139 (46\%) cases. Indication and baseline characteristics are displayed in Table 1. The final diagnosis was established before 24 weeks of gestation in 129 (92.8\%) cases, whereas it was obtained later in the remaining 10 cases. At parental counseling, 117/129 (90.7\%) patients opted for immediate ST, whereas 12/129 (9.3\%) patients opted for late ST. In 2 of these 12 cases, ST had to be performed earlier than scheduled, at 24\textsuperscript{12} and 28\textsuperscript{12} weeks, because of a cervical shortening below 10 mm, and delivery finally occurred at 26\textsuperscript{12} and 34\textsuperscript{15} weeks, respectively (Table 2).

Pregnancy and neonatal outcomes are presented in Table 3. GA at delivery was 37 and 37\textsuperscript{+5} weeks in the early and intermediate groups, compared with 33\textsuperscript{+4} weeks in the late group (\( p = 0.005 \)). Bonferroni ad-hoc analysis showed significant differences between late and early or intermediate procedures. Likewise, severe preterm delivery before 32 weeks of gestation occurred significantly more often in the late group (27.3\%) compared with the intermediate (18.2\%) and early (9.5\%) procedures. Pregnancy loss rate, excluding termination of pregnancy, was 6.9\% in those pregnancies with ST performed before 24 weeks. Intermediate ST showed a nonsignificant trend for a higher pregnancy loss rate than early ST (12.0\% vs. 3.1\%; \( p = 0.076 \)). After ST, a woman from the early group and another from the intermediate group opted for termination of pregnancy because of preterm prelabor rupture of membranes and persistent oligohydramnios of the ongoing fetus.

4 | DISCUSSION

The main findings of our study are that: (a) ST is a safe option in DC twin pregnancies with a discordant anomaly of a fetus, with an overall survival rate of more than 90\% at 28 days of life; (b) perinatal outcome, in terms of the risk of pregnancy loss, severe preterm birth, and neonatal survival, is better before 18 weeks of pregnancy rather than between 18 and 23 weeks; and (c) if local legislation permits, scheduling the ST around 30–32 weeks is a good option, especially in those cases diagnosed around 20 weeks.

The literature on ST complications and perinatal outcome is controversial. Faced with the diagnosis of a discordant anomaly in
TABLE 1  Reasons for selective termination and baseline characteristics in the study population stratified by gestational age at procedure

|                         | Total  | <18 weeks | 18<sup>th</sup>-23<sup>th</sup> weeks | ≥24 weeks<sup>+</sup> | p-value  |
|-------------------------|--------|-----------|----------------------------------------|-----------------------|----------|
| **Maternal age (years)**| 35 (17–44) | 34 (18–44) | 36 (17–42) | 36 (31–44) | 0.5912  |
| **Indication**          |        |           |                                       |                       | 0.092    |
| 1. Chromosomal abnormality | 68/139 (48.9%) | 40/66 (60.6%) | 19/51 (37.3%) | 9/22 (40.9%) |        |
| Trisomy 21              | 53/68 (77.9%) | 35/40 (87.5%) | 16/19 (84.2%) | 2/9 (22.3%) |        |
| Other trisomies (13, 18)| 8/68 (11.8%) | 3/40 (7.5%) | 1/19 (5.3%) | 4/9 (44.4%) |        |
| Other (deletions, monosomy) | 7/68 (10.3%) | 2/40 (5%) | 2/19 (10.5%) | 3/9 (33.3%) |        |
| 2. Structural abnormality | 52/139 (37.4%) | 18/66 (27.3%) | 25/51 (49%) | 9/22 (40.9%) |        |
| Heart defect            | 9/52 (17.3%) | 0(0) | 8/25 (32%) | 1/9 (11.1%) |        |
| Central nervous system defect | 21/52 (40.4%) | 12/18 (66.7%) | 6/25 (24%) | 3/9 (33.3%) |        |
| Other single defect     | 18/52 (34.6%) | 6/18 (33.3%) | 9/25 (36%) | 3/9 (33.3%) |        |
| Multiple malformation   | 4/52 (7.7%) | 0(0) | 2/25 (8%) | 2/9 (22.3%) |        |
| 3. Other                | 19/139 (13.7%) | 8/66 (12.1%) | 7/51 (13.7%) | 4/22 (18.2%) |        |
| Fetal hydrops           | 11/19 (57.9%) | 6/8 (75%) | 4/7 (57.1%) | 1/4 (25%) |        |
| Severe fetal growth restriction | 3/19 (15.8%) | 0(0) | 2/7 (28.6%) | 1/4 (25%) |        |
| Other                   | 5/19 (26.3%) | 2/8 (25%) | 1/7 (14.3%) | 2/4 (50%) |        |
| **Gestational age at diagnosis (weeks)** | 18 (11<sup>th</sup>–13<sup>th</sup>) | 15<sup>th</sup>(11<sup>th</sup>–17<sup>th</sup>) | 21 (14–22<sup>th</sup>) | 21<sup>th</sup> (15<sup>th</sup>–32<sup>th</sup>) | 0.0001 |
| **Cervical length at diagnosis (mm)** | 37 (0–51) | 39 (33–51) | 37 (0–48) | 28 (8–48) | 0.0018 |
| **Gestational age at procedure (weeks)** | 19 (12<sup>th</sup>–33<sup>th</sup>) | 16<sup>th</sup>(12<sup>th</sup>–17<sup>th</sup>) | 21 (18–23<sup>th</sup>) | 31<sup>th</sup>(24<sup>th</sup>–33<sup>th</sup>) | 0.0001 |

Data are presented as median (range) or number (percentage).
*Also includes patients diagnosed before 18<sup>th</sup> weeks and between 18<sup>th</sup> and 23<sup>th</sup> weeks that underwent selective termination ≥24 weeks.

TABLE 2  Procedures differed to third trimester

| Gestational age at diagnosis (weeks) | Reason for selective termination | Gestational age at procedure (weeks) | Gestational age at delivery (weeks) |
|-------------------------------------|----------------------------------|-------------------------------------|-------------------------------------|
| 16<sup>th</sup>                      | Trisomy 13                       | 33<sup>rd</sup>                     | 34<sup>th</sup>                     |
| 18<sup>th</sup>                      | Deletion 18p11.32p11.21          | 24<sup>th</sup>                     | 26<sup>th</sup>                     |
| 20<sup>th</sup>                      | Trisomy 21                       | 28<sup>th</sup>                     | 34<sup>th</sup>                     |
| 20<sup>th</sup>                      | Spina bifida                     | 31<sup>st</sup>                     | 37<sup>th</sup>                     |
| 20<sup>th</sup>                      | Congenital left diaphragmatic hernia | 30<sup>th</sup>                 | 39<sup>th</sup>                     |
| 20<sup>th</sup>                      | Agenesis corpus callosum and cleft palate | 31<sup>st</sup>             | 31<sup>st</sup>                     |
| 21<sup>st</sup>                      | Spina bifida                     | 32<sup>nd</sup>                     | 35<sup>th</sup>                     |
| 21<sup>st</sup>                      | Trisomy 21                       | 32<sup>nd</sup>                     | 33<sup>rd</sup>                     |
| 22<sup>st</sup>                      | Deletion 13q31.1-q31.1           | 32<sup>nd</sup>                     | 37<sup>th</sup>                     |
| 22<sup>st</sup>                      | Trisomy 18                       | 32<sup>nd</sup>                     | 33<sup>rd</sup>                     |
| 22<sup>st</sup>                      | Multiple malformation            | 24<sup>th</sup>                     | 39<sup>th</sup>                     |
| 22<sup>st</sup>                      | Trisomy 13                       | 32<sup>nd</sup>                     | 33<sup>rd</sup>                     |
a DC twin gestation with parental request for ST, the main concern is to provide the best care for the mother and the unaffected fetus. If the anomaly is lethal, one of the options is to maintain expectant management; however, it is known that there is a higher rate of preterm birth, which could mean a worse prognosis for the healthy twin. Otherwise, parents can request a ST, even at the risk of worsening the outcome of the healthy twin. It is crucial for ST to be performed by experienced medical teams, and for the timing of the procedure to be optimized to improve the final results. This paper supports relevant information that should be discussed with parents.

If we focus on pregnancy loss, Evans et al. reported for the first time, in a multicenter study, that ST performed before 16 weeks was associated with a lower rate of fetal loss compared with procedures performed later in pregnancy. Our early ST results show a rate of fetal loss (3.1%) similar to that reported by Evans et al. and by more recent series. In contrast, other series showed no differences between early and late ST. This can be explained either because a different cut off (20 weeks) was used in such series, or because, although a similar cut-off of 15 weeks was used, early procedures were mainly performed for multifetal pregnancy reduction upon parental request, and most of the late reductions were performed at around 20 weeks of gestation. Regarding our cases performed at 18-23 weeks of gestation, the rate of pregnancy loss is similar to that previously reported, and four times higher than in early procedures. In the same way, the rate of preterm birth before 32 weeks is similar to other groups, and was lower in those ST carried out before 18 weeks of gestation, when compared with intermediate and late ST. Although these results disagree with the study by Eddleman et al., differences could be due to a different GA cut-off for analysis: 18 weeks in our study and 20 weeks in theirs.

There is scant evidence on third-trimester ST, so our study provides relevant information on late procedures performed after 30 weeks of gestation. Importantly, we had no pregnancy losses in this late ST group, resulting in a neonatal survival of 100% at 28 days of life. On the other hand, we found a significantly lower GA at the time of delivery (33 weeks) compared with both early and intermediate ST (37 weeks), with a shorter time interval from procedure to delivery as well. Although around 90% of late ST were performed electively, with no signs of threatened preterm labor, a proportion of late procedures had to be advanced because of significant cervical shortening, or were even performed during advanced labor. In elective cases, we hypothesize that placental involution may have played a role in triggering labor. As mentioned above, preterm birth is one of the expected complications in developing twins, which may be even more frequent depending on the type of malformation. In this sense, our results are similar to a recent series by Dural et al., in which a survival rate of 100% and a preterm birth rate of 64% are reported. In contrast, Lipitz et al. reported a mean GA at delivery of 36.9 weeks in 36 pregnancies where ST was performed after 24 weeks of gestation. These differences could be explained by an earlier GA at the time of the procedure (25 weeks), compared with our study (30 weeks), and showing a GA at delivery similar to our intermediate ST group (37-35 weeks). Of note, our GA at delivery of 37 and 35 weeks in the early and intermediate groups, correspond to the expected GA in twin pregnancies.

Our study provides relevant information for clinical management. First, because results of ST are better in the early period, a routine anomaly scan at 14-16 weeks could be a good strategy to

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**Table 3** Pregnancy and neonatal outcomes in the whole population and stratified by gestational age at procedure

|                      | Total   | <18 weeks | 18-23-24 weeks | ≥24 weeks | p   |
|----------------------|---------|-----------|----------------|-----------|-----|
| Number of cases      | 139     | 66        | 51             | 22        |     |
| PPROM                | 32/139  | 15/66     | 11/51          | 6/22      | 0.786|
| Elective termination | 2/139   | 1/66      | 1/51           | 0/22      | 0.1076|
| Pregnancy loss       | 8/137   | 2/65      | 6/50           | 0/22      | 0.076|
| Delivery             |         |           |                |           |     |
| GA at delivery       |         |           |                |           |     |
| (weeks)              |         |           |                |           |     |
| 24-27.6              | 9/129   | 4/63      | 4/44           | 1/22      | 0.005|
| 28.0–31.6            | 11/129  | 2/63      | 4/44           | 5/22      | 0.005|
| 32.0–36.6            | 25/129  | 8/63      | 7/44           | 10/22     | 0.005|
| ≥37                  | 84/129  | 49/63     | 29/44          | 6/22      | 0.005|
| Survival             |         |           |                |           | 0.035|
| Overall              | 128/137 | 63/65     | 43/50          | 22/22     | 1.000|
| At delivery          | 129/129 | 63/63     | 44/44          | 22/22     | 0.508|
| Neonatal (30 days)   | 128/129 | 63/63     | 43/44          | 22/22     | 1.000|

Bold values indicate statistically significant.

Data are presented as median (range) or number (percentage).

Abbreviations: GA, gestational age; PPROM, Preterm prelabor rupture of membranes.

*Excluding termination of pregnancy.
implement in twin pregnancies. Second, to improve perinatal outcomes it is essential to reduce the total number of invasive procedures in twins. In this regard, it is highly recommended that invasive prenatal diagnostic procedures in twins are performed in centers with expert doctors who can undertake a further selective reduction, if this is the parental choice. Indeed, in our series, four out of the eight pregnancy losses occurred in patients who underwent three or more invasive procedures before ST, because of the lack of a precise identification of the affected fetus before being referred to our center. Third, in selected cases, and particularly in those in which the diagnosis is made after 18 weeks of gestation, a late procedure around 30 weeks appears to be safe, with better survival results for the normal co-twin. However, for this late ST, the legal aspects of each country, and psychological concerns of the mother and her family environment (father’s opinion, other siblings), must also be taken into consideration. It is also important to remember the increased risk of preterm birth for twins with a discordant abnormality, so strict monitoring of the cervical length by ultrasound is mandatory. Finally, a team of experienced maternal–fetal specialists who are ready to perform an emergency ST at any time is required.

A strength to highlight of our study is that it represents the most extensive clinical series of ST reported for discordant anomalies in a single center. Moreover, throughout these 16 years, ST has been performed by only four maternal–fetal specialists which, on the one hand, reduces the complications that can occur if a greater number of doctors intervene and, on the other, is more realistic and appropriate than those centers in which a single expert specialist performs all of them, because it has allowed us to carry out unscheduled procedures, such as during vacation periods, holidays, or even at night. We also acknowledge some limitations. First, retrospective data analysis could decrease its accuracy, though survival at delivery and neonatal survival at discharge are reliable data obtained from medical records and interviews with parents. Second, our study includes two different periods of clinical management, according to Spanish regulations on pregnancy termination, because during the first period (before 2010), late terminations were not allowed beyond 22 weeks. Finally, the option of postponing the ST procedure to the third trimester was more accepted by women who lived near the hospital in Catalonia rather than by women who lived at a great distance, mainly linked to concerns of having a premature delivery of a viable fetus before the ST could be carried out. This fact could represent a selection bias.

5 | CONCLUSION

Our study demonstrates that ST in DC twin pregnancies with discordant fetal anomaly in which women opt for termination of the affected fetus, has an optimal perinatal outcome in more than 90% of cases. ST has to be performed by experienced specialists, so it is associated with a low rate of pregnancy loss and with high neonatal survival, particularly when performed before 18 weeks. If local legislation allows, most cases scheduled for ST at 30–32 weeks could be performed, providing maximum survival for the healthy twin.

CONFLICT OF INTEREST

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

AUTHOR CONTRIBUTIONS

MB contributed to clinical management, data review, and manuscript writing. JP contributed to data review and statistical analysis. XT contributed to data review and manuscript writing. OG, JS, AB, and JMM contributed to clinical management and manuscript review. EG contributed to manuscript review.

ORCID

Mar Bennasar https://orcid.org/0000-0003-3935-1935

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