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ORIGINAL ARTICLE

Premiere use of Integra™ artificial skin to close an extensive fetal skin defect during open in utero repair of myelomeningocele

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Abstract
Background There are fetuses demonstrating very large myelomeningocele lesion which can not be covered with autochothonous skin.
Material and Methods We use Integra™ artifical skin for intrauterine coverage of the back lesion. A reverse latissimus dorsi flap was used postnataly to reinforce the repair site.
Conclusion Integra™ appears to be a suitable coverage for large soft tissue defects in utero. Moreover, a postnatal reverse latissimus dorsi flap appears to markedly strengthen tissue coverage over a spinal cord rescued in utero.

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Keywords Fetal surgery · In utero repair · Myelomeningocele · Spina bifida · Integra artificial skin · Latissimus dorsi flap

Introduction

In the early 1990's, a fundamentally new way of understanding the pathogenesis of myelomeningocele (MMC) was introduced. The newly developed "two-hit-hypothesis" proposed that the postnatal MMC lesion was the combined product of early gestational failure of neurulation ("first hit") and subsequent progressive destruction of the open unprotected spinal cord tissue during the remainder of gestation ("second hit") [4, 6]. This novel view lead to the assumption that early in utero intervention might stop the otherwise ongoing neural tissue destruction and so significantly reduce the neurologic deficit seen at birth.

In fact, a sizeable experimental [7, 16] as well as preliminary clinical [1, 3, 6, 18] body of evidence gathered over the past 2 decades has indicated that in utero repair of MMC may significantly improve neurologic outcome. The very best data supporting in utero repair as a new standard of care for selected fetuses with MMC was produced by the Management of Myelomeningocele Study (MOMS), a prospective randomized trial recently published in a milestone article in the New England Journal of Medicine [2].

As a direct consequence of the quoted evidence, we have opened a fetal surgery program at our center in close cooperation with The Center for Fetal Diagnosis and Treatment of the Department of Surgery of the Children's Hospital of Philadelphia. So far, nine maternal–fetal surgeries for MMC have been performed [9].

Obviously, there are numerous substantial operative challenges the fetal surgeon faces during these highly

demanding interventions. The last step of the fetal operation is skin closure over the repair site that may prove particularly difficult or even not feasible, especially when the skin defect is large and when there is marked tissue frailty as in earlier gestational fetuses. The goal of this article is to detail our initial experience using Integra™ (Integra LifeScience, Plainsboro, NJ, USA) to close an extensive skin defect during open fetal MMC repair.

Case report

Diagnostic workup and prenatal counseling

A healthy 25-year-old G1P1 female was diagnosed with a male fetus demonstrating a spina bifida in the 21st week of gestation. On ultrasound, the fetus had a large, wide open lumbosacral spina bifida with the exposed neural placode resting at the bottom of the open spinal canal (Fig. 1). Thus, the diagnosis of a lumbosacral myeloschisis with a cranial level of lumbar 4–5 was made. Moreover, the fetus exhibited the typical Chiari II malformation and a mild ventriculomegaly (10 mm). Lower extremity movements at hip, knee, ankle, and toe levels were normal bilaterally. The urinary bladder demonstrated normal cycling and the fluid filled stomach was well discernable. No other malformations were found. The preoperative fetal MRI confirmed these findings and did not reveal any other pathology.

Both mother and fetus met all other inclusion criteria for fetal surgery set forth by the MOMS-Trial and they did not fulfill any of the exclusion criteria [2]. Both parents underwent extensive multidisciplinary non-directive counseling. All known risks and potential benefits associated with maternal–fetal surgery were explicitly discussed. In addition, all problems and handicaps presumably present, when standard postnatal care would be chosen, were explained in detail. Parents were given sufficient time to decide and were also told that they could change their decision at any time. The parents opted for fetal surgery and a written informed consent was obtained.

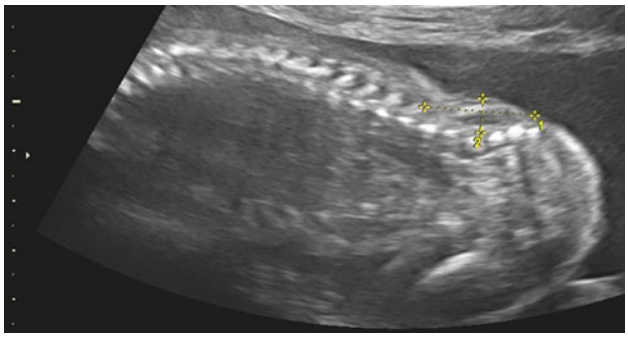

Fig. 1 Cross section through the lesion at level L5/S1. The open spine is clearly visible and so is the spinal cord tissue that rests at the bottom of the spinal canal. The absence of a cystic sac makes this lesion a classical myeloschisis

Maternal–fetal surgery

Maternal–fetal surgery was performed at 22 3/7 weeks of gestation according to the protocol used for the MOMS-Trial [2]. A generous transverse lower abdominal laparotomy was performed and the uterus was partly exteriorized. Because of an anterior wall placenta, the uterus was opened on the posterior wall. Subsequently, the fetus was positioned by gentle manipulation so that the lesion was well exposed. We found a large (2.8 × 1.8 cm) myeloschisis with the open dura mater merging circumferentially into the normal-looking surrounding skin (Fig. 2). The dura was then dissected free, the dura flaps were flipped over and sutured together over the spinal cord after the filum terminale had been severed in order to attain the obligatory untethering. Because of the very large and mainly sacral lesion, we could not prepare adequately sized paraspinal myofascial flaps, and also, it was definitely impossible to achieve primary skin closure over the defect. Therefore, we decided to implant a piece of Integra™. The product was shaped to suit the defect, placed over the defect, and sewn to the surrounding skin edges with a running suture (PDS 4.0, RB-1, Ethicon, Johnson & Johnson, Norderstedt, Germany) (Fig. 3). After returning the fetus deep into the amniotic cavity, the amniotic fluid was restored to an appropriate volume with lactated Ringers solution by continuous infusion during uterine closure. The uterus was closed using an

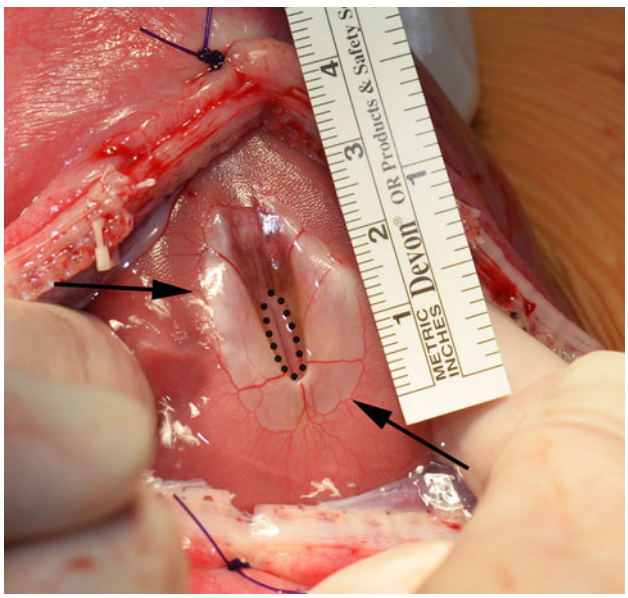

Fig. 2 Overview of the fetal lesion just prior to commencing repair. The open dura mater is shiny and merges into the intact skin (*arrows*) that surrounds the lesion. The non-neurulated spinal cord is macroscopically intact (*within dotted line*)

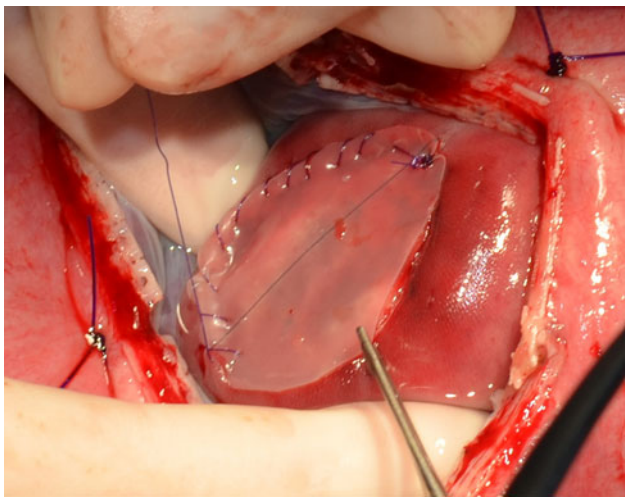

Fig. 3 A patch of Integra™ is being implanted into the skin defect and fixed with a running suture. The shiny surface is the upper layer consisting of silicon (the lower layer is dull and consists of extracellular matrix material, not visible)

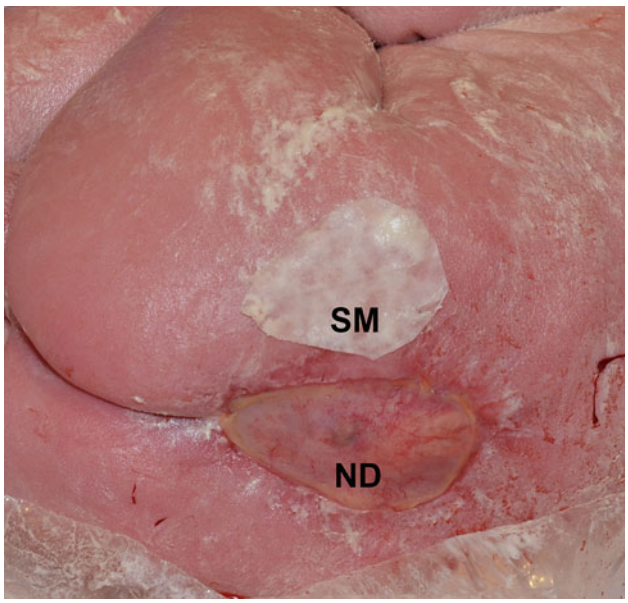

Fig. 4 This picture shows the repair site immediately after birth. The former back lesion is covered with a thin, well vascularized, but non-epithelialized connective tissue membrane (neodermis, ND5 × 4 cm). There are no signs of inflammation nor is there a CSF leak detectable. We have put the silicon membrane (SM) that was found in the left inguinal area adjacent to the repair site

inner running suture and multiple interrupted outer sutures, and the suture line was sealed with an omental flap. The maternal laparotomy was closed in layers.

Continuation of pregnancy, post-interventional fetal MRIs, and Cesarean section

At 4 and 8 weeks after the prenatal intervention, fetal MRIs were obtained demonstrating complete reversal of hindbrain herniation, a growing posterior fossa, absence of significant ventriculomegaly, an unremarkable repair site, and good leg function. The Integra™ patch could not be identified as such with a high level of confidence.

Pregnancy continued uneventfully with a mild tocolytic regimen until week 37 0/7 at which time point the fetus was electively delivered by Cesarean section. The mother had an uncomplicated postoperative course and was discharged from the hospital on postoperative day 5.

Management of the newborn baby

The baby boy (head circumference 34 cm [P: 25–50], weight 3,090 g [P: 50], length 46.5 cm [P: 3–10]) adapted normally (Apgar 7/9/9), demonstrated vigorous bilateral leg movements with clearly present extension and flexion patterns at all joint levels, and had a normally configured anus. The repair site was solidly healed with a well vascularised, non-epithelialized, and apparently watertight membrane at the former Integra™ implantation site (Fig. 4). This "neodermis", measuring 5 × 4 cm, was firmly attached to the skin and there was no leak of cerebrospinal fluid detectable. When the baby cried we could observe a slight outward bulging of the membrane. The surface of the neodermis was macroscopically clean, there was no inflammatory reaction nor were there visible traces of vernix caseosa or meconium. The upper silicone layer of the originally bilayered product was found sticking to the left inguinal area.

Because of the obviously very thin tissue coverage over the spinal cord, we decided to further strengthen the cord protection with additional tissue. Therefore, the left-sided latissimus dorsi muscle was conceived as a distally based pedicled flap, detached from the humeral base, and prepared free down to the iliac crest area, where 3 sizeable sets of perforator vessels were identified to perfuse the entire flap. The muscle was then turned over, swung over the lesion, and fixed to the adjacent tissue with single stitches (Fig. 5). The most distal part of the defect was closed primarily after undermining the surrounding soft tissue. The clinically well perfused muscle surface was covered with 0.1-mm-thick non-meshed split skin harvested from the adjacent left gluteal area.

The patient was placed in a prone position for 3 weeks and his postoperative course was uneventful with healing of the muscle flap and skin graft (Fig. 6a). During this time, the baby repeatedly had normal neurologic examinations except for a slightly diminished plantar flexion of the right foot, normal head growth (P: 10–25), and normal voiding functions. Bladder manometry was normal. A baseline MRI, performed on day 20 of life, corroborated the findings from the two post-interventional fetal MRIs and also demonstrated a robust and viable muscle flap covering the

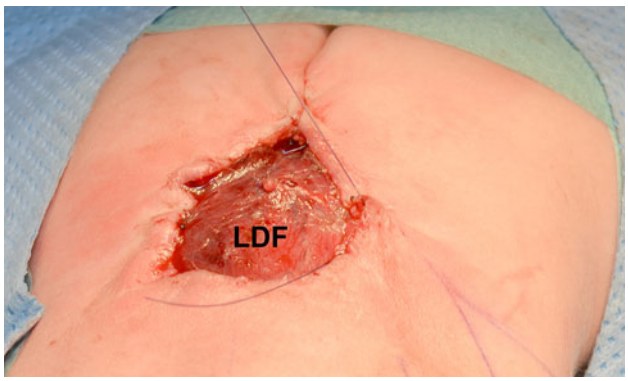

Fig. 5 The left-sided, distally pedicled and well perfused latissimus dorsi flap (LDF) was turned over and is now being sutured to the wound edges

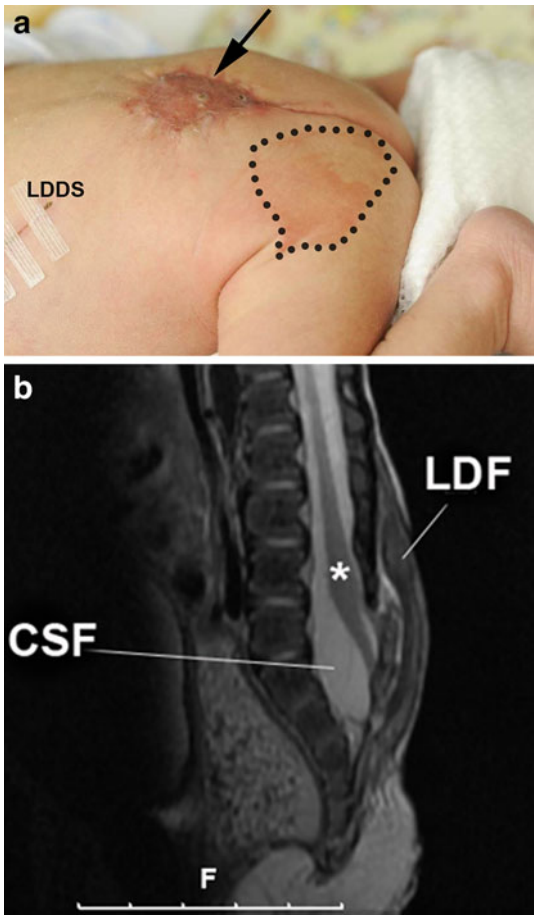

Fig. 6 **a** Perfectly healed repair site (*arrow*) 3 weeks after performing the reverse latissimus dorsi coverage and split thickness skin grafting. *LDDS* latissimus dorsi donor site, *dotted line* split skin donor site. **b** Postnatal MRI obtained 3 weeks post birth. *Asterisk* spinal cord, *CSF* cerebrospinal fluid, *LDF* latissimus dorsi muscle flap

lesion (Fig. 6b). The patient was discharged home on his second day of life. At last follow-up (3 months of age), the patient was doing well with stable neurologic exam and normal bladder manometry.

Discussion

We report the successful implantation of Integra™ during fetal surgery as primary skin coverage in the context of a very large MMC defect (deeper layers closed with autochthonous tissues). Furthermore, this is also the first report on the use of an immediate postnatal reverse latissimus dorsi flap to provide additional soft tissue coverage for a prenatally salvaged spinal cord.

Basically, we used the same simple technique for the Integra™ implantation used for postnatal application [14]. A custom tailored piece of Integra™ was circumferentially sewn to surrounding fetal skin using a running suture so as to completely cover the residual skin defect after MMC repair was completed. Before returning the fetus back to his natural amniotic fluid environment, there was a solid contact of the lower Integra™ layer, i.e., the extracellular matrix (=dermal template), with the wound bed, and the suture line appeared tight and waterproof. It is reasonable to assume that Integra™ showed a similar biological behavior as seen when used postnatally. Likely, the extracellular matrix was rapidly populated by cells migrating from the wound bed, especially fibroblasts and vascular endothelial cells. These two cell types are seen as key players orchestrating the transition from the acellular dermal template, consisting of an array of typically arranged extracellular matrix molecules, to a viable, visibly vascularised, and functionally competent connective tissue membrane, as present at birth [14, 17, 19].

When used postnatally, the dermal template is usually well vascularised and solidly integrated into the wound bed 3–4 weeks post implantation [13–15, 17]. At that time point, the upper silicon layer is peeled off and the neodermis is covered with a very thin split thickness skin graft so as to complete skin reconstruction.

In this case, Integra™ was hidden from view for about 4 months, and the silicone membrane was detached at birth. This is not surprising since the silicon layer tends to spontaneously detach after 4–6 weeks when used in the postnatal setting. We speculate that the silicon sheet was gradually disengaged during gestation as the maturing neodermis grew into an autonomous and compact structure.

Experimentally, Integra™ was successfully used in conjunction with a cellulose sheet to cover skin defects in fetal sheep [12]. Moreover, we have a favorable, long-standing and extensive clinical experience using this product in burns [17], scar revisions [17], avulsion injuries [13], and naevus surgery [14] in children. Nevertheless, the following potential problems, specific to the fetal setting, might have jeopardized success. First, the continued presence of amniotic fluid might have led to fluid collection beneath the product with failed integration of the dermal template into the wound. Second, in contrast to postnatal

application, there was no dressing over the Integra™ assuring tight contact with the wound bed with again the risk of failed integration. Finally, after the protective silicon sheet was detached, the freshly grown and, therefore, fragile connective tissue membrane might have been damaged traumatically (rubbing against and bumping into uterine wall) or biochemically (enzymes and toxic molecules increasingly present in the amniotic fluid towards the end of gestation). Even though we did not see any of these problems, it takes more cases to quantify these risk factors.

The literature does not provide formal publications on coverage alternatives when there is a big residual skin defect. Yet, Mazzola et al. mention that AlloDerm® patches (LifeCell™, Bridgewater, NJ, USA) have been used as skin substitutes during fetal surgery followed by skin flaps performed neonatally [5].

The postnatal back wound management deserves a comment. Clearly, the repair site was in need of a definitive skin coverage that could have been easily realized with a split thickness skin graft. Given the obvious tissue thinness covering the neural tissue that was almost visible through the neodermis, and the consequent vulnerability of the spinal cord, we decided to additionally shield this locus minoris resistentiae with a distally pedicled, reverse latissimus dorsi flap. This technique has been used by ourselves and others postnatally to provide adequate soft tissue coverage over very large MMC defects [20]. In addition, we reported on successfully using latissimus dorsi flaps for in utero repair of experimental MMC in fetal sheep [7, 8, 11]. And finally, we published a feasibility study in aborted human fetuses of different gestational ages showing that almost the entire spine can be reached with proximally or distally pedicled latissimus dorsi flaps [10]. There is no literature on using the latissimus dorsi flap in neonates with a history of fetal surgery. Yet, both our clinical and postnatal MRI findings (Fig. 6a, b) indicate that this maneuver markedly reinforces the vitally important spinal cord and should be considered in similar situations. There is no study looking at the functional long-term outcome after neonatal use of latissimus dorsi flaps. The only information available comes from three of our own patients with MMC who underwent latissimus dorsi flap plasties (2 × monolateral, 1 × bilateral) as neonates (on days 2, 3, and 5 of life). Their shoulder function was recently analyzed in detail at ages 6, 11, and 16 years, respectively. There was no significant functional deficit with regard to shoulder/arm function (Osinga, unpublished data).

In summary and conclusion, this appears to be the first report on the successful use of Integra™ as a skin substitute during open human fetal surgery for MMC, and it also appears to be the first report on the use of the latissimus dorsi muscle to maximally strengthen soft tissue coverage over a prenatally rescued spinal cord immediately after birth.

Conflict of interest The authors declare that they have no conflict of interest.

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