Long-term neurodevelopmental outcome after fetal therapy

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Chapter 11

Perinatal outcome after selective feticide in monochorionic twin pregnancies

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Abstract

Objective
To evaluate the incidence and risk factors of adverse perinatal outcome in complicated monochorionic twin pregnancies treated with selective feticide.

Methods
This was a retrospective analysis of prospectively collected data from a consecutive, national cohort. All monochorionic twin pregnancies treated with selective feticide at Leiden University Medical Center between June 2000 and November 2011 were included. Obstetric and neonatal data were recorded. The primary outcome measure was adverse perinatal outcome, including fetal or neonatal demise or severe neonatal morbidity.

Results
Data on perinatal outcome were obtained in all cases (n=131).Overall perinatal survival rate was 67.2% (88/131). Median gestational age at delivery was 34 (interquartile range, 23–38) weeks. Neonatal mortality and morbidity rate in liveborn children was 4.3% (4/92) and 12.0 % (11/92), respectively. Severe cerebral injury was detected in three children. The overall incidence of adverse perinatal outcome was 41.2% (54/131). Median gestational age at occurrence of preterm prelabor rupture of membranes (PPROM) was 19.0 weeks and 32.0 weeks in cases with and without adverse perinatal outcome, respectively (P = 0.017). Liveborn children with adverse perinatal outcome were born at a lower median gestational age (29.0 weeks) than were children without adverse perinatal outcome (38.0 weeks) (P < 0.001).

Conclusions
The risk of adverse perinatal outcome after selective feticide is high and associated with low gestational age at occurrence of PPROM and low gestational age at delivery. Long-term follow-up to assess neurodevelopmental outcome in survivors is required.

Introduction

The incidence of complications and perinatal mortality is higher in monochorionic (MC) twin pregnancies than in dichorionic (DC) twin pregnancies, owing to the presence of placental vascular anastomoses. These vascular connections can lead to specific complications including twin–twin transfusion syndrome (TTTS),[1] twin anemia–polycythemia sequence,[2] and twin reversed arterial perfusion (TRAP).[3;4] In addition, selective intrauterine growth restriction (sIUGR) occurs more frequently in MC pregnancies and is associated with an increased risk of morbidity and mortality. When intrauterine death of one fetus occurs, the risk of death or cerebral damage in the cotwin is increased, owing to acute exsanguination through the placental anastomoses.[5–7]

Several indications have been described for selective feticide in MC twin pregnancies, including TTTS, TRAP, sIUGR, severe congenital anomalies and higher-order multiple pregnancies.[5;8;9] Reported methods for selective feticide include fetoscopic laser coagulation, bipolar cord coagulation, radiofrequency ablation (RFA), cord occlusion by ligation or photocoagulation and interstitial laser coagulation.[5;6;10;11] Associated complications are premature rupture of membranes in up to 30% of cases and preterm delivery.[5;12] Perinatal survival rates vary between 65 and 92%, depending on technique and indication.[5] However, data on the risk of neonatal complications and long-term neurodevelopmental outcome in surviving twins are limited.[6;13]

The primary objective of this study was to evaluate the incidence of perinatal mortality and neonatal morbidity in a series of MC twin pregnancies treated with selective feticide in a large national cohort. Our secondary objective was to assess possible risk factors for adverse outcome in order to find ways to improve care.

Methods

All MC pregnancies treated with selective feticide at our center between June 2000 and November 2011 were included in this consecutive cohort study. The Leiden University Medical Center is a tertiary medical center and is the national referral center for fetal therapy (including selective feticide) in The Netherlands.[1] MC triplets (or higher order pregnancies) were excluded from the study.

The following obstetric data were recorded: indication for selective feticide and technique used, gestational age at intervention, preterm prelabor rupture of membranes (PPROM) before 37 weeks, gestational age at delivery and mode of delivery. The techniques used comprised fetoscopic laser coagulation, bipolar cord coagulation, interstitial laser coagulation and RFA. For fetoscopic cord coagulation performed before

18 weeks, an embryoscope was used with a diameter of 1.0 mm. For cord coagulation after 18 weeks, a 1.3-mm fetoscope was used through an 8-F introduction sheath. Criteria for intervention in TRAP were signs of cardiac compromise in the pump twin based on abnormal ductus venosus flow.

The following neonatal data were recorded: gender, birth weight, presence of respiratory distress syndrome (RDS), chronic lung disease, patent ductus arteriosus, necrotizing enterocolitis (NEC) ≥ Stage II,[14] neonatal sepsis (defined as a clinically ill neonate with positive bacterial culture), renal failure and severe cerebral injury on cranial ultrasound examination. Severe cerebral injury was defined as the presence of at least one of the following findings on ultrasound scan: Intraventricular hemorrhage (IVH) ≥ Grade III,[15] periventricular leukomalacia ≥ Grade II,[16] ventricular dilatation, arterial or venous infarct or other cerebral anomalies associated with adverse neurological outcome.

The primary outcome measure was a composite outcome termed 'adverse perinatal outcome', which included intrauterine fetal death (IUFD), neonatal death (NND), termination of pregnancy (TOP) or severe neonatal morbidity. NND was defined as the death of a liveborn child delivered after 23 weeks' gestation. Severe neonatal morbidity was defined as the presence of any of the following: RDS, NEC, neonatal sepsis, renal failure or severe cerebral injury. The incidence of adverse perinatal outcome was described by technique employed. Following analyses in recent studies,[5] we evaluated the outcome in the groups treated with selective feticide at ≤ 18 weeks' gestation and > 18 weeks' gestation.

Categorical variables were compared using Fisher's exact test or the chi-square test, as appropriate. Continuous variables were compared using unpaired Student's *t*-test, median test or the Mann-Whitney U-test. Statistical analysis was performed with SPSS version 20.0 (SPSS Inc., Chicago, IL, USA).

Results

A total of 131 MC twin pregnancies were treated with selective feticide during the study period. In cases of DC triplets with an MC component (n=7), only the MC cotwin pair was analyzed. Figure 1 shows mortality within the study population. Information on indication and technique for selective feticide is given in Table 1.

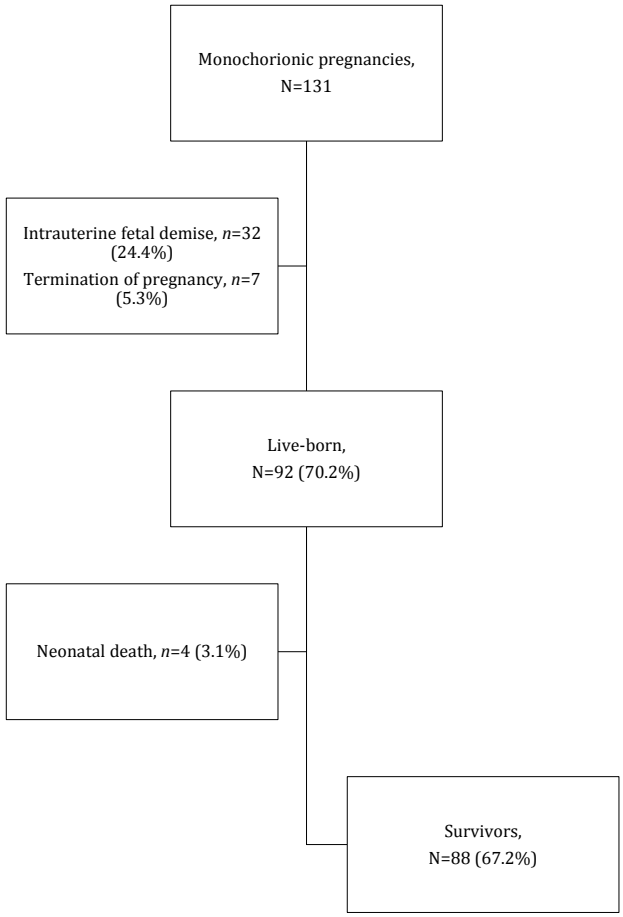

Figure 1 Flowchart showing mortality in study population of 131 monochorionic twin pregnancies that underwent selective feticide.

Table 1 Baseline characteristics in 131 monochorionic pregnancies undergoing selective feticide.

Characteristic	N (%)
Indication	
Twin-twin transfusion syndrome	40 (30.5)
Twin reversed arterial perfusion	39 (29.8)
Congenital malformation,	38 (29.0)
Selective intrauterine growth restriction	11 (8.4)
Other*	3 (2.3)
Technique	
Fetoscopic laser coagulation	69 (52.7)
Bipolar cord coagulation	36 (27.5)
Interstitial laser coagulation	15 (11.5)
Radiofrequency ablation	11 (8.4)
Cesarian delivery	24 (18.3)

* History of preterm delivery and uterus didelphus (n=1), history of preterm delivery and conization of the cervix (n=1), psycho-emotional reasons and amniotic band syndrome (n=1).

IUFD occurred in 32 cases, and in seven cases the pregnancy was terminated after selective feticide. In the 32 IUFD cases, fetal death occurred on average 1.67 (range, 0.0–9.0) weeks after the operation (median gestational age at therapy 16.0 weeks, median gestational age at delivery 17.5 weeks). Reasons for TOP were persistent severe fetal hydrops (*n*=1), chromosomal abnormality (*n*=2) and PPROM (*n*=4). Four liveborn neonates died during the neonatal period because of complications related to prematurity, Potter sequence or severe brain injury. Overall perinatal survival rate was 67.2% (88/131). Perinatal survival rate was higher in the group treated after 18 weeks' gestation than in the group treated before 18 weeks, at 80% (64/80) and 47.1% (24/51), respectively ($P < 0.001$).

Perinatal outcome by technique is given in Table 2. Feticide was performed successfully in all but one pregnancy. In this case, fetoscopic laser coagulation was discontinued because of complex entanglement of the umbilical cords in a monoamniotic twin, with too high a risk of damaging the cord of the healthy twin. This pregnancy was subsequently completely terminated because of mosaicism for trisomy 18.

The reasons for selective feticide in the TTTS group included technical issues (*n*=9), anterior placenta location (*n*=5), severe fetal malformation (*n*=11), severe sIUGR (*n*=6), severe cerebral injury (*n*=3), reversal of TTTS (*n*=2) and parental choice (*n*=4). Quintero stage at time of intervention was Stage 1 (*n*=5), Stage 2 (*n*=6), Stage 3 (*n*=21) and Stage 4 (*n*=8). Higher Quintero stage at intervention was not associated with increased risk of adverse perinatal outcome ($P = 0.29$).

PPROM occurred in 26 (19.8%) cases at a median gestational age of 25.5 weeks, of which 15 (57.7%) occurred before 28 weeks, three (11.5%) between 28 and 32 weeks and eight (30.8%) between 32 and 37 weeks. Four of these pregnancies were terminated because of anhydramnios, in two cases IUFD occurred and one child died in the neonatal period. Median gestational age at therapy was comparable between cases with and without PPROM, at 17.0 and 17.5 weeks, respectively ($P = 0.490$). Median gestational age at delivery in the subgroups with and without PPROM was 30.0 weeks and 35.0 weeks, respectively ($P = 0.047$).

Median gestational age at delivery in the 92 liveborn children was 37 (range, 33-39) weeks. Twenty-five neonates (27.2%) were born between 32 and 37 weeks' gestation, 15 (16.3%) between 28 and 32 weeks and five (5.4%) were born extremely prematurely (before 28 weeks). Detailed information on neonatal morbidity in one case was not available because the mother moved to another country shortly after the operation. She delivered in a foreign hospital at 26 weeks' gestation and the premature neonate died subsequently. Gender and birth weight are unknown.

Severe neonatal morbidity occurred in 15 neonates (16.3%). A total of 27 (29.3%) neonates required admission to the neonatal intensive care unit (NICU) and four of them died in the neonatal period (Figure 1). Detailed information on the cases with adverse perinatal outcome is given in Table 3.

Table 2. Perinatal outcome according to technique used for selective feticide in 131 monochorionic twin pregnancies.

	Fetoscopic laser coagulation (n=69)	Bipolar cord coagulation (n=36)	Interstitial laser coagulation (n=15)	Radiofrequency ablation (n=11)	All cases (n=131)
GA at therapy (weeks)	16.0 (15.0-19.0)	20.5 (18.0-22.0)	16.0 (15.0-18.0)	15.0 (14.0-18.0)	17.0 (15.0-21.0)
GA at delivery (weeks)*	33.0 (20.5-38.0)	35.5 (29.0-38.8)	26.0 (18.0-35.0)	34.0 (20.0-39.0)	34.0 (23.0-38.0)
PPROM	18 (26.1)	5 (13.9) (1 mist)	2 (13.3)	1 (9.1)	26 (19.8)
IUFD	15 (21.7)	5 (13.9)	8 (53.3)	4 (36.4)	32 (21.4)
TOP	7 (10.1)	0	0	0	7 (5.3)
NND	1 (1.4)	3 (8.3)	0	0	4 (3.1)
Survival per indication:					
TTS	15/22	12/16	1/1	0/1	28/40 (70.0%)
TRAP	16/23	-	4/11	4/5	24/39 (61.5%)
Congenital malformation	13/20	11/14	1/2	1/2	26/38 (68.4%)
sIUGR	2/3	4/5	1/1	1/2	8/11 (72.7%)
Other	0/1	1/1	-	1/1	2/3 (66.6%)
Survival rate	46 (66.7)	28 (77.8)	7 (46.7)	7 (63.6)	88/131 (67.2)
Birth weight (g)	2614 ± 1005	2839 ± 1582	2339 ± 1066	3101 ± 1162	2706 ± 1238
Adverse perinatal outcome	27 (39.1)	11 (30.6)	9 (60.0)	7 (63.6)	54/131 (41.2)

Data shown as median (interquartile range), *n* (%), *n*/*n* or mean }SD. GA, gestational age; IUFD, intrauterine fetal death; NND, neonatal death; PPROM, preterm premature rupture of membranes; sIUGR, selective intrauterine growth restriction; TOP, termination of pregnancy; TRAP, twin reversed arterial perfusion; TTTS, twin–twin transfusion syndrome.

Table 3 Cases of selective feticide complicated by neonatal morbidity and/or perinatal mortality in monochorionic twin pregnancies.

Case	Indication for selective feticide	GA at therapy (weeks)	Technique	PPROM (weeks)	GA at birth (weeks)	Birth weight (g)	Neonatal outcome
Neonatal death							
1	Congenital malformation	21	BCC	No	30	1560	NND within a few hours after birth; lung hypoplasia due to congenital renal failure (Potter sequence), neonatal sepsis
2	Congenital malformation	22	BCC	No	26	900	NND on day 10; asphyxia, RDS, IVH Grade IV, renal failure, heart failure
3	Congenital malformation	17	BCC	NA	26	NA	NND; neonatal morbidity unknown
4	TTTS	18	FLC	Yes (19)	30	800	NND after 7 weeks; RDS, PDA, vein of Galen malformation, heart failure, neonatal sepsis
Neonatal morbidity							
5	Congenital malformation	22	BCC	No	25	845	RDS, neonatal sepsis
6	TTTS	14	FLC	Yes (16)	30	2000	RDS, severe neuropathy of auditory nerve (CMV infection)
7	sIUGR	17	ILC	Yes (25)	26	1345	RDS
8	TRAP	18	FLC	Yes (29)	29	1675	RDS
9	TTTS	20	FLC	Yes (25)	28	955	RDS, neonatal sepsis
10	sIUGR	19	FLC	No	26	875	RDS
11	sIUGR	20	RFA	No	28	1150	Neonatal sepsis
12	Congenital malformation	23	BCC	No	29	1512	RDS
13	Other	12	RFA	Yes (34)	34	2165	IVH Grade IV
14	TTTS	21	BCC	No	29	1060	Neonatal sepsis
15	TTTS	21	FLC	Yes (22)	29	1486	RDS

BCC, bipolar cord coagulation; CMV, cytomegalovirus; FLC, fetoscopic laser coagulation; GA, gestational age; ILC, interstitial laser coagulation; IVH, intraventricular hemorrhage; NA, not available; NND, neonatal death; PDA, patent ductus arteriosus; PPROM, preterm premature rupture of membranes; RDS, respiratory distress syndrome; RFA, radiofrequency ablation; sIUGR, selective intrauterine growth restriction; TRAP, twin reversed arterial perfusion; TTTS, twin–twin transfusion syndrome.

Overall, the rate of adverse perinatal outcome (including perinatal mortality and severe neonatal morbidity) was 41.2% (54/131). The rates of PPROM in cases with and without adverse perinatal outcome were 24.1% (13/54) and 16.9% (13/77), respectively (P = 0.275). However, the median gestational age at occurrence of PPROM was significantly lower in cases with than in those without adverse perinatal outcome, at 19.0 weeks and 32.0 weeks, respectively (P = 0.017). In addition, liveborn children with adverse perinatal outcome were born at a lower median gestational age (29.0 weeks) than were children without adverse perinatal outcome (38.0 weeks; $P < 0.001$).

Detailed information on brain imaging was obtained in 28/92 neonates (30.4%). Severe cerebral injury was detected on ultrasound scan in three neonates, including IVH Grade IV (n=2) and vein of Galen malformation (n=1). The case of the child with vein of Galen malformation has been reported previously.[17] Two children with severe cerebral injury died in the neonatal period. In the majority of neonates (64/92), routine ultrasound scans were not performed. Most of these children were in good clinical condition and were discharged from the hospital shortly after birth.

Other neonatal complications in the group of liveborn infants were nine cases of RDS (9.8%), two of chronic lung disease (2.2%), six of patent ductus arteriosus (6.5%), four of neonatal sepsis (4.3%) and one of NEC (1.1%).

Discussion

In this study we evaluated the perinatal outcome after selective feticide in a large cohort (n=131) of MC twin pregnancies and report an overall perinatal survival rate of 67.2%. Survival rates of 65–92% have been reported in the literature.[5] Rossi and D'Addario[5] reported an overall survival rate of 79% in a systematic review. However, care should be taken when comparing results of different studies, as overall perinatal outcome depends on various factors including indication for, and technique and timing of, the selective feticide procedure. Analysis of our results after stratification by type of surgical technique shows that interstitial laser coagulation and RFA are associated with the lowest survival rates, at 46.7% and 63.6%, respectively. Rossi and D'Addario[5] in contrast found the highest survival in the RFA group (86%). Nevertheless, important methodological issues (primarily related to the small number of patients included) prevent accurate comparison between the various reports. Larger studies are urgently needed to reach reliable conclusions on outcome after RFA and interstitial laser coagulation.

Our study also shows that perinatal survival is higher (86.3%) when intervention is performed after 18 weeks' gestation than it is when performed before 18 weeks

(47.1%). Our findings are in accordance with those of Rossi and D'Addario.[5] who also found a higher survival rate (89%) when the procedure was performed after 18 weeks than when it was performed earlier (69%), irrespective of the indication for selective feticide. In support of the hypothesis that gestational age at therapy is associated with adverse perinatal outcome, Lanna et al.[18] found an incidence of miscarriage of 3% when bipolar cord coagulation was performed after 19 weeks' gestation, compared with 45% when performed before 19 weeks. Overall survival rate in this large study (n=118) was 71%, which is comparable with our results. The findings in our study and other reports suggest that intervention should be postponed until after 18weeks' gestation, when possible.[5;18]

The reported rate of neonatal morbidity and mortality (16.3%; 15/92) in our study was higher than the reported rate of 7.0% (19/273) in the systematic review of Rossi and D'Addario.[5] Discrepancies in the results may be due to methodological differences such as under-reporting of neonatal morbidity and/or the use of different definitions of morbidity in the papers included in the review. In addition, most studies included in the systematic review of Rossi and D'Addario had a relatively high rate of loss to- follow-up, whereas we were able to report the perinatal and neonatal outcomes in all cases.

Our study confirms PPROM as one of the major risk factors for adverse perinatal outcome after invasive fetal interventions. In our cohort, in all but one case, neonatal mortality and morbidity occurred in neonates delivered at a gestational age of ≤30 weeks. Our data are in agreement with a recent study by Bebbington et al.[19] of 146 cases treated with selective feticide. The authors report a similar increased rate of PPROM and premature delivery and a clear association with adverse outcome. However, neonatal morbidity was not evaluated or reported.

In two small studies with six and 13 survivors, no neonatal morbidity was detected,[6;20] whereas in another small study, by Tsao et al.[21], one out of 13 children died from complications of prematurity. Lewi et al.[13] found a survival rate of 83% in a group of 80 pregnancies treated with fetoscopic laser and/or bipolar cord coagulation. These authors only described neonatal morbidity (asphyxia and NEC) in the subgroup with neonatal death and cerebral injury only in children who had developmental delay in long-term follow up. Robyr et al.[22] reported 8.7% prematurity-related deaths (4/46) after bipolar cord coagulation, without further describing neonatal morbidity in survivors. Paramasivam et al.[23] reported brain abnormalities in two cases in a group of 32 survivors after treatment with RFA, however other neonatal problems were not discussed. Ilagan et al.[24] reported that 48% of neonates required admission to the NICU after bipolar cord coagulation because of various neonatal morbidities. Perinatal mortality was 3/27 (11.1%). Their conclusions were unfortunately marred owing to a large loss-to-follow-up rate, as only 55% of the patients gave consent for follow-up.

Care should be taken when interpreting our results because of the limitations associated with the retrospective nature of this study. In our cohort, different techniques were used depending on various clinical factors and the operator's preference, and the indications for selective feticide varied. The population was therefore inhomogeneous and difficult to compare with those of other studies. A risk-factor analysis comparing different techniques or indications was envisaged but considered inappropriate owing to small sample size per technique.

Although only a few cases with severe cerebral injury were found, it is possible that some were missed since cranial ultrasound scans were not routinely performed. More research is needed to determine the value of routine ultrasound scans in all liveborn survivors after selective feticide, or in fact after all fetal interventions. Also, because it is difficult to predict long-term outcome based on findings on cranial ultrasound scan, long-term follow-up should be performed to determine quality of life and neurodevelopmental outcome of survivors.

Few studies describe neurodevelopmental outcome in children treated with selective feticide. Moise et al.[6] reported that all of the six survivors in a study of RFA in nine patients were doing well based on telephone follow-up at a mean neonatal age of 4 months. Lewi et al.[13] described long-term follow up in 67 survivors, of whom five had some form of developmental delay. Robyr et al.[22] found one child with developmental delay at age 18 months, although without any abnormalities on brain imaging. Large long-term follow-up studies in survivors after selective feticide are urgently required in order to acquire the knowledge necessary to counsel parents reliably.

In conclusion, selective feticide is associated with a high risk of adverse perinatal outcome. Further research is warranted to find ways to minimize the risks of selective feticide, by optimizing indications, timing and methods used. Outcome studies should include long-term follow-up to assess neurodevelopmental outcome in survivors.

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