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Inclusion Cysts after Fetal Spina Bifida Repair: A Third Hit?

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Fetal MMC repair · Spina bifida repair · Inclusion cysts · Dermoid

Abstract
Introduction: Fetal spina bifida repair (fSBR) has proven effective in the reversibility of hindbrain herniation, lower rate of shunt-dependent hydrocephalus, and independent ambulation. Besides distinct advantages, there are also concerns related to fSBR. One of these is the postnatal occurrence of inclusion cysts (IC). ***Methods:*** In a prospective study, 48 children who underwent fSBR were followed up. Postnatal assessment included clinical examination, cystometry, and spinal MRI. Indication for IC resection was the evidence of a spinal mass on MRI in the presence of deteriorating motor or bladder function, pain, or considerable growth of the IC. ***Results:*** Fourteen children (30%) developed IC, all within the first 2 years of life. Six children underwent IC resection; 4 children due to deteriorating function, 2 children due to doubling of the mass on MRI within 1 year. Following IC resection, 4/6 children (67%) demonstrated altered motor function and 6 children (100%) were diagnosed with neurogenic bladder dysfunction. ***Conclusions:*** Systematic follow-up of patients with a history of fSBR revealed a high incidence of IC. Whether these are of dysembryogenic or iatrogenic origin, remains unclear. Since both IC per se and IC resection may lead to loss of neurologic function, IC can be considered a "third hit".

Introduction

The rationale for performing fetal spina bifida repair (fSBR) was the observation of an ongoing, accumulative damage to spinal cord structures in utero, known as the "two-hit-hypothesis" [1, 2]. The first hit is the segmental failure of the neural placode to tubularize, while the second hit is the in utero acquired damage of the spinal cord caused by its exposure to neurotoxic amniotic fluid constituents, direct trauma, hydrodynamic

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pressure, or their combination. In utero protection of the exposed spinal cord structures prevents or at least significantly reduces severe morbidities, such as hindbrain herniation, hydrocephalus, and lower extremity disability [3], as well as neurogenic bladder [4], and hence has been accepted as a novel standard of care for selected fetuses with myelomeningocele (MMC) or myeloschisis.

Before the era of fetal surgery, inclusion cysts (IC) already represented a significant problem, occurring in up to 16% of patients with spinal dysraphism [5–8], and causing severe functional deterioration. However, there is only limited literature on the occurrence of IC after fSBR. Mazzola et al. [9] reported an incidence of 6%, Danzer et al. [10] reported an incidence of 26%, where all patients presented with a loss of motor function in lower extremities and/or progressive bladder dysfunction, at an average age of 10 months.

The aim of this study was to present our experience with IC after fSBR, with focus on incidence, management, outcome, and etiology.

Methods

Patient Population

A review of the prospectively collected data was conducted for all patients who underwent open fSBR at the "Zurich Center for Fetal Diagnosis and Therapy" between December 2010 and December 2016. Patients and their mothers were selected according to the (slightly modified) MOMS-protocol [3]. Written informed consent and approval by the local Ethics Committee were obtained (KEK-ZH-No. 2015-0172).

In Utero Surgery

All fetal surgeries were performed by the same team of specially trained pediatric surgeons (using 3.5× loupes), obstetricians, and anesthesiologists. After low transverse laparotomy and hysterotomy, the fetal back was exposed. Around the verge of the zona medullovasculosa, the zona epithelioserosa was completely excised using a monopolar needle tip. Maximal care was taken to macroscopically remove all cutaneous tissues around the placode. The closure of the open spinal canal was achieved using dura and myofascial flaps. Whenever a distinct plane between dura and fascia could not be established, a conjoined duromyofascial layer was used. A dura substitute was used if the dural layer was not large enough, to provide secure closure. The skin was closed primarily, occasionally using transposition flaps [11]. When direct skin closure was not feasible, a skin substitute (Integra® [12] or Alloderm®) was implanted.

Standardized Follow-Up

All patients underwent routine postnatal follow-up at our "Pediatric Spina Bifida Center," after birth, at the age of 3, 6, 12, 18, and 24 months, and thereafter annually. Each visit included clinical evaluation by a pediatric neurologist, pediatric rehabilitation physician, pediatric neurosurgeon, and pediatric urologist. Renal ultrasound and cystometry were conducted on every visit, spinal MRI was performed postnatally and annually, provided the clinical course remained uneventful.

Radiographic diagnosis of IC was based on the following imaging characteristics: uni- or multilobular round or ovoid mass localized at the conus medullaris or cauda equina, causing no compression but displacement of fibers, isointense or mildly hyperintense to cerebrospinal fluid on T1-weighted sequence, hyperintense on T2-weighted sequence, and with pronounced diffusion restriction.

Resection of IC

Indication for IC resection was a spinal mass on MRI in the presence of deteriorating motor and/or bladder function, or considerable growth documented on serial MRI (doubling of size within 1 year) in asymptomatic children.

Surgeries for IC were performed by pediatric neurosurgeons. Laminectomy was performed when necessary to expose the dural layer cranial and caudal to the cyst. IC resection was performed using an operating microscope, taking care to leave the cyst wall intact. An electric stimulator probe was used to identify critical neural structures. A water-tight and tension-free closure of the dura followed by subcutaneous tissue and skin concluded the procedure. After IC resection, children underwent follow-up MRI within 5 days. Outpatient consultations, as described above, were scheduled postoperatively at 3 months and 1 year or when required by clinical evolution.

Statistics and Level Definitions

Data are expressed as median and range, absolute values, or percentages (Microsoft Excel®). The anatomical level was defined as the first dysraphic vertebral body. The functional level was defined as the lowest functionally unrestricted myotome.

Results

Patient Population

Of the 48 patients undergoing fSBR between December 2010 and December 2016, one child was excluded due to neonatal demise, leaving 47 patients for analysis.

Patients without IC

Thirty-three children (70%) did not present clinical symptoms or radiographic signs suggestive of IC. Demographic details are listed in Table 1. Closure of the pia and tubularization of the neural placode was performed in 19/33 fetuses (58%). Spinal canal closure was realized by duromyofascial flaps in 24/33 fetuses (73%), by myofascial flaps in 4/33 fetuses (12%), and by separate dural and myofascial closure in 4/33 fetuses (12%). In 4/33 fetuses (12%), the use of a dura substitute was required.

Table 1. Patients' demographic and surgical characteristics

	Total, *n*	Gender		Gestational age, weeks, mean (range) at		Neural tube defect		Anatomical level	Closure of defect								
		f	m	fetal surgery	birth	MMC	MS		tubularization of pia mater	Spinal canal					Skin		
										DMF	MF	D + MF	DP	D	di	SS	RF
No IC	33	18	15	24.2 (22.9–26.1)	35.2 (25.3–37.4)	26	7	Th12–L5	19	24	4	4	4	1	23	3	7
IC	14	9	5	24.6 (22.4–25.6)	36.0 (31.3–37.4)	6	8	Th12–L5	2	9	2	2	2	1	9	3	2
Resection	6	5	1	24.4 (22.4–25.1)	35.6 (31.3–37.3)	1	5	L2–L5	0	5							
Symptoms	4	3	1	24.8 (24.6–25.1)	34.8 (31.3–36.7)	1	3	L3–L5		4			2		2		2
No symptoms	2	2	0	23.6 (22.4–24.7)	37.1 (37.0–37.3)	0	2	L2–L5		1							
No resection	8	4	4	24.8 (23.7–25.6)	36.4 (34.9–37.4)	5	3	Th12–L5	2	4	2	2			7	1	

DMF, duromyofascial flap; MF, myofascial flap; D + MF, dura separately + myofascial flap; DP, durapatch; D, dura only; di, direct; SS, skin substitute; RF, rotational flap.

Table 2. Clinical characteristics of patients with IC resection

Patients with IC resection	MRI				Motor function		Bladder function		Last follow-up, months
	mass on postnatal MRI	indication for following MRI	age at following MRI	max. cyst diameter, mm	before IC resection	after IC resection	before IC resection	after IC resection	
Symptoms									
Case A	–	Swelling along repair site	6 months	50	S1	L5, partly S1	Normal	Neuropathic	11
Case B	–	New bladder hyperactivity	8 months	52	L4, partly S1	L4, partly S1	Neuropathic	Neuropathic	3
Case C	–	New bladder hyperactivity	12 months	15	S1	L5, partly S1	Neuropathic	Neuropathic	4
Case D	–	Secretion from repair site	11 months	33	L5, partly S1	L4, partly S1	Normal	Neuropathic	8
No symptoms									
Case E	–	Annual follow-up	1 year	25	L4, partly S1	L4, partly S1	Normal	Neuropathic	12
			2 years	52					
			3 years	58					
Case F	3 mm	Annual follow-up	1 years	25	S1	L4, partly S1	Normal	Neuropathic	7
			2 years	45					

Direct skin closure was accomplished in 23/33 fetuses (70%), a random pattern transposition flap was used in 7/33 fetuses (21%), and alloplastic material was implanted in 3/33 fetuses (9%).

Patients with IC

Fourteen children (30%) presented either clinical symptoms and/or radiographic signs consistent with IC. Demographic details are listed in Table 1. Closure of the pia and tubularization of the neural placode was performed in 2/14 fetuses (14%). Spinal canal closure was realized by duromyofascial flaps in 9/14 fetuses (64%), by myofascial flaps in 2/14 fetuses (14%), and by separate dural and myofascial closure in 2/14 fetuses (14%). In 2/14 fetuses (14%), the use of a dura substitute was required.

Direct skin closure was accomplished in 9/14 fetuses (64%), a random pattern transposition flap was used in 2/14 fetuses (14%), and alloplastic material was implanted in 3/14 fetuses (21%).

Patients with IC Undergoing Resection

Six of 14 children with IC (43%) required IC resection. Four of the 6 children developed the following symptoms, and IC resection was indicated at a median age of 10 months (range 6–12 months; Table 2). One patient showed a tender swelling along the repair site, 2 patients with previously normal bladder function presented with

bladder hyperactivity, and 1 patient who had undergone surgery for a spinal cord abscess, presented with recurrent secretion from the repair site. MRI investigation demonstrated IC (Fig. 1) and prompted resection. The median cyst diameter was 42 mm (range 15–52 mm).

Two of the 6 children were asymptomatic and IC resection was indicated at a median age of 31 months (range 25–36 months; Table 2). These patients presented with significant progression of a nodular cystic mass on follow-up MRI (volume increase of 180 and 200% within 1 year). The median cyst diameter was 52 mm (range 45–58 mm).

All IC were located intradurally, with 2 patients exhibiting additional extradural lesions. After macroscopically complete resection (Fig. 2), all specimens proved to be dermoid cysts histologically.

Motor Functional Outcome after IC Resection

Two children showed a stable motor level at a median follow-up of 8 months (range 3–12 months; Table 2). Four children showed a worsening of their motor level at a median follow-up of 8 months (range 4–11 months; Table 2).

Urological Outcome after IC Resection

At the time of IC diagnosis, 4 children demonstrated normal bladder function. Two children who had normal bladder function since birth, developed neurogenic detrusor overactivity at the age of 8 and 10 months, prompting MRI investigation by which IC were diagnosed. These patients were started on anticholinergics and clean intermittent catheterization. Immediately after IC resection, 5 of the 6 patients developed urinary retention. During the follow-up, 3 patients showed neurogenic detrusor underactivity. The 2 patients preoperatively diagnosed with neurogenic bladder dysfunction continued to show detrusor overactivity (Table 2; Fig. 3). One patient kept a normal bladder function directly after IC resection, but demonstrated neurogenic detrusor overactivity 7 months postoperatively. The bladder dysfunction remained stable during the observation period, and all patients had to be treated with clean intermittent catheterization and in case of detrusor overactivity with anticholinergics. Hence, all patients with previously normal bladder function developed neurogenic bladder dysfunction as a consequence of IC formation and resection.

Recurrence

None of the operated patients suffered from recurrent IC at a median follow-up of 4 months (range 3–11 months).

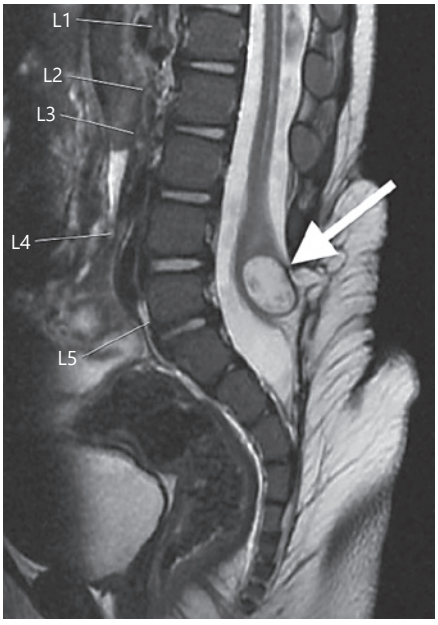
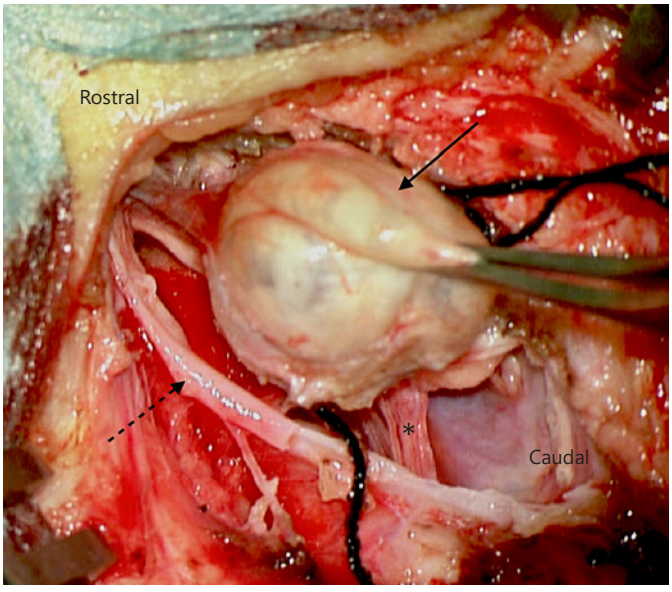


Fig. 1. MRI demonstrating a spinal inclusion cyst (arrow) in a 13-month-old child after fetal spina bifida repair.



Color version available online

Fig. 2. Intraoperative image demonstrating a spinal inclusion cyst (bold arrow: inclusion cysts [IC], interrupted arrow: opened dura, asterisk: spinal nerve roots) in a 13-month-old child.

Patients with Non-Operative IC Management

Among 47 children who underwent fSBR, 8 patients (17%) were found to have IC on surveillance MRI (Table 1). They have not (yet) undergone resection, since they were asymptomatic and did not show significant growth

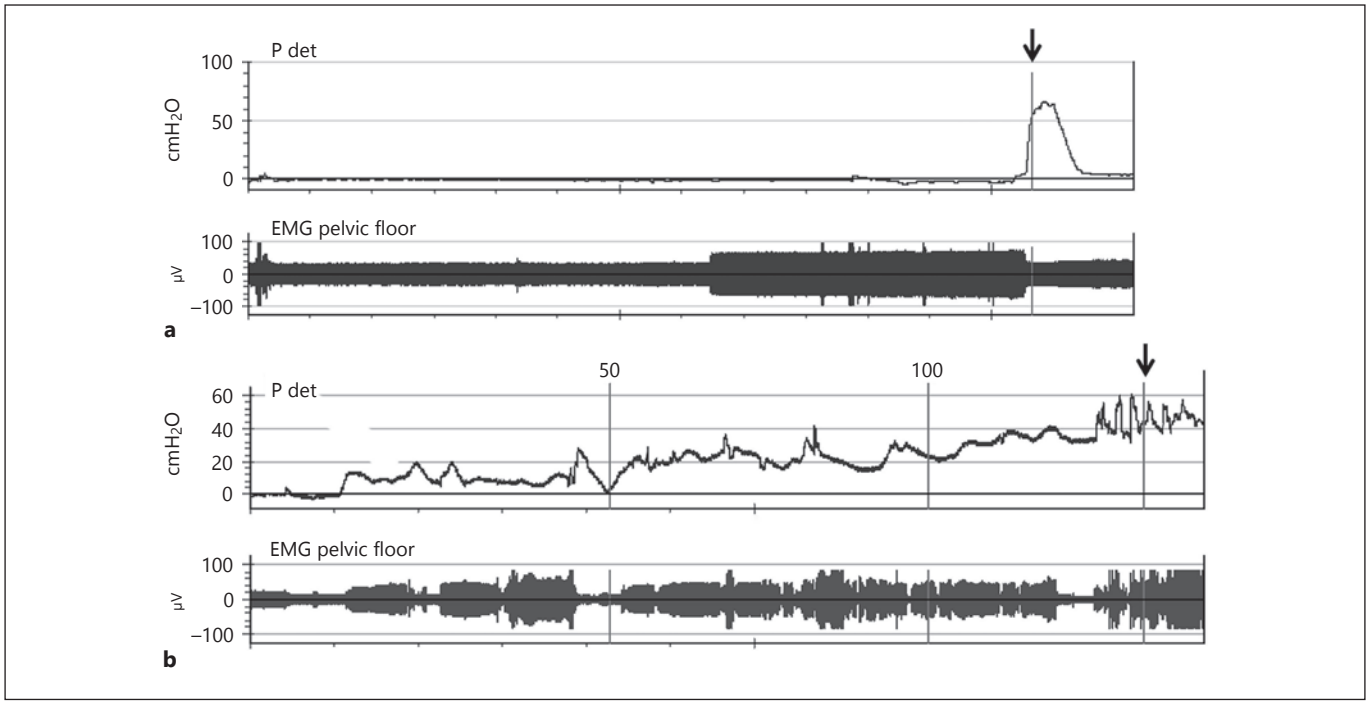


Fig. 3. Urodynamic study in a 4-month-old girl (case D) before (**a**) and 8 months after (**b**) inclusion cysts (IC) resection. **a** Normal urodynamic pattern: formal detrusor contraction after stable filling, associated with voiding (arrow). Pelvic floor EMG (electromyography) showing synergic sphincter activity. **b** Neuropathic bladder dysfunction: unstable bladder demonstrating detrusor overactivity decreased compliance and leakage of urine (arrow) at increased detrusor pressure. Pelvic floor EMG showing dyssynergic sphincter activity.

on serial MRI. The first identification of IC on MRI occurred at a median age of 12 months (range 1–24 months; Table 3).

Table 3. MRI characteristics of patients with non-operative IC management

Patients with non-operative IC management	Mass on MRI at age				
	postnatal	1 year	2 years	3 years	4 years
Case G	3 mm	10 mm	10 mm		
Case H	–	–	5 mm	8 mm	10 mm
Case I	–	–	13 mm		
Case J	–	–	3 mm		
Case K	–	18 mm			
Case L	–	9 mm			
Case M	–	5 mm			
Case N	5 mm				

Discussion

This study reveals a 30% incidence of IC following fSBR. The fact that 14 of 47 children developed IC within the first 2 years of life, and particularly that all 6 patients with IC resection suffered from significant and likely irreversible postoperative functional problems raises concern.

Incidence

The reported incidence of IC after postnatal spina bifida repair ranges from 2 to 16% [5–8], with the age at presentation between 1 and 12 years. However, these numbers depict a population of patients with tethered cord syndrome, thus the true incidence could be higher, since imaging and surgery were only performed in patients with functional deterioration. Adzick et al. [3] reported 1 case of IC (2%) 1 year after postnatal spina bifida repair and 2 cases of IC (3%) 1 year after fSBR. Mazzola et al. [9] reported IC in 6% of patients undergoing surgery for tethered cord syndrome after previous fSBR, and Danzer et al. [10] observed IC in 26% of fSBR patients; 10 cases of IC among 16 children with loss of motor or bladder function, another 4 cases of IC demonstrated on surveillance MRI in asymptomatic children.

Our results are consistent with the most recently published literature, and importantly, all reports share that IC

were diagnosed within the first 2 years of life, which highlights the importance of regular clinical and radiological follow-up.

Clinical Outcome

None of the 6 patients required IC resection due to deteriorating ambulation or gait problems. However, following IC removal, 67% of patients demonstrated motor function deficits. Deteriorating bladder function was the indication for IC resection in 2 patients. Their postoperative bladder function, however, did not improve. Even more dramatic, all patients with previously good spontaneous micturition developed neurogenic bladder dysfunction after IC resection. One patient, whose indication for surgery was a painful swelling at the repair site, was asymptomatic after IC resection.

These observations are consistent with the latest reports. Danzer et al. [10] demonstrated 100% pain relief; however, none of the patients with previous bladder dysfunction improved as a result of IC resection, and 67% of patients with previously good spontaneous micturition developed neurogenic bladder dysfunction. Similarly, Scott et al. [13] reported 4 cases of pain relief (and return of previous motor function) after IC resection; however, urinary incontinence did not improve.

We found one patient with chronic wound breakdown after treatment for a spinal cord abscess. MRI revealed that IC were resected and the further course remained uneventful. Similarly, Argenta et al. [14] reported on a patient developing chronic wound breakdown after surgical release of tethered cord. The patient required surgical exploration, whereby an intraspinal IC was found and resected, where after the wound healed without further delay.

Etiology

Two theories are discussed. Due to incomplete excision of the zona epithelioserosa during spina bifida repair, cutaneous tissue left behind becomes trapped in the repair site and later forms IC. This thesis was addressed by Nelson et al. [6], when reviewing outcomes of more than 800 MMC-patients. Of 49 children undergoing surgery for symptomatic re-tethering, 16% were found to have IC.

Even with sufficient fetal surgical experience, maximal alertness, and loupe magnification, it may be challenging to precisely delineate the borderline between zona epithelioserosa and medullovasculosa. It is even more difficult to precisely distinguish the epithelialized (i.e. "IC-genic") and the non-epithelialized parts of the zona epithelioserosa. In our cohort, tubularization of the neural placode, was performed in only 14% of patients with IC. This may suggest that tubularization of the neural placode does not impose a risk for the development of IC.

The second possible pathway is dysembryogenic in nature. There is incomplete separation between ectoderm and neuroectoderm during neurulation. Hence, cutaneous islets residing within or adjacent to spinal cord tissue will generate IC. This explanation is supported by Storrs [15], describing hamartomatous lesions (epidermoid/dermoid/lipoma) in 41% of zona epithelioserosa specimens resected during the initial repair, and in 24% of resection specimens in tethered cord surgeries. Chadduck and Roloson [16] and Ramos et al. [17] reported dermoid tumors surrounding the placode during initial postnatal spina bifida repair. The tumors showed no continuity with the skin, providing evidence that IC may form primarily within the neural tube, independent of previous surgery. In accordance with this, we found that IC were located exclusively intradurally in 4 of 6 patients undergoing resection.

Previous reports implied that the use of alloplastic material for dural or skin closure may contribute to IC formation [9, 10, 15]. We found no obvious difference regarding the use of a synthetic patch for dural closure between the groups with and without IC. Regarding skin closure, 9% of patients without and 21% with IC required a skin substitute for closure. This difference is not statistically significant ($p = 0.25$).

Timing of MRI and Surgery

Historically, in patients with postnatal repair, MRI was only performed upon symptoms of tethered cord and thus the incidence of IC is probably underestimated, compared to surveillance imaging after fSBR.

Concerning the indication for IC resection, no formal consensus has been reached to date. Some authors report that most patients showed complete resolution of symptoms following IC resection indicated by motor deficits or pain. In contrast, deteriorating bladder function did not improve after IC resection [10, 13]. Our experience is less favorable in that we did not see functional improvement but rather loss. We suggest that symptoms and/or significant growth are adequate parameters to indicate an operation. Yet, we need more data to make evidence-based recommendations.

Intraoperative Neurophysiological Monitoring

Tethered cord surgery carries the risk of iatrogenic injury to nerve roots embedded in scarred tissue. Jackson et al. [18] and Heuer et al. [19] recommended neuromonitoring during tethered cord surgery and IC resection after

fetal MMC repair. In our practice, we use an electric stimulation probe to identify neural structures. Yet we consider continuous neurophysiological monitoring as adjunct to prevent injury to neural structures.

Limitations

Because of our small cohort and short follow-up time, we cannot exclude the possibility of more patients developing future clinical or radiographic signs of IC. Furthermore, we cannot make evidence-based recommendations regarding optimal timing of surgery, nor can we stratify significant risk factors regarding the technical aspects during fSBR.

Conclusion

We have encountered a substantial incidence of IC in the context of fetal surgery for spina bifida. Since both IC per se and IC resection can lead to irreversible loss of neural function previously spared, IC development is a potentially devastating aftermath that can be considered a "third hit".

Disclosure Statement

The authors declare no conflicts of interest.

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