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Received: 10 March 2023 | Revised: 22 April 2023 | Accepted: 7 May 2023

DOI: 10.1002/pd.6385

ORIGINAL ARTICLE

PRENATAL DIAGNOSIS WILEY

Perinatal outcome after selective fetal reduction in monochorionic twin pregnancies: A comparison of techniques over a 20-year period

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Abstract

Objective: To assess the perinatal outcome after fetal reduction in complicated monochorionic (MC) twin pregnancies by comparing different techniques.

Methods: A retrospective cohort study at a national referral center comparing data between four techniques: interstitial laser coagulation, radiofrequency ablation (RFA), fetoscopic laser coagulation (FLC) and bipolar cord coagulation (BCC). The primary outcome was the mortality of the co-twins. Secondary outcomes were preterm pre-labor rupture of membranes (PPROM), gestational age at delivery and neonatal morbidity.

Results: 259 MC twin pregnancies underwent selective fetal reduction: 29 IL, 64 RFA, 85 FLC and 81 BCC. The perinatal mortality rate was 29% and fetal demise of the co-twins occurred in 19%. The lowest mortality rate was seen after BCC (17%, $p = 0.012$). PPROM occurred in 18% patients without significant differences between techniques. The mean gestational age at delivery in liveborn children was 35 weeks and did not differ between techniques. Severe cerebral injury and neonatal morbidity were reported in 4% and 14%, respectively, without significant differences between techniques.

Conclusions: Selective fetal reductions in MC twins are precarious procedures with an increased risk of perinatal mortality of the co-twins. Our results show the lowest mortality rates after BCC. However, high PPROM rates were seen irrespective of the technique.

Key points

What is already known about this topic?

- Selective fetal reductions are precarious procedures and can be carried out using different techniques.
- It has been suggested that radiofrequency ablation has superior outcomes because of the smaller diameter of the instrument, resulting in fewer complications.

- To date, there is no international consensus on which technique for which the indication is ideal and has the best perinatal outcome.

What does this study add?

- Selective fetal reductions in monochorionic twins have the lowest mortality rate of the co-twin after bipolar cord coagulation and the highest after interstitial laser coagulation.
- High preterm pre-labor rupture of membranes rates before 32 weeks gestational age was seen irrespective of the technique.
- The selection of the most ideal technique should be made per pregnancy, considering gestational age, indication and feasibility.

1 | INTRODUCTION

Monochorionic (MC) twin pregnancies carry a higher risk of perinatal morbidity and mortality than dichorionic pregnancies due to placental sharing and vascular anastomoses.[1,2] Unique complications such as twin-to-twin transfusion syndrome (TTTS), twin anemia polycythemia sequence (TAPS), selective fetal growth restriction (sFGR), twin reversed arterial perfusion (TRAP) and discordance for structural anomalies can occur.[3,4] These conditions may lead to fetal demise (FD) in one of the twins. Acute exsanguination can lead to fetal demise or severe cerebral injury in the co-twin in 15% and 26%–34% of the cases, respectively.[5,6] To optimize outcomes for the co-twins, selective fetal reduction can be offered.[7]

In MC twins, selective reductions are carried out using several techniques that aim to immediately stop the intertwin exchange of blood. The occlusion of the umbilical cord by intrafetal procedures (interstitial laser coagulation [ILC] and radiofrequency ablation [RFA]) or coagulation of the umbilical cord (fetoscopic laser coagulation [FLC] and bipolar cord coagulation [BCC]) can prevent acute exsanguination. BCC and FLC often require the insertion of a relatively large instrument into the amniotic sac, which poses a significant risk of complications, such as premature pre-labor rupture of membranes (PPROM), hemorrhage, infections and preterm labor.[8] However, BCC or FLC can be the preferred option due to, for example, technical predilection, gestational age and size of the fetus, or the need for transection in case of mono-amniotic twins. Various studies have suggested that RFA has better outcomes due to the smaller diameter of the instrument, resulting in fewer complications.[8,9] It has been speculated that a more advanced gestational age (GA) with a larger fetus in RFA has unfavorable outcomes due to larger intrahepatic vessels that impede the ablation process, resulting in a longer period of hemodynamic instability.[10] Thus far, there is no international consensus on which technique for which the indication is superior and has the best perinatal outcome.[7,11]

The primary objective of this study was to compare the perinatal outcome in complicated MC twin pregnancies treated with selective reduction using ILC, RFA, FLC, or BCC.

2 | METHODS

In this 20-year retrospective cohort study, obstetric, perinatal and neonatal data between June 2000 and December 2020 from the Leiden University Medical Center, the national referral center for fetal therapy, were evaluated. All consecutive MC twin pregnancies that underwent selective fetal reduction were included. Mono-amniotic twin pregnancies were also included in this analysis. Triplets and higher order pregnancies were excluded. Selective fetal reductions are performed before 24 weeks' GA at our center abiding by the Dutch Abortion Law. Data including obstetric history, treatment details, delivery information and neonatal outcomes were extracted from the medical records. We contacted the referring clinicians to collect the relevant data for patients who did not deliver at our center. In this study, we compared four techniques for selective reduction: ILC, RFA, FLC and BCC. Some of the cases included in this study were previously reported in other publications from our group.[12,13] This study was approved by the ethics committee of our center (G21.018).

2.1 | Indications for selective fetal reduction

The following complications in MC twin pregnancies were amenable for selective fetal reduction: TRAP, TTTS, sFGR, TAPS and discordant congenital anomalies. TRAP was defined as the partial or complete absence of development of the heart in one twin, and the presence of a pump-twin that provides circulation through vascular anastomoses for the acardiac co-twin.[14] TTTS was defined as oligohydramnios in the donor sac with a maximum vertical pocket of ≤2 cm, and ≥8 cm in the recipient sac or ≥10 cm after 20 weeks gestation and was staged according to Quintero.[15] Selective fetal reductions in this group were performed when laser coagulation of vascular anastomoses was technically not feasible or in the presence of severe congenital anomalies. sFGR was defined as a growth restriction in one fetus with an estimated fetal weight <10th centile and intertwin estimated fetal weight discordance of ≥25%, and was categorized according to Gratacos.[16] Discordant congenital anomalies include malformations of the circulatory system, nervous system, respiratory system,

digestive system, urinary system, musculoskeletal system, and face and neck observed on ultrasound examination.[17] TAPS was defined as discordant middle cerebral artery peak systolic velocity (MCA-PSV) (>1.5 multiples of the median (MoM) in donors and <1.0 in recipients) without signs of oligo- and polyhydramnios and was classified into stage I-V.[18] In 2018, delta MCA-PSV >0.5 MoM was implemented as a new diagnostic criterion for TAPS.[19]

2.2 | Techniques

All patients were counseled about possible risks of the procedure, such as fetal demise, PPROM, preterm delivery and intrauterine infection, against expectant management or other interventions. The procedures were performed by experienced fetal surgeons. Patients received intravenous antibiotics prior to the procedure (cefazolin) and a tocolytic agent (indomethacin) before and after the procedure. Local anesthetics and sedation were chosen appropriately. In the case of oligohydramnios and BCC or FLC, amnioinfusion was performed prior to the procedure to expand the amniotic sac.

2.2.1 | Intrafetal techniques

ILC was performed using an 18- or 19-G needle that was inserted into the fetal abdomen aiming for the umbilical vein. Vessels were ablated under ultrasound guidance using a Diode or Nd:YAG laser-fiber in short bursts until the cessation of blood flow was confirmed with color Doppler.

In RFA, a 17G needle tip was positioned in the fetal abdomen aiming for the umbilical vein in the liver. The applied energy generated changes in the alternating current between 200 and 1200 kHz until the target temperature of 100°C was reached. At least two cycles were performed, and additional cycles if necessary, until the cessation of blood flow was confirmed on color Doppler.

2.2.2 | Umbilical cord coagulation

In FLC, the fetoscope or embryoscope was inserted through an introduction sheath. The sizes of the instruments were a 1.0 mm embryoscope through a 5.6 Fr sheath, a 1.3 mm scope through an 8 Fr sheath, or a 2.0 or 3.0 mm scope through a 10 Fr sheath. Using a Diode or Nd:YAG laserfiber, the umbilical cord was ablated either close to the fetal abdomen or at the cord insertion at the placenta until cessation of blood flow was confirmed with color Doppler. Cord transection was performed using the laserfiber after cord coagulation in mono-amniotic twins.

In BCC, bipolar forceps were inserted through a 10 Fr sheath into the amniotic cavity of the targeted fetus. The cord was grasped and occluded at multiple sites under continuous ultrasound guidance. Complete cessation of flow was confirmed afterward with color Doppler. In case of mono-twins, cord transection was performed with a fetoscopic laser using the previously inserted sheath.

The following day, ultrasound examination was performed and the patients were discharged home. When fetal anemia was suspected, Doppler interrogation of the MCA was performed. After 2 and 4 weeks after the procedure, another ultrasound examination was performed to assess the fetal brain. In case of suspected cerebral injury, fetal MRI was followed. Eventually, the patients were referred back to their referring clinician.

2.3 | Primary and secondary outcome

The primary outcome was perinatal mortality, defined as fetal demise, termination of pregnancy, immature delivery and neonatal death (NND) before 28 days of life. In the Netherlands, neonates born before 24 weeks GA are considered non-viable. Secondary outcomes consisted of neonatal morbidity, GA at birth and the occurrence of PPROM before 32 weeks GA. Neonatal morbidity included respiratory distress syndrome (RDS) requiring surfactant and/or mechanical ventilation; necrotizing enterocolitis (NEC) ≥ stage 2 according to Bell[20]; neonatal sepsis confirmed with a positive blood culture; severe cerebral injury; renal failure; and patent ductus arteriosus (PDA) needing surgical closure or medication. Severe cerebral injury was defined as at least one of the following findings on ultrasound examination: intraventricular hemorrhage (IVH) ≥ grade 3,[21] periventricular leukomalacia (PVL) ≥ grade 2,[22] ventricular dilatation >97th percentile,[23] arterial or venous infarction, or other cerebral anomalies associated with adverse neurological outcome.

2.4 | Statistical analyses

Statistical analyses were performed using SPSS version 25.0 (IBM). Data are presented as mean with standard deviation for normally distributed variables, frequency or percentage for categorical data, median with interquartile range or odds ratio with 95% confidence interval. Chi-square test was used with post hoc testing using the Bonferroni correction for categorical data. For nominal data, the analyses were performed using ANOVA or ANOVA Welch test, as appropriate, to compare multiple groups, and with the independent *t*-test to compare two groups. Multivariable logistic regression was performed to investigate the association between multiple variables and perinatal mortality. A p value of <0.05 was considered to indicate statistical significance.

3 | RESULTS

Between June 2000 and December 2020, 282 selective fetal reductions were performed. After exclusion of 23 higher order pregnancies, 259 complicated MC twin pregnancies were included for analysis: 29 pregnancies were treated with ILC (11%), 64 with RFA

(25%), 85 with FLC (33%) and 81 with BCC (31%). An outline of the indications for selective reduction per technique is given in Figure 1.

3.1 | Perinatal mortality

Table 1 displays an overview of the perinatal outcomes according to the different procedures for selective reduction. Comparing the perinatal mortality rate following the four different techniques showed that perinatal mortality of the co-twin was significantly higher following ILC (48%, 14/29) compared with treatment with BCC (17%, 14/81, $p = 0.006$). Fetal demise within 24 h after the procedure occurred in 18 pregnancies (7%), without significant discrepancies between techniques ($p = 0.588$). 10 pregnancies (4%) were terminated after selective fetal reduction, varying from 2 to 107 days (median 22 days) after the procedure. Reasons for TOP included anhydramnios after PPROM ($n = 6$), mosaicism for ring chromosome 20 ($n = 1$), mosaicism for trisomy 18 ($n = 1$), and cerebral anomalies on fetal MRI ($n = 1$). In one case, TOP and delivery took place at another hospital and the reason for termination is unknown. Overall, 9 pregnancies (4%) ended in immature delivery before 24 weeks' GA and neonatal death occurred in 5 cases (2%) without significant differences between techniques.

Stratifying for indication, MC pregnancies complicated by sFGR had the highest survival rate (92%, $p = 0.028$), with a significant difference from pregnancies complicated by TRAP (65%, $p = 0.019$) and congenital anomalies (64%, $p = 0.022$). Pregnancies complicated by congenital anomalies had a significantly lower survival rate when treated with RFA (33%) compared with treatment with BCC (83%, $p = 0.027$). In TTTS and TAPS cases, no significant differences in mortality rates were seen between donors and recipients (for TTTS 41/76 recipients with 24.4% mortality rate vs. 35/76 donors with 31.4% mortality rate, $p = 0.494$; for TAPS 1/7 recipients with 0% mortality rate vs. 6/7 donors with 16.7% mortality rate, $p = 0.659$). Mortality rates between TTTS Quintero stages were not significantly different (Q1 [10/76] showed a 10.0% mortality rate, Q2 [15/76] 13.3%, Q3 [34/76] 41.2%, Q4 [17/76] 23.5%, $p = 0.096$).

3.2 | Perinatal outcome

Overall, PPROM <32 weeks occurred in 18% (45/252) of the MC pregnancies and were most frequent after treatment with BCC (24%, 19/79), followed by FLC (19%, 16/84) and RFA (15%, 9/62, $p = 0.098$). The lowest PPROM rate was seen after ILC (4%, 1/27).

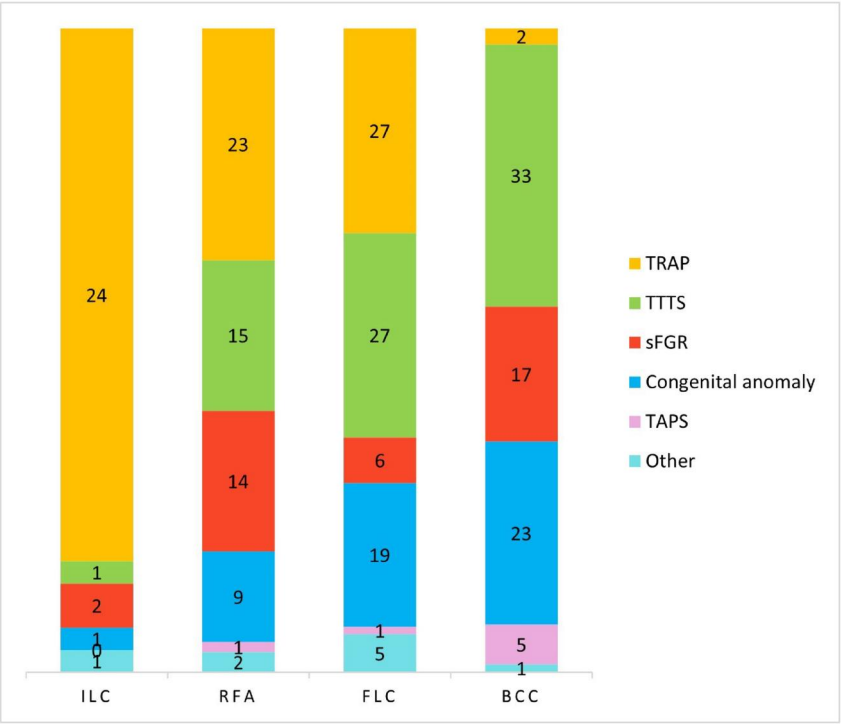

FIGURE 1 Indications per technique of 259 monochorionic twin pregnancies. Data shown as *n*. BCC, bipolar cord coagulation; FLC, fetoscopic laser coagulation; ILC, interstitial laser coagulation; RFA, radiofrequency ablation; sFGR, selective fetal growth restriction; TAPS, twin anemia polycythemia sequence; TRAP, twin reversed arterial perfusion; TTTS, twin-to-twin transfusion syndrome. Indications for selective reduction in the 76 pregnancies with TTTS were persistence or recurrence of TTTS after laser coagulation of the vascular anastomoses ($n = 10$), laser being technically not feasible ($n = 23$) (decided before laser treatment in 9 or during treatment in 14 pregnancies), coexistence of severe congenital anomalies ($n = 22$), termination on the request of the parents ($n = 8$), and are unreported in 13 cases. In 9 of the 39 sFGR cases, selective reduction was performed because of coexistent congenital anomalies. 9 cases with uncommon indications were placed in the "Other" group that included 7 elective reductions (on grounds of psychosocial factors, mono-amniocity or uterus didelphidus) and 2 of umbilical cord strangulation in mono-amniotic twin pregnancies. [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Perinatal outcome after selective reduction per technique for 259 monochorionic twin pregnancies.

Perinatal outcome	ILC (n = 29)	RFA (n = 64)	FLC (n = 85)	BCC (n = 81)	p-value	Total (n = 259)
GA at therapy (completed weeks)	16.1 (5.1)	16.7 (2.6)	16.9 (2.9)	20.7 (2.9)	<0.001	17.9 (3.7)
PPROM[a]	1 (3.7%)	9 (14.5%)	16 (19.0%)	19 (24.1%)	0.098	45 (17.9%)
GA at birth[d] (completed weeks)	35.3 (5.1)	35.6 (5.2)	35.2 (5.6)	34.4 (4.5)	0.592	34.9 (5.0)
Birthweight[d,b] (grams)	2585 (1049)	2668 (973)	2621 (989)	2331 (856)	0.205	2526 (948)
Mortality	14 (48.3%)	20 (31.3%)	26 (30.6%)	14 (17.3%)	0.012	74 (28.6%)
Fetal demise	14 (48.3%)	15 (23.4%)	12 (14.1%)	9 (11.1%)	<0.001	50 (19.3%)
TOP	0 (0.0%)	2 (3.1%)	8 (9.4%)	0 (0.0%)	0.009	10 (3.9%)
Non-viable (<24 weeks)	0 (0.0%)	2 (3.1%)	5 (5.9%)	2 (2.5%)	0.427	9 (3.5%)
Neonatal demise	0 (0.0%)	1 (1.6%)	1 (1.2%)	3 (3.7%)	0.529	5 (1.9%)
Survival per indication						
TRAP	11/24 (45.8%)	17/23 (73.9%)	19/27 (70.4%)	2/2 (100.0%)	0.109	49/76 (64.5%)
TTTS	1/1 (100.0%)	9/15 (60.0%)	20/27 (74.1%)	25/33 (75.8%)	0.624	55/76 (72.4%)
sFGR	2/2 (100.0%)	12/14 (85.7%)	6/6 (100.0%)	16/17 (94.1%)	0.659	36/39 (92.3%)
Congenital anomaly	0/1 (0.0%)	3/9 (33.3%)	11/19 (57.9%)	19/23 (82.6%)	0.027	33/52 (63.5%)
TAPS	-	1/1 (100.0%)	1/1 (100.0%)	4/5 (80.0%)	0.792	6/7 (85.7%)
Other	1/1 (100.0%)	2/2 (100.0%)	2/5 (40.0%)	1/1 (100.0%)	0.308	6/9 (66.7%)
Neonatal morbidity[e,c]	2 (15.4%)	6 (14.0%)	5 (8.6%)	12 (18.8%)	0.456	25 (14.0%)

Note: Data shown as mean ± SD, n (%) or n/n (%).

Abbreviations: BCC, bipolar cord coagulation; FLC, fetoscopic laser coagulation; GA, gestational age; ILC, interstitial laser coagulation; Non-viable, born before 24 weeks' GA; PPROM, premature pre-labor rupture of membranes; RFA, radiofrequency ablation; sFGR, selective fetal growth restriction; TAPS, twin anemia polycythemia sequence; TOP, termination of pregnancy; TRAP, twin reversed arterial perfusion; TTTS, twin-to-twin transfusion syndrome.

[a]7 missing values.

[b]9 missing values.

[c]12 missing values.

[d]In liveborn children (n = 199).

[e]In viable liveborn children (n = 190).

PPROM rates did not differ between the four techniques (p = 0.098). Mean GA at birth in liveborn children was 34.9 weeks (±5.0) and did not differ between techniques.

Of the 190 liveborn neonates, 52% (98/190) were admitted to the NICU or neonatal ward after birth. Neonatal morbidity occurred in 14% (25/178) and consisted of severe cerebral injury (4%, 7/178), RDS (10%, 18/178), sepsis (4%, 7/178), PDA (3%, 6/178), renal failure (1%, 1/178) and NEC (1%, 1/178). Severe cerebral injury included PVL grade 2 or 3 (n = 2), IVH grade 3 or 4 (n = 4), and venous infarction (n = 1) and was diagnosed postnatally in all cases. Two of these children died in the neonatal period (after 10 and 16 days).

In logistic regression analysis, the odds of mortality decreased by 62% for patients who underwent FLC compared to ILC (95% CI 0.14–0.99, p = 0.048), and by 78% for BCC compared to ILC (95% CI 0.07–0.72, p = 0.012), controlling for GA at therapy and indication (Table 2). The odds of mortality increased 5.14 times for TTTS compared with sFGR (95% CI 1.38–19.18, p = 0.015), and 7.49 times for congenital anomalies compared with sFGR (95% CI 1.93–29.05, p = 0.004), controlling for GA at therapy and technique. GA at therapy was not significantly associated with a higher mortality rate.

3.2.1 | Mono-amniotic twins

Of the 259 pregnancies, 38 were spontaneous mono-amniotic. In 31 cases after cord occlusion, transection of the umbilical cord was also performed. In 9 of these cases, cord occlusion was performed using BCC and a fetoscopic laser was used for transection. In the other 22 cases, the cord was coagulated and dissected with laser. Sub-analyses of the 9 cases treated with BCC followed by transection with fetoscopic laser showed no differences in perinatal mortality; hence, they are included in the BCC group. Incomplete transections (n = 4, all following FLC) were due to bleeding of the umbilical cord (n = 1), amnio-chorion dehiscence (n = 1), or complex umbilical cord entanglement (n = 2). In 7 mono-amniotic pregnancies no transection was

TABLE 2 Multivariate analysis of the effect of technique on perinatal mortality, controlled for indication and GA at therapy.

Independent variables	OR (95% CI)	*p*-value
Technique		
ILC	Ref	
RFA	0.49 (0.18–1.30)	0.150
FLC	**0.38 (0.14–0.99)**	**0.048**
BCC	**0.22 (0.07–0.72)**	**0.012**
Indication		
sFGR	Ref	
TRAP	3.71 (0.97–14.15)	0.055
TTTS	**5.14 (1.38–19.18)**	**0.015**
Congenital anomaly	**7.49 (1.93–29.05)**	**0.004**
TAPS	2.86 (0.24–33.87)	0.406
Other	4.01 (0.59–27.10)	0.155
Gestational age at therapy (weeks)	0.95 (0.86–1.04)	0.269

Note: $N = 259$ cases. The bold values are statistically significant.
Abbreviations: BCC, bipolar cord coagulation; FLC, fetoscopic laser coagulation; GA, gestational age; ILC, interstitial laser coagulation; RFA, radiofrequency ablation; sFGR, selective fetal growth restriction; TAPS, twin anemia polycythemia sequence; TRAP, twin reversed arterial perfusion; TTTS, twin-to-twin transfusion syndrome.

performed because of double FD during the procedure ($n = 1$), dislocation of the fetoscope and bleeding ($n = 2$), or technical impossibility ($n = 4$).

3.2.2 | Incomplete procedures

In 2% (6/259) of the MC pregnancies post-operative cessation of blood flow in the umbilical cord was not achieved. Causes of incomplete procedures were complex cord entanglement (FLC), double fetal demise peri-operative (FLC), scope dislocation due to maternal vomiting (FLC), deep panniculus (ILC) and two cases treated with RFA with unknown cause. In three additional cases, re-intervention was necessary to completely coagulate the umbilical cord, whereafter delivery at term was followed in all cases. The interval between the first intervention and re-intervention ranged from 1 to 7 days, and the first attempts were with FLC, ILC and RFA.

4 | DISCUSSION

This study describes a large cohort of complicated MC twin pregnancies that underwent selective fetal reduction at a national referral center for fetal therapy over a 20-year period. Selective fetal reductions are precarious procedures with a high risk of perinatal mortality. Our results show the lowest mortality rates after the use of BCC. The poorest outcomes were seen after ILC.

The survival rates found in our cohort correspond to Bebbington et al.,[8] reporting survival rates for RFA and BCC of 71% and 85%, respectively. Similarly, Dadhwal et al.[24] reported survival rates after RFA, BCC and ILC in 71%, 75% and 50%, respectively. In our cohort, MC pregnancies complicated by congenital anomalies had lower survival after RFA (33%) than after BCC (83%). This result may be due to the small number of cases that underwent RFA, but it is also observed in the study of Bebbington et al.,[8] who reported survival rates of 33% after RFA and 85% after BCC. Another possible explanation is that RFA is technically less effective in fetuses with congenital abnormalities owing to the need for intra-abdominal insertion. Overall, it seems that the outcomes in sFGR pregnancies are relatively favorable, with a survival rate of 92%. This is supported by the findings of Parra et al.[25] who only examined sFGR cases treated with BCC or laser coagulation and found a 93% survival rate. Our hypothesis is that the favorable outcomes in sFGR may be due to the absence of disbalance in intertwin transfusion, resulting in a better condition of the remaining fetus.

PPROM is considered to be one of the most frequent complications after selective reduction. Other studies have reported an overall PPROM rate between 20% and 41%.[7,8,11,12,26] In accordance with our study, previous studies reported lower PPROM rates after RFA compared to BCC or FLC, with differences ranging from 11% to 14%.[8,11,26,27] The most reasonable explanation for this is the use of a smaller instrument in RFA, resulting in a smaller defect of the membranes. The overall mean GA at birth in our cohort was 35 weeks. Previous studies have reported comparable values for GA at birth varying from 32.2 to 35.1 weeks for BCC and 34.5–34.7 weeks for RFA.[8,27,28]

Since BCC and RFA are more commonly the two techniques being used, we analyzed the odds of mortality and PPROM following BCC compared with RFA in a chi- square test without Bonferroni correction. Results for mortality were borderline significant in favor of BCC ($p = 0.049$). Results were non-significant for PPROM ($p = 0.159$).

Neonatal morbidity occurred in 14% and led to neonatal death in 2%. In our series, 4% of the liveborn children were diagnosed with severe cerebral injury. Other studies have reported NND rates varying from 3% to as high as 12%.[7,12,27–29] Rossi et al.[7] reported 7% neonatal morbidity, with an NND rate of 4%. The study of Peng et al.[26] reported similar rates of neurological injury in 5% of their neonates, and Lanna et al.[29] found severe neurologic morbidity after BCC in 2% of patients at follow-up between 1 and 9 years. The study by van Klink et al.[13] on long-term outcomes after selective reduction reported neurodevelopmental impairment in 7% of survivors at a median age of 54.5 months using standardized psychometric tests in all survivors, which is higher than in the general population. Standardized follow-up studies beyond the age of 5 years are needed to provide clinicians and future parents with reliable information on the long-term neurodevelopmental status of co-twin survivors.

The limitations of our study are its retrospective and observational nature. It is difficult to compare groups in this large cohort because for each patient, the technique used is carefully selected

based on indication, gestational age and feasibility. The study period of 20 years could have affected outcomes due to improvements over time in for example, neonatal care, anesthesia, instruments and a learning curve in surgeons. Furthermore, we did not have access to data on several peri-operative characteristics (e.g. presentation of the fetus) from which we know they could affect outcome.[30] Important strengths are the large cohort size and the fact that all procedures are being performed at a single national referral center by a small group of experienced surgeons. The procedures have been performed by a total of 6 surgeons, rotating over a period of 20 years.

In conclusion, our findings confirm that selective fetal reduction is a precarious procedure that has a high perinatal mortality rate with differences between techniques and indications. Further studies are required to evaluate the long-term neurodevelopmental outcome in survivors. Since selective fetal reduction can be an emotional experience for parents, research into the psychological sequelae is warranted.

ACKNOWLEDGMENTS

We thank our Fetal Therapy nurses for their valuable support in conducting this research and collecting the data. We received no financial support for the research, authorship, and/or publication of this article.

CONFLICT OF INTEREST STATEMENT

No conflict of interest is declared by the authors.

DATA AVAILABILITY STATEMENT

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

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How to cite this article: van Hoek MJC, van Klink JMM, Verweij EJT, et al. Perinatal outcome after selective fetal reduction in monochorionic twin pregnancies: a comparison of techniques over a 20-year period. *Prenat Diagn*. 2023;43(8):1028-1035. https://doi.org/10.1002/pd.6385