Biocellulose patch technique for fetoscopic repair of open spina bifida in twin pregnancy

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KEYWORDS: discordant dichorionic twins; discordant monochorionic twins; monochorionic twins; myelomeningocele; myeloschisis; open spina bifida cystica; rachischisis; spinal dysraphism

CONTRIBUTION

What are the novel findings of this work?

Twin pregnancy is an exclusion criterion for prenatal surgery for open spina bifida (OSB). We report on seven twin pregnancies in which fetoscopic percutaneous repair was feasible and resulted in a good outcome for both babies. The skin-over-biocellulose for antenatal fetoscopic repair (SAFER) technique could be a new alternative for parents seeking treatment in twin pregnancy.

What are the clinical implications of this work?

Parents faced with a prenatal diagnosis of OSB in one or both twins could be offered prenatal repair using the SAFER technique. As fetal surgery for OSB in twins has not previously been reported in the literature, the present series offers preliminary data for counseling parents.

ABSTRACT

Objectives Twin pregnancy is currently an exclusion criterion for prenatal repair of open spina bifida (OSB). The main objective of this study was to report on our experience of treating twin pregnancies with OSB using the skin-over-biocellulose for antenatal fetoscopic repair (SAFER) technique. We also discuss reconsideration of the current exclusion criteria for fetal OSB repair.

Methods Eight fetuses with OSB from seven twin pregnancies underwent successful prenatal repair. Six

pregnancies were dichorionic diamniotic with only one twin affected, and one was monochorionic diamniotic with both twins affected. Percutaneous fetoscopy was performed under CO_2 insufflation of the sac of the affected twin. Neurosurgical repair was performed using a biocellulose patch to protect the placode, with the skin sutured to hold the patch in place, with or without a myofascial flap. Neurodevelopment was assessed using the pediatric evaluation of disability inventory scale in babies older than 6 months of adjusted age, whereas the Alberta scale was used for babies younger than 6 months of adjusted age.

Results All 14 fetuses were liveborn and none required additional repair. Gestational age at surgery ranged from 27.3 to 31.1 weeks, and gestational age at birth ranged from 31.6 to 36.0 weeks. Four out of eight affected twins developed sepsis, but had a good recovery. No sequela of prematurity was found in any of the unaffected twins. Short-term neurodevelopment was normal in all evaluated unaffected twins (5/5) and in all but one affected twins (7/8). In the affected group, only one baby required ventriculoperitoneal shunt placement.

Conclusions Prematurity is frequent after fetal surgery, and the risk is increased in twin pregnancy. Nevertheless, prenatal surgery using the SAFER technique is feasible, with low risk to both twins and their mother when performed by a highly experienced team. Long-term cognitive assessment of the unaffected twin is needed.

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INTRODUCTION

Twin pregnancy was established as an exclusion criterion for prenatal open spina bifida (OSB) repair in the Management Of Myelomeningocele Study (MOMS) trial and, more than 10 years later, it remains a contraindication¹. Excluding twin pregnancy was largely justified at the conception of the MOMS trial due to the unclear benefits to the fetus undergoing prenatal repair of OSB, the unknown maternal and fetal risks and the uncertainty regarding feasibility of exteriorizing the large uterus in a twin pregnancy.

Since the publication of the MOMS trial, advances to develop a minimally invasive approach for OSB prenatal repair have resulted in two main fetoscopic techniques²: the laparotomy-assisted approach and the completely percutaneous approach³. Different percutaneous techniques have been proposed. The skin-over-biocellulose for antenatal fetoscopic repair (SAFER) technique protects the defect using a biocellulose patch, followed by the addition of a myofascial layer and suturing of the skin⁴. The approach proposed by Chmait $et al.^5$ is similar to the SAFER technique, but instead uses a bovine or collagen patch to cover the placode, given the lack of approval of the biocellulose patch in the USA. Moreover, in the approach proposed by Chmait et al.⁵, the larger trocar is placed through a 3-cm mini-laparotomy incision to secure the membrane to the myometrium before the trocar entrance, whereas other trocars are placed under ultrasound guidance without securing the membranes. Kohl⁶ and Graf et al.⁷ used a different technique aiming to achieve primary watertight dural closure, utilizing several small staples to fix the patch to the dura and then closing the skin in the midline, if possible.

Although the benefits of fetal repair are unequivocal, currently, no repair protocol is available for twin pregnancy. The percutaneous SAFER technique has already been performed in more than 170 cases in Brazil, constituting the largest cohort worldwide to undergo this procedure⁸. As Brazil does not allow termination of pregnancy or selective feticide, currently, postnatal repair is the only option for parents with a twin pregnancy facing the diagnosis of OSB, despite all the reported benefits of prenatal repair^{1,9,10}.

As awareness of the improved outcome associated with prenatal OSB repair increased, parents started to come to our center to discuss the possibility of prenatal surgery on their twins. In this study, our aims were to report on the outcome of seven twin pregnancies that underwent the SAFER technique in Brazil, and to discuss some of the current exclusion criteria for prenatal repair of OSB. To the best of our knowledge, this is the first series to be published on prenatal repair of OSB in twins. Of particular interest, this study includes a monochorionic diamniotic pair in which both babies were affected.

METHODS

Ethics

Seven women with a twin pregnancy self-referred to our center for fetal repair of OSB. A multidisciplinary team evaluated the cases, and an extensive ethical discussion was held before offering the surgery. Ethical principles of preserving the integrity of the unaffected twin as well as respecting the autonomy of the mother and duty to improve outcome in affected fetus were considered¹¹. We agreed to proceed with the surgery after obtaining approval of our ethics committee board (reference number, CAE: 48991021.0.0000.0071), based mainly on the principle of justice for both children^{12,13}. It was agreed that surgery would be performed at a later gestational age in an attempt to balance the best interests of the affected fetus and the harm threshold due to prematurity for the unaffected fetus^{12,13}.

The SAFER technique for fetal treatment is considered an established procedure in our center according to the proposed classification of Verweij et al.¹⁴. It has also been shown to be safe for the mother as part of the International Fetoscopic Neural Tube Defect Repair Consortium². However, repair in twins was considered on compassionate grounds due to the lack of previous reports. Parents were informed regarding the novelty of the procedure since twin pregnancy is still considered an exclusion criterion for prenatal repair. In addition, in the case of a monochorionic diamniotic pregnancy in which both fetuses were affected, the following options were discussed with the parents: (1) repairing only one fetus, (2) repairing each fetus separately within an interval of a few weeks and (3) repairing both fetuses at the same time. In this case, the parents decided that both fetuses would be operated on at the same time.

Prenatal evaluation

All cases underwent an anomaly scan up to 9 days before surgery, performed by the same operator (D.A.L.) who was blinded to previous motor assessment results. Motor level assessment is performed routinely and classified for each leg according to the description of Carreras *et al.*¹⁵. In case of asymmetric motor level, the worst level was considered. Prenatal motor assessment was compared with postnatal neurological clinical assessment.

Surgical protocol

The preoperative protocol included betamethasone administration for fetal lung maturation 2 days before surgery, prophylactic tocolysis using 100 mg of indomethacin via the rectum 12 h before surgery and 50 mg of intravenous indomethacin every 12 h within the 24-h interval following surgery. The prophylactic

trocars were placed in the second amniotic sac, which was also inflated to 15 mmHg. Intraoperative fetal monitoring using Doppler ultrasound did not show signs of acute fetal decompensation, i.e. acute twin-twin transfusion syndrome, fetal distress or unexpected complications. The placode was dissected and covered with a biocellulose patch (Bionext®; Bionext, Paraná, Brazil), and the dura mater was not sutured. Subsequently, a myofascial flap was applied above the biocellulose patch whenever possible. Surgical details are illustrated in Figure 1. Both fetuses were monitored every 15-30 min by Doppler ultrasound. Amnioinfusion was performed only in the affected twin sac, through careful ultrasound-guided placement of the trocar. Patients were discharged on the third day after surgery without recommendation for strict bed rest. We recommended weekly monitoring in a hospital close to the woman's home until delivery. After birth, data were obtained using the neonatal intensive care unit (NICU) discharge report, and follow-up contact was made every 6–12 months by our research nurse. Neurodevelopment was assessed in both twins by our certified occupational therapist and the trained research team (G.C., L.T.). When children were younger than 6 months of adjusted age, the Alberta scale was applied, while the pediatric evaluation of disability inventory (PEDI) scale was used once they were over 6 months of adjusted age.

Statistical analysis

Data were stored and analyzed using STATA 13 (StataCorp., College Station, TX, USA). Categorical variables are presented as n (%) and continuous variables



Figure 1 Prenatal repair of open spina bifida in a monochorionic diamniotic twin pregnancy with both twins affected (a-c) and a dichorionic diamniotic pregnancy with only one fetus affected (d,e). (a) Trocar placement for repair of both affected twins. Maternal head is at top of image. Twin 1 (maternal right side) had cephalic presentation and Twin 2 (maternal left side) had breech presentation. Four trocars for Twin 1 and three trocars for Twin 2 can be seen. (b) Defect of Twin 2 (dashed arrow) and head of Twin 1 (solid arrow) can be seen through intertwin membrane. (c) Defect of Twin 2 that was operated on in breech presentation. (d) Repaired skin of affected fetus (arrows). Unaffected cotwin's legs and feet are seen through intertwin membrane. (e) View from affected twin sac insufflated with gas. Unaffected twin can be seen through intact intertwin membrane. Unaffected sac retained its amniotic fluid.

stability.

end of the surgery.

antibiotic treatment of 2 g of cephalexin was administered

intravenously, as well as inside the uterine cavity at the

Surgery was performed under higher-than-usual doses of total intravenous anesthesia (TIVA). Inhalation agents

were used only if deeper sedation was required or

if contractions were noticed, in which case, minimum

alveolar concentration of 0.4-1% of sevoflurane was

used. Anesthesia was induced with propofol at 2 mg/kg

and maintained with intravenous propofol infusion to

keep the bispectral index at 40. Remifentanil infusion

at 0.25 µg/kg/min was added to maintain cardiovascular

placental and fetal position, maternal lateral decubitus

position was used to facilitate surgical access and to

minimize the venous return reduction effect due to the

larger uterus. No external version was performed, and

fetal presentation was maintained and used as reference

for the insertion of trocars. When only one fetus was

operated on, we used three or four trocars (one 5-mm

and two or three 11-Fr trocars). Insertion of trocars

was always ultrasound guided. In the monochorionic

diamniotic case, four trocars (one 5-mm and three 11-Fr

trocars) were used for Twin1 and three trocars (one

5-mm and two 11-Fr trocars) were used for Twin2.

Two teams were present and were prepared to operate

simultaneously if necessary. As the mother and fetuses were stable during surgery, Twin 1 was operated on first

under CO₂ pressure of 15 mmHg. An unintentional injury of membranes occurred during surgery, so we decided not

to remove the trocars or deflate the first amniotic sac.

Therefore, after the end of surgery on Twin 1, three other

After maternal-fetal anesthesia, depending on the

are presented as median and interquartile range (IQR). Pearson's χ^2 or Fisher's exact test was used to compare categorical variables and Wilcoxon rank-sum test was used to compare continuous data. *P*-values < 0.05 were considered significant.

RESULTS

All cases that were screened underwent prenatal surgery. There was a total of eight fetuses with OSB in seven twin pregnancies, including six dichorionic diamniotic pregnancy (Table 1). In the monochorionic diamniotic pregnancy, both fetuses presented with OSB. All fetuses underwent successful repair, and no maternal complications occurred during surgery or later. Details regarding pregnancy, surgery, postsurgery and postnatal period characteristics are available in Table S1.

Table 1 Maternal, surgical and postnatal postsurgical characteristics of seven twin pregnancies with eight fetuses undergoing prenatal repair of open spina bifida using skin-over-biocellulose for antenatal fetoscopic repair (SAFER) technique

Characteristic	Value
Maternal	
Maternal age (years)	36.9 (31.8-38.4)
Parity	1 (1-2)
BMI	28.1 (21.9-29.3)
Preconception folic acid	6/7 (85.7)
IVF pregnancy	4/7 (57.1)
Type of twin pregnancy	
Dichorionic diamniotic	6/7 (85.7)
Monochorionic diamniotic	1/7 (14.3)
Surgical	
GA at surgery (weeks)	28.3 (27.7-29.8)
Total intravenous anesthesia	8/8 (100)
Humidified CO ₂ insufflation	8/8 (100)
Number of trocars	3 (3-4)
Posterior placenta	4/7 (57.1)
Myofascial flap	4/8 (50.0)
Duration of surgery (min)*	145 (132-151)
Postsurgical	
PPROM	4/8 (50.0)
GA at PPROM (weeks)	32.1 (31.6-33.1)
GA at delivery (weeks)	32.4 (31.6-33.9)
Interval from surgery to delivery (weeks)	4.3 (3.1-4.4)
Postnatal postsurgical	
Motor level \geq prenatal motor level	7/7 (100)†
Optimal neurological evaluation	
Affected twin	7/8 (87.5)
Unaffected twin	5/5 (100)‡
Cerebrospinal fluid diversion	1/8 (12.5)
Neonatal scar dehiscence	0/8 (0)
Tethered cord	0/8 (0)

Data are given as median (interquartile range) or *n*/*N* (%). *Duration of surgery was considered as skin-to-skin. †One case did not undergo postnatal motor function evaluation due to orthopedics plaster treatment. ‡One unaffected case did not undergo neurological evaluation. BMI, body mass index; GA, gestational age; IVF, *in-vitro* fertilization; PPROM, preterm prelabor rupture of membranes. The gestational age varied from 27.3 to 31.1 weeks at surgery and from 31.6 to 36.0 weeks at delivery, with a median interval of 4.3 weeks from surgery to delivery. The median duration of surgery was 145 min. TIVA and humidified CO₂ were used in all surgeries. The myofascial flap was performed in half of the cases due to technical difficulties. The number of trocars in the affected twin sac was three in five (62.5%) and four in three (37.5%) cases. Unintentional injury to the intertwin membrane occurred only in the monochorionic diamniotic pregnancy (14.3%; 1/7).

Four pregnancies had preterm prelabor rupture of membranes at a median gestational age of 32.1 (IQR, 31.6-33.1) weeks. Placental abruption occurred in two of the seven cases. The median birth weight was 1611 (IQR, 1413-1693) g and 1965 (IQR, 1790-2160) g in affected and unaffected cases, respectively (P = 0.046) (Table 2). No neonatal death occurred. The affected twins stayed in the NICU for a median of 49 (IQR, 27-62) days, while the median NICU stay among unaffected twins was 23 (IQR, 19–29) days (P = 0.052). No sepsis or any other sequela of prematurity was found in the unaffected twins; however, sepsis was present in four of the eight affected cases. Within the affected group, one fetus had mild aortic stenosis and another one had a right aortic arch with Kommerell's diverticulum, both diagnosed on prenatal echocardiography.

Motor assessment

Neonatal motor level assessment was performed in seven of the eight affected newborns. One case with congenital

 Table 2 Postnatal characteristics and prematurity complications of fetuses that underwent prenatal open spina bifida (OSB) repair and unaffected cotwins from seven twin pregnancies

	OSB	Unaffected
Characteristic	(n = 8)	(n = 6)
OSB type		
Myeloschisis	3 (37.5)	N/A
Myelomeningocele	5 (62.5)	N/A
Liveborn	8 (100)	6 (100)
Birth weight (g)	1611	1965
	(1413 - 1693)	(1790 - 2160)
1-min Apgar score	8 (6-8)	8 (8-8)
5-min Apgar score	9 (9-9)	9 (8-9)
NICU stay (days)	49 (27-62)	23 (19-29)
Prematurity complication		
Bronchopulmonary dysplasia	0 (0)	0(0)
Retinopathy of prematurity	1 (12.5)	0 (0)
Necrotizing enterocolitis	2 (25.0)	0(0)
Patent ductus	0 (0)	0(0)
Seizures	2 (25.0)	0(0)
Intraventricular hemorrhage	0 (0)	0(0)
Periventricular leukomalacia	0 (0)	0(0)
Perinatal sepsis*	1 (12.5)	0(0)
Neonatal sepsis (> 72 h)	3 (37.5)	0(0)
Neonatal death	0 (0)	0 (0)

Data are given as n (%) or median (interquartile range). *Sepsis prior to, during or up to 72 h after delivery. N/A, not applicable; NICU, neonatal intensive care unit.

clubfoot started orthopedic treatment (bilateral caskets) before we could evaluate them. Prenatal presurgical motor evaluation was performed at a median gestational age of 28.1 (IQR, 27.3–29.5) weeks and was compared with motor level at birth. Motor level was the same in six cases and improved at birth in one case (P = 0.317).

Neurological outcome

No affected twin needed revision of the repair site or had cerebrospinal fluid leakage at birth. Five affected cases were followed up to ≥ 12 months, and only one of them required ventriculoperitoneal shunt placement during the NICU stay. None of the cases presented with a tethered cord.

All eight affected twins underwent neurological assessment. Five of the six unaffected twins were also evaluated. The median chronological age of the pairs at evaluation was 12.5 (IQR, 2.7–18.1) months, and the median adjusted age was 10.9 (IQR, 1.2–16.1) months. The PEDI and Alberta scales were normal in all evaluated unaffected twins (5/5) and in all affected twins except one (7/8).

DISCUSSION

OSB in twins is a rare occurrence. A recent review found a total of 24 pregnancies with OSB, of which 11 pairs were dizygotic and eight were monozygotic (zygosity not specified in the remaining five twin pairs)¹⁶. In this study, we present seven twin pregnancies with OSB, including one case of dual defect in a monochorionic diamniotic pregnancy.

Ethics

Ethical decisions surrounding twins affected discordantly by a malformation are largely influenced by the perception of risk to the unaffected twin, according to Riggan *et al.*¹⁷. However, the advances in fetal surgery and the increasing awareness of new surgical techniques through social media promote self-referrals of challenging cases. Parents that do not accept termination of pregnancy search for new medical procedures and question doctors about their views and perspectives. The principles of ethics in fetal surgery consider the interests of two patients, the mother and the baby. As the field is evolving, maternal risks are decreasing and fetal benefits are increasing, introducing new dilemmas.

In the past, fetal surgery was offered only for lethal malformations, but its indications have been changing^{11,18,19}. An ethical discussion regarding fetal surgery in twins discordant for diaphragmatic hernia concluded that certain maternal–fetal surgical interventions may be ethically permissible if the risk to the unaffected twin is minimal and the procedure improves the likelihood of survival of the compromised fetus¹⁷. Although OSB is not lethal, the benefits of prenatal surgery are established^{1,2,8,20,21}. We believe the risk to the unaffected twin may be minimized by delaying surgery to 28–30 gestational weeks to mitigate the risk of extremely preterm birth in case delivery is required during surgery.

Safety of mother and unaffected twin

The safety for the unaffected twin of using volatile agents during anesthesia is uncertain^{22,23}. However, in animal models, maternal general anesthesia did not affect brain development of non-operated pups^{20,24}. Therefore, we counseled our patients that the risk to the unaffected twin associated with the anesthetic should be similar to that of laparoscopic surgery during pregnancy (which has been shown to carry no additional risk to the fetus²⁵). In our cohort, each evaluated unaffected fetus had normal neurodevelopmental assessment and outcome.

Maternal and fetal safety can be jeopardized by the occurrence of placental abruption, which occurred in 28.6% (2/7) of cases. We believe that this is a major concern, and it seems to be more frequent in twin compared with singleton pregnancies undergoing OSB repair, in which the incidence has been described to be as high as $9.3-17.8\%^{4,26}$. Therefore, patients should be advised to remain close to the hospital in which their baby will be delivered. We believe that the high rate of placental abruption may be related to oligohydramnios that persists after surgery and/or to the detachment of membranes since we do not suture the membranes prior to or after surgery. This is a limitation of our technique, which we believe can be improved on with the development of a method to fix the membranes before trocar insertion without opening the maternal abdomen, which has already been studied²⁷.

Finally, in the context of operating at a later gestational age, some may argue that it would be better to deliver early, correcting the malformation after birth and sparing the mother from an invasive procedure. However, in this scenario, prematurity would be certain and immediate repair would not be feasible due to the increased risk of infection and damage to the exposed spinal cord. Furthermore, since the benefits of prenatal surgery are clear^{1,2,8,20,21}, delaying surgery until after birth may be considered unethical.

Revisiting inclusion and exclusion criteria for prenatal repair

During development of the MOMS trial protocol, very strict inclusion criteria were established since benefits of prenatal surgery were still unknown and maternal risks associated with open fetal surgery were high. Exclusion criteria were extensive and restrictive to the point that only one-third of referred cases met the criteria for prenatal surgery²⁸. Considering new studies on fetoscopic repair of OSB have shown that an improvement in maternal safety can be achieved without jeopardizing

fetal neuroprotection^{2,14}, we believe some of the exclusion criteria should be revisited.

We aimed to provide evidence that prenatal repair of OSB can be offered in selected twin cases, even in monochorionic pairs. We acknowledge that fetal OSB repair in twins is challenging and should be attempted only by teams that have already passed the steep phase of the learning curve. Our first prenatal OSB repair in a twin pregnancy was performed after we had performed the procedure in 95 singleton pregnancies. Moreover, we believe that counseling is an important step when considering surgery in pregnancies with discordant twins. Although feticide is not allowed in Brazil, we acknowledge that selective feticide or termination of pregnancy is offered in other countries. All our cases said they would decline termination even if it was available in Brazil. For the same reason, the presence of a non-lethal malformation or a mild genetic disorder should not be considered an exclusion criterion for fetoscopic prenatal surgery.

In our center, we no longer use anatomical level for case selection or counseling; instead, we use the motor level determined by ultrasound. We believe that motor prognosis can be predicted reliably by prenatal ultrasound. In our cohort, it could predict neonatal motor level with good accuracy, even in fetuses undergoing surgery after 26 weeks' gestation²⁹.

We strongly believe that prenatal surgery should be performed after 26 weeks' gestation to avoid complications associated with extreme prematurity. Larger numbers are needed to confirm our findings and, if confirmed, we may not only increase the upper gestational age limit for surgery but also modify the exclusion criteria for OSB repair.

Limitations

One important limitation is that we performed the repair only in cases in which it was deemed technically feasible, leading to selection bias. The small number of cases is another limitation of this study. We acknowledge that only groups using the fully percutaneous technique will likely be able to perform repair in multiple pregnancy due to the difficulty in exteriorizing the larger uterus in laparotomy-based repair techniques.

Conclusion

We believe that prenatal repair of OSB in twin pregnancy is the next step in the evolution of fetoscopic procedures. The procedure is feasible and appears to be safe for both twins when performed by a highly experienced team. Avoiding early fetoscopic repair by delaying gestational age at surgery seems to improve the protection of the cotwin from complications related to extreme prematurity. Local ethics committee overview is advisable in cases of twins discordant for structural anomalies, and larger cohorts are needed to assess risks and benefits, especially for the unaffected twin.

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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Table S1 Pregnancy, surgery, postsurgery and postnatal period characteristics of each operated case (eight twins, seven pregnancies)