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BIOMATERIALS IN FETAL SURGERY

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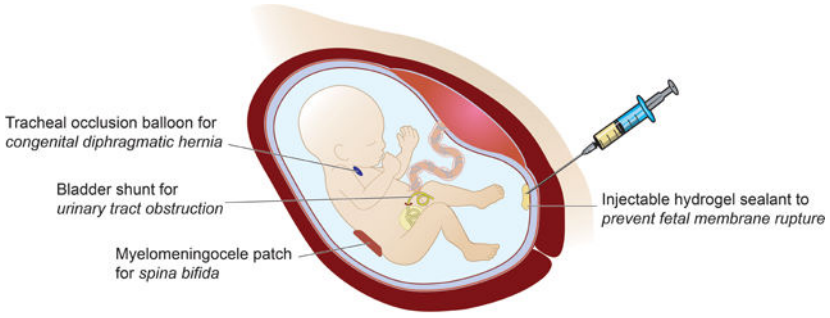
Abstract

Fetal surgery and fetal therapy involve surgical interventions on the fetus *in utero* to correct or ameliorate congenital abnormalities and give a developing fetus the best chance at a healthy life. Historical use of biomaterials in fetal surgery has been limited, and most biomaterials used in fetal surgeries today were originally developed for adult or pediatric patients. However, as the field of fetal surgery moves from open surgeries to minimally invasive procedures, many opportunities exist for innovative biomaterials engineers to create materials designed specifically for the unique challenges and opportunities of maternal-fetal surgery. Here, we review biomaterials currently used in clinical fetal surgery as well as promising biomaterials in development for eventual clinical translation. We also highlight unmet challenges in fetal surgery that could particularly benefit from novel biomaterials, including fetal membrane sealing and minimally invasive myelomeningocele defect repair. Finally, we conclude with a discussion of the underdeveloped fetal immune system and opportunities for exploitation with novel immunomodulating biomaterials.

Graphical Abstract



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Contributions

S.M.W. wrote the manuscript with input from P.B.M. and M.R.H.

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Keywords

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Introduction

Since the first successful surgery on a human fetus in the 1980s [4], fetal surgery has evolved from high-risk open surgeries, in which the uterus is opened, and the fetus partially exposed and operated on, to fetoscopic, minimally invasive procedures in which instruments or needles are inserted through small incisions in the mother's abdomen. The history, state of the art, and future potential of minimally invasive fetal surgery were expertly reviewed by Graves and colleagues [5]. While the number of fetal surgeries has increased, and the surgical techniques used in fetal surgery have advanced in the past 30 years, the materials used in these procedures have not seen such progress. For the most part, the materials and devices utilized in fetal surgeries have been modified from existing devices already in use in adults or neonates. The development of biomaterials tailored for fetal surgery represents a significant opportunity for biomaterials engineers to address an unmet clinical need. Furthermore, the immune privilege and relatively short duration of pregnancy present unique materials requirements and opportunities for fetal treatment compared to biomaterials used in adult patients.

For a patient to be a candidate for fetal surgery, the potential benefits of the surgery must outweigh the risk to the fetus and mother. Given the current limitations of fetal surgery, especially the risk of membrane rupture and subsequent preterm birth, surgical procedures have been limited to those conditions for which no intervention would mean fetal or perinatal death or loss of limb or organ function. For fetal surgery to be considered in a specific case, the fetus must be affected enough to merit intervention, but not so severely affected that the intervention would not improve chances of survival. Modalities for determining fetal health status include ultrasound, amniocentesis and other genetic diagnostics, fetal MRI, and fetal echocardiogram. Criteria to stage the severity of a condition, such as lung area to head circumference ratio measurements in congenital diaphragmatic hernia, should be established before considering performing fetal surgeries to address that condition. Additionally, ample pre-clinical evidence of an intervention's success in animal models is necessary prior to deploying new strategies on human patients; animal models of fetal surgery were recently reviewed by Kabagambe and colleagues [6]. Patient-specific inclusion and exclusion criteria vary depending on the type of surgery being performed, and a representative set of criteria first established in 1982 [1] and still utilized today [2] is shown in Box 1.

Maternal-fetal surgery also raises important ethical issues. These include establishment of clinical equipoise in clinical trials, determining "patienthood" in the context of maternal-fetal surgery, resisting the "urge to intervene," and ensuring accurate representation of surgery's risks and benefits to patients, especially in the context of potential fetal or neonatal palliative care [7–12]. Clinicians and engineers should take care that, whenever possible,

potential fetal treatments are evaluated in the context of a randomized trial with multi-specialty clinical expertise. Due to small patient populations (made smaller by the fact that mothers may choose conservative management or pregnancy termination rather than enroll in a trial), many of the most successful randomized controlled trials are conducted as multi-center or even multi-national trials. Examples of such multi-center trials include Management of Myelomeningocele Study (MOMS), which compared outcomes from fetal vs. neonatal repair of myelomeningocele (spina bifida) neural tube defects [3]; the percutaneous vesicoamniotic shunting versus conservative management for fetal lower urinary tract obstruction (PLUTO) trial, which compared *in utero* bladder shunting to conservative management for urinary tract obstructions in utero [13, 14]; and a study from the EuroFoetus consortium that compared laser ablation of placental anastomoses versus serial amnioreduction for the treatment of twin-twin transfusion syndrome (TTTS) [15].

The use of biomaterials in fetal surgery has begun to improve clinical outcomes for human patients (Figure 1), for example the use of balloons for tracheal occlusion in congenital diaphragmatic hernia (Figure 1a) [16] and bladder shunts to drain lower urinary tract obstructions *in utero* (Figure 1b) [17]. Other biomaterials solutions are being actively explored in large animal models with promising results, such as patches to prevent damage to abnormally exposed neural tissue in cases of spina bifida (myelomeningocele, Figure 1c) [18]. Yet other materials are being developed and investigated in laboratory settings, such as novel fetal membrane sealant materials (Figure 1d) [19]. Efforts to design and test materials specifically for fetal surgery will not only spur materials innovation in an underexplored area of medicine but also provide the best chance at a healthy life for fetuses and infants with otherwise grim prognoses.

Risk in fetal surgery

Risks associated with fetal surgery can be significantly reduced by decreasing the invasiveness of the procedure [20]. Recent trends in fetal surgery have transitioned away from open fetal surgery, in which the fetus is delivered in a partial Cesarean section (without disruption of placental blood supply), an intervention is performed, and the fetus is returned to the uterus for the duration of pregnancy [3]. In Fetoscopic surgery (Fetendo), small ports are placed in the amniotic space, an endoscope projects the image on a screen, and the surgeon manipulates small diameter instruments under endoscopic guidance to accomplish the surgery. Most Fetendo procedures are done percutaneously, but some require maternal laparotomy. Finally, in image guided fetal surgery, small instruments or needles deliver therapy or perform minor interventions under ultrasound guidance. Such minimally invasive interventions are often termed fetal therapy, and include fetal blood or stem cell transfusion [21], injection or aspiration of amniotic fluid [15], and some laser ablation procedures [22]. Instruments and devices used in fetal surgery and fetal therapy were expertly reviewed by Klaritsch and colleagues [23]. Most fetal procedures are performed in the first or second trimester of pregnancy, and many before the limit of viability (about 25 of a full 40 weeks of gestation) [3]. In its current form, fetal surgery still presents a significant risk to the fetus; thus, it is only performed on those fetuses at-risk for fetal or neonatal demise or loss of limb or organ function, but healthy enough that they will likely benefit from intervention. Major risks are discussed below.

Maternal morbidity in fetal surgery—Maternal morbidity is generally low in cases of fetal surgery and the underlying conditions that require fetal surgery. No maternal deaths following open fetal surgery have been reported [7, 24], but potential serious maternal sequalae of fetal surgery include placental abruption, premature rupture of membranes, premature birth, chorioamnionitis (infection of the membranes), loss of ability to carry future pregnancies, and sepsis [5]. Following open fetal surgery, delivery of the fetus in any future pregnancy must be via Caesarian section [25].

Fetal membrane rupture and preterm birth—In any fetal surgery, as well in fetal therapies and some diagnostic procedures like amniocentesis [26], the fetal membranes (amniotic sac) must be breached. The fetal membranes (FM) are the amnion and chorion, two closely associated membrane tissues that line the uterus and enclose the fetus and amniotic fluid during gestation (Figure 1d). They are largely avascular and do not heal after rupture or surgical cut or puncture [27–30], though recent evidence suggests collagen remodeling may contribute to a small degree of re-sealing [31]. This breaching of the FM is what makes fetal surgery so risky, as it can lead to premature preterm rupture of membranes (PPROM) and preterm birth and its associated sequelae [32, 33]. Today, most fetal surgeries are performed via a minimally invasive approach; nonetheless iatrogenic (surgically caused) PPROM (iPPROM) occurs in about 30% of fetoscopic fetal surgery cases, but this rate varies from 11–50% depending on the intervention or practitioner [20, 34, 35]. iPPROM during the intervention is rare; iPPROM usually happens in the days or weeks following surgery, up to the 37th week, after which time the pregnancy is considered term [20]. Most fetal surgeries are performed during the second trimester, making the risk of iPPROM particularly high as fetuses are unable to survive outside the uterus prior to the limit of viability (25 weeks) [3], and delivery before 32 weeks' gestation carries significant fetal and neonatal risk including perinatal death [36]. iPPROM has accordingly been deemed the "Achilles heel" of fetal surgery; several materials strategies for reducing iPPROM have been investigated (detailed in Membrane Sealing section, below), but no viable solution has been widely adopted. A solution to reduce iPPROM incidence would drastically decrease the overall risk of all fetal surgeries and make fetal surgery a viable option for more patients [20, 35].

Materials and devices in fetal surgery

Materials solutions for preventing fetal membrane rupture—To access the fetus, fetal surgeons necessarily must puncture the fetal membranes, and this puncture site can later rupture, leading to preterm birth. Over the past few decades, rates of neonatal survival and survival without impairment following preterm birth have remained steady, and the limit of viability relatively unchanged, indicating that the limits of post-natal intervention may have been reached [36]. For fetuses that undergo fetal surgery, there is still an unmet clinical need to keep the fetuses in the uterus until at least 37 of 40 weeks' gestation and to reduce the instances of membrane rupture and preterm birth.

Some attempted strategies for fetal membrane repair following fetal surgery (see Table 1) include mixtures of maternal platelets and fibrin cryoprecipitate with and without dry collagen/gelatin plugs ("amniopatch") [26, 37–39], synthetic polymer sealants [40, 41], laser

welding [42], scaffold-type plugs manufactured directly from decellularized amnion [28, 43–45], and tissue engineering approaches [46]. These have had limited success, and no clear pathway to a clinically viable solution has emerged after more than a decade of research. These strategies rely on depositing a material at or near the defect site after the membranes have been punctured surgically. However, recent research on benchtop models of the fetal membranes suggests that applying an adhesive sealant material to the space between the fetal membranes and the uterus prior to surgical membrane puncture can help stabilize membranes during surgery, decrease the size of surgical membrane defects, maintain a watertight seal of the membranes during and after surgery, and decrease the probability of catastrophic membrane rupture [5, 47, 48]. Future development of adhesives for fetal membrane sealing could potentially use a seal-then-puncture membranes strategy ("presealing") with great success. We contend that an ideal material solution for membrane sealing may have some of the following properties: have similar mechanical properties to the fetal membranes, be fluid impenetrable, be nonimmunogenic and not cause an adverse tissue response, maintain adhesive and/or mechanical properties for an appropriate timescale to extend pregnancy (e.g., 4 weeks or up to 24 weeks), stabilize the membranes during and after surgery, be resistant to biofouling, or encourage cellular regrowth when applicable.

Some sealants and adhesives initially designed to seal tissues elsewhere in the body have been studied in benchtop, animal, or clinical models of fetal surgery [19, 49]; many such materials are summarized in Table 1, along with other materials designed specifically for fetal membrane sealing. Thus far, no material has become widely accepted as a clinical solution for fetal membrane sealing, and there exists an opportunity for biomaterials engineers to design or identify a material capable of strong, robust adhesion in the wet and biologically sensitive amniotic space.

Patches in Fetal Surgery

Myelomeningocele: One of the biggest success stories for fetal surgery is in the treatment of severe spina bifida, or myelomeningocele (MMC). Spina bifida affects about 3.5 per 10,000 live births in the US [65], and 25–40% of MMC-affected fetuses are aborted [66, 67]. Briefly, in this condition, the skin and vertebrae do not fully form around the lower portions of the spinal cord. Children with myelomeningocele often have limited lower limb function, develop Arnold-Chiari II malformations (hindbrain herniation), and accumulate excess cerebrospinal fluid in their brains (hydrocephalus), which often requires repeated shunting to drain the fluid throughout the patient's lifetime [3]. The development and progression of MMC follows the two-hit hypothesis where the first "hit" is the failure of the neural tube to become fully enclosed and the second "hit" is the damage to spinal tissue that occurs during gestation due to degradation by enzymes in the amniotic fluid [68, 69]. Fetuses with myelomeningocele can sometimes move their lower limbs during early gestation, but they are often born with total or partial loss of lower limb function because enzymes in the amniotic fluid degrade the spinal cord tissue [70]. It was hypothesized that repairing the defect *in utero* would protect it from such degradation. A large, multi-site clinical trial, the Management of Myelomeningocele Study (MOMS), demonstrated the benefits of open fetal surgery for myelomeningocele repair compared to traditional postnatal repair: increased use of lower limbs and decreased need for cerebrospinal fluid (CSF) shunting due to

hydrocephalus. Risks of the repair surgery included membrane rupture leading to preterm birth and its associated complications [3]. In the MOMS trial, most cases were performed via an open surgical access technique, and the fetus's skin surrounding the spinal cord defect was stretched to cover the exposed neural tissue and sutured in place. This trial, as well as the preceding animal trials and human case studies, was excellently reviewed by Adzick [68] and the state of the field of *in utero* repair of MMC defects in the post-MOMS era was reviewed by Moldenhauer and Adizick [71].

Researchers have also investigated endoscopic and other minimally invasive approaches to tissue closure of MMC defects [72, 73]; tissue engineering approaches towards minimally invasive MMC repair were reviewed by Watanabe, et al. [18]. Recent animal data suggest the potential for the use of materials to aid in closure of MMC defects and to isolate exposed neural tissue from AF enzymes and from surrounding tissues to prevent spinal cord tethering and its long-term sequelae [18, 74–82]. Table 2 describes some of this preliminary work. Materials utilized as scaffolds and/or defect coverings for *in utero* MMC defect repair in animal models include collagen- or gelatin-based scaffolds, small intestinal submucosa, and polymeric materials including silicone, high density poly ethylene, and polypropylene [18]. Covering MMC defects with a biomaterial could drastically reduce the FM defect size necessary to perform MMC closures compared to open surgery. In one example of biomaterials use for MMC defect coverage, Watanabe and colleagues used an ovine model of *in utero* myelomeningocele [83]. Fetal lambs with surgically-created MMC defects were treated with gelatin or gelatin-collagen sponges laced with bFGF (basic fibroblast growth factor) secured around the defect site with Dermabond cyanoacrylate adhesive with or without a gelatin sheet atop the sponge. Though all sheets detached from the defect site, sponges remained, and compared with sham-operated control animals, treated animals had less hindbrain herniation and more neural tube coverage. Animals treated with bFGF-laced sponges had more granulation and epithelial tissue covering the neural tube compared to non-bFGF controls. This work suggests the potential for eventual clinical translation, though more studies are required to assess the toxicity of the materials used, perfect minimally invasive surgical technique, improve or maintain a water-tight seal, and investigate the potential for spinal cord tethering at the defect site.

Gastroschisis and omphalocele: Gastroschisis and omphalocele are abdominal wall defect conditions that are promising targets for fetal surgery. In gastroschisis, muscles of the fetal abdomen do not fully close around the internal organs, and the abdominal organs are exposed to the amniotic fluid [89]. Omphalocele is a similar condition, except that the organs are surrounded by a thin sac and not exposed directly to amniotic fluid. These conditions are diagnosed and staged *in utero* using ultrasound imaging, with more severe cases presenting with a larger defect and more organs developing outside the abdominal cavity. Most patients have good outcomes following post-natal intervention. However, in 10–20% of fetal gastroschisis patients, prolapsed organs experience long-term damage. Experiments in fetal sheep demonstrate that intestinal damage at birth is likely due to restricted blood flow and enzymatic degradation of the tissues by the amniotic fluid [90–92]. Gastroschisis cases with severe intestinal evisceration are also at risk for oligohydramnios (insufficient amniotic fluid) [89]. Animal models of gastroschisis have been established in

fetal chickens [93], rats [94], rabbits [95], and sheep [84, 90, 96]. Biomaterial patches developed for myelomeningocele may also be adapted for use treating gastroschisis or omphalocele. However, minimally invasive large animal models must first be developed to confirm the efficacy and improve the safety of procedures to deploy biomaterials tissue patches to cover gastroschisis or omphalocele defects in utero before they are attempted in human patients [97].

Materials considerations for tissue patch materials: Several considerations must be made in the development of biomaterials for direct application to internal fetal tissues, such as in the repair of myelomeningocele or gastroschisis defects or, potentially, sealing of FM defects. Materials should be deliverable via a minimally invasive surgical approach, for example a liquid adhesive that cures *in situ* or a patch that can be rolled up to fit into a 4 mm trocar. As these materials will be in direct contact with internal fetal organs, cytocompatibility is an extremely important consideration. Materials should be able to accommodate the fetus's growth throughout pregnancy and should isolate the exposed tissue from the surrounding amniotic fluid in a fluid-impenetrable manner. Attention should be paid to the post-natal and long-term role of the materials implanted in *utero*, and decisions about whether to design removable, degradable, or permanent materials should be application- and tissue-specific. Tatu and Lin [98] present a set of materials characterization experiments that should be considered when developing new fetal patch materials or choosing existing materials to use for these applications.

Occlusion and ablation in fetal surgery and fetal therapy

Congenital diaphragmatic hernia: Congenital diaphragmatic hernia (CDH) occurs in about 1 in 3000 live births when the diaphragm fails to form properly during development, allowing the liver, intestines, stomach, and/or other abdominal organs to invade the lung cavity. Thus, development of one or both lungs is restricted. Most infants with severe CDH defects undergo corrective surgery after birth, but in the most severe cases, prenatal treatment is considered to increase the lung volume of affected neonates at birth. Fetal lung area to head circumference ratio (LHR) is used to stage the severity of CDH, with severely affected fetuses having lower LHRs [99]. Saxena expertly reviewed the materials used for post-natal repair of large congenital diaphragmatic hernia defects [100]; none of the materials used were developed specifically for CDH repair, a trend also seen in fetal surgery and in the medical device industry in general. Jeanty, et al., reviewed non-surgical strategies with promise to address CDH *in utero*, including stem cell and pharmacologic methods [101], and Eastwood reviewed strategies that have been pursued in *in utero* animal models for reducing pulmonary hypoplasia resulting from CDH [102]. Over the years, several different types of biomaterials have been investigated for use addressing CDH *in utero* (Figure 2) including polymer fabrics [103], balloons [104], metal clips [99], hydrogels [105], and tissue engineered materials [106]. The first successful in utero CDH repair was reported in 1990 [103]; a Gore-Tex (PTFE fabric) patch was used to repair the diaphragm and another to cover the abdomen (Figure 2a). However, *in utero* repair of fetal CDH defects did not prove superior to the standard of care, post-natal surgery and monitoring [103, 107].

Eventually, *in utero* hernia repair was replaced with *in utero* tracheal occlusion. Occluding the trachea allows fluid to build up in the lungs, and the lungs expand, pushing the abdominal organs out of lung cavity. Initially, open surgery was performed to clamp Silastic-coated titanium clips around the trachea to occlude it (Figure 2b). This was replaced by the less invasive Fetendo approach, in which a maternal laparotomy is performed to expose the uterus [99, 108, 109]. Then, endoscopic tools were used to place titanium clips around the trachea. In 2005, Deprest and colleagues published the first successful FETO balloon trial, in which an inter-tracheal silicone balloon is deployed laparoscopically and inflated to approximately 2 cm long and 0.5 mm in diameter to occlude the trachea (Figure 2c), eliminating the need for a maternal laparotomy [16, 104]. The timing and removal of tracheal occlusions is an ongoing area of research; titanium clips are removed via a neck incision at birth via an EXIT procedure, whereas balloons can be punctured transcutaneously *in utero* or punctured and removed at birth (vaginal or EXIT). Recently, *in situ* gelating hydrogels have been pursued as an alternative to balloon occlusion. Muensterer and colleagues tested fibrin glue (Tisseel), porcine gelatin, bovine collagen, cyanoacrylate, perfluorocarbon gel, and recombinant thrombin for their abilities to plug tracheal lumens *ex vivo* and found that fibrin glue performed best [110]. Fibrin glue was further studied in a fetal rabbit model of tracheal occlusion and increased lung mass (beneficial) and airway resistance (detrimental) [110]. Similarly, in another study of fibrin glue on a fetal rabbit tracheal occlusion model, lung performance measures were not improved with tracheal occlusion [105]. Nevertheless, given the minimally invasive potential of this intervention, opportunities exist for further investigation and development of hydrogel sealants for intrauterine tracheal occlusion. Recent animal data suggest that the use of a hydrogel sealant to secure the balloon in the trachea and prevent balloon dislodgement [111] could be a promising strategy. Additional strategies that incorporate biomaterials are currently under development in animal and preclinical studies. In one example, researchers are looking to repair congenital diaphragmatic hernias postnatally with autologous tendon tissue seeded with circulating cells from the amniotic fluid [106].

Monochorionic twin conditions: In twin pregnancies, several circulation-related abnormalities sometimes indicate the use of fetal surgery. In a monochorionic twin pregnancy (about 70% of monozygotic, or identical, twin pregnancies), the fetuses share a placenta, but each has their own amniotic sac [112]. Vessels of the shared placenta sometimes anastomose abnormally, leading to twin-twin transfusion syndrome (TTTS) in 8–10% of monochorionic pregnancies [112]. Blood from one twin (donor) crosses into the other twin (recipient). In TTTS, one twin's heart pumps blood to both twins and causes delayed organ development in the donor twin and polyhydramnios and fetal hydrops (accumulation of excess fluid in fetal organs) in the recipient twin. Untreated, 70–80% of TTTS twins will die, and survivors may have severe organ damage [113]. The standard of care for TTTS is radiofrequency ablation of the vessels connecting the two twins. A 2004 multinational randomized controlled trial of 142 pregnant women with TTTS demonstrated that this method is more effective than serial amnioreduction of the polyhydramniotic sac [15]. Twins treated with laser coagulation (via a 3.3-mm cannula and a neodymium:yttrium–aluminum–garnet or diode laser under fetoscopic guidance) had significantly higher survival

rates and lower rates of neurologic complications. However, survival of at least 1 twin to 6 months was still only 76% in the treatment group.

In Twin Reversed Arterial Perfusion (TRAP), which affects around 3% of monochorionic twin pregnancies, one twin is structurally normal, but, due to aberrant blood vessel formation in the placenta, the other twin lacks a heart and head. Untreated, 50% of normal "pump" twins, whose heart pumps blood both to themselves as well as to their acardiac twin, die *in utero* or as neonates [114]. To treat TRAP, a 1 mm diameter needle is inserted through the maternal abdomen and into the abdomen of the acardiac twin. Radiofrequency ablation is performed through needle to heat and coagulate the vessels of the acardiac twin. This serves to stop blood flow between the twins without exposing the pump twin to the potentially harmful byproducts of the dying acardiac twin. Initial reports suggest a pump twin survival rate of around 90% [115].

Selective intrauterine growth restriction (SIUGR) is another twin abnormality in which unequal sharing of placental blood between monochorionic twins can result in an extreme difference in weight between the twins. In the most severe cases, one twin is drastically underdeveloped and poses a risk to the healthy twin because intrauterine death of the smaller twin could lead to neurological impairment of the healthy twin. In these cases, selective termination of the underdeveloped twin in a way that does not damage the healthy twin is considered [116]. When termination of the non-thriving twin is indicated and desired, similar care is needed to prevent harm to the healthy twin. Radiofrequency ablation is also used in this case, as is bipolar cord coagulation. Bipolar cord coagulation is more invasive (>3mm FM incision) and involves using ultrasound guidance to clamp the umbilical cord of the unhealthy twin and ablate it with radiofrequecy [117, 118].

Shunting in fetal surgery

Fetal Urinary Tract Obstruction: Lower urinary tract obstruction (LUTO) occurs in approximately 1–5 of 10,000 live births when the lower urinary tract fails to develop properly, and urine swells the fetal bladder. This can lead to fluid accumulation in the kidneys or other parts of the renal system (eg. hydronephrosis), renal failure, and oligohydramnios, and is associated with high rates of premature birth and/or perinatal death due to pulmonary hypoplasia (underdeveloped lungs). LUTO affects lung development because amniotic fluid is largely composed of fetal urine; when urinary outflow is obstructed, insufficient amniotic fluid hinders lung maturation. Postnatal repair to address urinary blockage remains the standard of care for this condition, but since severely affected infants often die of pulmonary hypoplasia soon after birth, fetal surgery to place a shunt to allow fluid to flow from the bladder to amniotic fluid during gestation (vesicoamniotic shunting) is an active area of research [119]. Current state of the art for fetal interventions for urinary tract obstructions were recently reviewed by Brock and Clayton [17]. After many case studies in human patients suggested that shunting may improve perinatal outcomes in fetuses with a poor outlook [120–122], a randomized controlled trial was conducted to study LUTO shunting in male fetuses, the percutaneous vesicoamniotic shunting versus conservative management for fetal lower urinary tract obstruction (PLUTO) trial [123, 124]. Though the PLUTO trial was terminated early due to low recruitment, the infants treated

with *in utero* shunting had lower rates of perinatal lung failure-related death. However, shunt treatment did not appear to have a drastic benefit on renal function; two of seven treated and zero of three untreated infants alive at 2 years had normal renal function, respectively. Issues including membrane rupture, shunt dislodging, and shunt blockage were cited as contributing to fetal or infant demise in the treatment group. Further work to develop shunts specifically for fetal bladder shunting is needed.

Unfortunately, little attention has been paid to the materials of the shunts themselves, in urinary tract obstruction, as well as in shunting to address fetal hydrocephalus and drain fetal lungs (see below). In fact, the identity and physicochemical properties of materials used for shunting are often not mentioned in the medical literature. In a report of all 73 fetal obstructive uropathy cases reported to International Fetal Surgery Registry between 1982 and 1985, for example, shunt architecture and materials were not reported [120]. In the PLUTO prenatal urinary tract obstruction clinical trial, a pigtail catheter was inserted with a King's College/Rocket introducer (n = 5) or a Harrison shunting set (n = 10). Double pigtail shunts are commonly used in fetal surgery as they are designed to stay in place and are unlikely to interfere with fetal development. However, a recent analysis revealed that half of shunts used to correct fetal urinary tract obstructions become dislodged [125]. And while shunts have multiple holes on each side, shunt failure due to clogging is common [120, 126, 127]. Future research should focus on the development of shunts with an internal antibiofouling surface coating to reduce biomolecule fouling and clogging of the shunt and valves, and alternative shunt architectures, such as the double basket catheter [128], to ensure the shunt stays in place for the duration of pregnancy.

More than half of fetal lower urinary tract obstructions are caused by posterior urethral valves (PUV) that occlude or block urine flow; this occurs in 1 of 8000 live births [129]. To repair urine flow and reduce fluid buildup in kidneys, some researchers have begun to use fetal cystoscopy and laser ablation to remove the aberrant valves [130]. In a series of 40 cases of diagnostic fetal cystoscopy to enable visualization of PUV formation, 23 fetuses received laser ablation to correct PUV, 14 fetuses survived to birth, and 12 survived with intact renal function. However, in addition to the risks associated with all fetal surgeries (maternal morbidity, preterm birth, spontaneous membrane rupture, etc.), laser fulguration was also associated with the development of urological fistulas (4 fetuses). Fistulae development was found to be associated ($P < 0.01$) with the materials and instruments used in the procedure, including catheter sheath shape and laser type, power, and energy [131]. Other opportunities for valve disruption for this indication include micro scissors, balloon disruption, or guidewires [131]. At least one case of successful in utero urethral stenting with a 0.9mm stent has been reported in fetus with fetal cystoscopy-confirmed urethral stenosis [132]; the stent material was not reported. In a retrospective analysis comparing fetal cystoscopy and vesicoamniotic shunting in the treatment of severe LUTO cases, Ruano and colleagues found that while both therapies increase the 6-month survival rate, only fetal cystoscopy improves renal function in PUV patients [133]. A randomized controlled trial to compare the efficacy of fetal cystoscopy and vesicoamniotic shunting is planned (trial ID: NCT01552824).

Fetal pleural and pericardial fluid: Similar double-pigtail shunts are also sometimes used *in utero* to drain fluid from the lungs and chest cavity into the amniotic space. Pleural effusion (PE) and macrocystic congenital cystic adenomatoid malformation (CCAM) are rare conditions in which fluid builds up in the pleural sac surrounding the lungs and in cystic lung tissue, respectively [134]. Untreated, severe fetal pleural effusion can have a mortality rate between 57–100% [135]. In a retrospective of 48 cases of fetal hydrothorax (PE of lymphatic fluid) in the Netherlands from 2001–16, overall fetal survival through the neonatal period following *in utero* thoracoamniotic shunting was 75% [136]. A retrospective study from Children's Hospital of Philadelphia (1998–2001) found postnatal survival of treated fetuses to be 67% (6 of 9 fetuses) for PE and 70% (7 of 10 fetuses) for CCAM [134]. These survival rates and rates of adequate lung function following fetal thoracoamniotic shunt placement are similar to those first reported in 1988 – 75% survival of 8 treated fetuses [135]. Many fetuses with fluid accumulation in the chest will not need fetal surgery, but the procedure is considered when the fetus develops severe fetal hydrops and/or the fluid accumulation constricts surrounding organs.

Fetal Hydrocephalus: Severe cerebrospinal fluid (CSF) buildup in the ventricles of the fetal brain (ventriculomegaly) can delay the development of other brain structures and often requires post-natal placement of a ventricoperitoneal shunt to drain excess CSF to the abodmen. These shunts are prone to infection and clogging, and serial shunt replacement throughout the child's lifetime is often required. Some cases of fetal vesicoamniotic shunting (between brain ventricles and AF) have been reported in human patients [120, 137, 138], though overall prognoses remain grim. One factor that contributes to poor outcomes in these fetuses is that most cases of hydrocephalus are accompanied by co-morbidities including neural tube defects, oligo- or polyhydramnios, and other congenital abnormalities [138]. A 2014 report of 222 cases in Poland of fetal hydrocephalus repair conducted between 1992–2012 used Orbis-Sigma and Accu-Flow valves and Cook's shunts to drain fluid from the ventricles into the amniotic sac. In this study, 44% of neonates were preterm, and only 12.5% had normal mental development at age 3 [139]. The study demonstrated that fetal shunting decreased ventricular size, but as this was not a randomized trial, it cannot be fully established that this treatment is better than the standard of care. Other case studies show similarly inconclusive results [126], and a retrospective case study suggests that fetal shunting results in higher rates of severe neurological impairment [140]. A voluntary moratorium against *in utero* shunting for fetal hydrocephalus has since been imposed until more information about the natural progression of fetal hydrocephalus could be established. In many of these early studies, patient selection was poor as it was difficult to identify which fetuses may benefit most from intervention, however improved fetal diagnostic methods may allow for advances fetal surgery for hydrocephalus in the future [140].

Immune tolerance and exploitation in fetal surgery and fetal therapy

Biomaterial interaction with the innate and adaptive immune systems has long been an area of research in adult patients, but less is known about the response of the fetal immune system to implanted biomaterials. The fetal immune system develops throughout gestation and continues to develop after birth; preterm infants are likely to be born with more immature immune systems, making them especially susceptible to bacterial or viral

infections [141]. A certain degree of fetal immune tolerance or immaturity is necessary to accommodate the presence of maternal alloantigens in the fetal circulation [141, 142]. However, recent evidence in mouse models suggests that fetal interventions, including fetal surgery, increase trafficking of maternal T cells to the uterus and increase maternal T cell recognition of the fetus. This trafficking could contribute to adverse outcomes like preterm birth and immune-mediated fetal demise [143, 144]. Nonetheless, the fetus's lack of a complete immune system could present a unique opportunity for biomaterials development. For example, the complement activation system is incomplete; circulating complement factors in newborns are 10–80% lower than in adults [141]. To our knowledge no study has set out to specifically address questions of long-term biomaterial interactions in the fetus. However, in studies in which materials were implanted in human or animal fetuses, little to no evidence of negative immune response (inflammation, fibrous capsule formation, foreign body response, etc.) was detected, though analysis of tissue-material interactions are underreported in the clinical fetal surgery literature [3, 13, 59, 83]. Though further investigation is needed, it seems that some immune responses elicited by implanted biomaterials are less pronounced in fetuses, possibly creating a more permissive environment for biomaterials in the fetal patient.

Researchers have begun to take advantage of the immature fetal immune system to develop stem cell treatments for alpha thassalemia major (ATM, Hemoglobin Bart's) and other inherited genetic conditions that are incompatible with life and detectable *in utero* [21, 145–147]. Fetal stem cell and genetic therapies, and initial animal and clinical data thereof, were reviewed by Witt and colleagues [148]. Without intrauterine treatment, fetuses with ATM are severely anemic and will die *in utero* or during the neonatal period or, rarely, survive with major neurological impairments. ATM also presents with significant maternal morbidities including pre-eclampsia and hypertension. Intrauterine blood transfusions to reduce fetal anemia have led to improved outcomes in severely affected patients [149, 150]; transfused fetuses who survive to infancy generally have a good outlook but are reliant on lifelong blood transfusions, medications, and/or bone marrow stem cell transplantations from matched donors [151]. An emerging strategy to combat ATM (and other inherited genetic diseases incompatible with life) is *in utero* hematopoietic cell transplantation (IUHCTx). By introducing donor stem cells before immune maturity, donor specific tolerance could be induced to improve outcomes in affected fetuses [145]. However, only limited cases have been reported in human patients, and maternal rejection of donor cells is an issue [145, 152]. One promising area of investigation is the use of maternal cells as donor cells in fetal transplantation because fetal cells are already de-sensitized to the antigens of the mother [143, 153]. The first news report of a fetus with ATM surviving to birth after serial *in utero* blood transfusions and a bone marrow stem cell transplant from maternal cells was released in May 2018 from the UCSF Fetal Treatment Center [154]; the clinical trial, from which this is the first reported case, is ongoing (ClinicalTrials.gov ID NCT02986698) [152]. Additionally, MacKenzie and colleagues published a consensus statement about the future of fetal stem cell transplantation and gene therapy [155]. Beyond ATM, other candidate conditions include sickle cell anemia and osteogenesis imperfecta. Future work in IUHCTx could utilize novel materials for delivery of stem cells or other therapies to the fetus as cell engraftment remains low.

Early fetal surgeons observed that fetuses exhibit gestational age-dependent scarless healing following fetal surgery [156]. The mechanism underlying this scarless healing has been an active area of investigation [157] and piqued interest in the potential of fetal surgery to improve infant outcomes relative to post-natal (scar-inducing) intervention. This regenerative-type healing could also be used to the advantage of engineers designing biomaterials for the fetal milieu.

Conclusion

Fetal surgery is a growing and promising field of medicine that has the potential to drastically improve or save lives of children with debilitating or terminal diagnoses. In this review, we have presented the progress of several biomaterials solutions for fetal surgery and have suggested potential avenues for further exploration. As the field continues to transition from open surgeries to minimally invasive procedures, biomaterials are poised to become more widely used; for example, in the prenatal repair of myelomeningocele defects, it could be far easier to insert a biomaterial patch through a cannula than to do a full surgical repair of MMC defect *in utero*. Similarly, successful *in utero* gastroschisis repair may also rely on the development of an appropriate biomaterial patch. Perhaps biomaterials can have the greatest impact on fetal surgery and fetal therapy through the development of adhesives to prevent fetal membrane rupture following fetal surgery. The risk of iatrogenic membrane rupture, the “Achilles heel” of fetal surgery, is still the riskiest part of most fetal surgeries; a robust method to prevent membrane rupture (and thus subsequent preterm birth) would make fetal surgery accessible to more families by decreasing the overall risk of the procedure, tipping the balance on the risk-benefit analysis. Fetal blood transplantation and stem cell therapy remain an ongoing area of clinical and basic science research; in the future, biomaterials strategies may be useful to improve engraftment or delivery of these cells. As prenatal diagnostic technologies improve, clinicians will be better able to identify patients well-suited for fetal surgery; this trend has already started and demand for fetal surgery centers at major pediatric hospitals is growing. Today, over 30 hospitals have fetal therapy programs registered with NAFTANet (North American Fetal Therapy Network), and other fetal treatment centers exist internationally outside the NAFTANet system. As recently as the 1980s, fetal surgery was accessible to only 10s of patients a year; today it is the standard of care for thousands of patients per year in the United States. Moving forward, targeted biomaterial development will enable fetal surgery to help even more families deliver healthy, thriving children.

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Glossary

Clinical equipoise

The assumption that it is unknown which of two or more treatment options is better. In the context of clinical trials, it is ethical to establish clinical equipoise between treatment groups.

EXIT procedure
Ex Utero Intrapartum Treatment, a type of Caesarian section in which the baby is kept attached to the umbilical cord to receive oxygenated blood from the placenta until breathing or breathing support can be established. Used in cases where fetal airway obstruction is known or suspected.

Fetal surgery vs. fetal therapy
Fetal therapy usually refers to procedures that have limited number of instruments entering the uterus, for example fetal blood transfusions, while fetal surgery often is used to refer to more complicated invasive procedures like shunt placement or open surgery.

Iatrogenic
Used to describe symptoms or conditions that are caused by medical intervention or treatment. For example, iatrogenic membrane rupture is membrane rupture that results from *in utero* interventions.

Laparotomy
Surgical incision into the abdominal cavity, for example to expose the uterus for fetal surgery.

Amnioreduction
Insertion of a needle to aspirate amniotic fluid from the uterus to reduce amniotic fluid volumes in cases of polyhydramnios.

Oligohydramnios
Insufficient amniotic fluid present during gestation. This can hinder lung maturation and lead to perinatal morbidity.

Polyhydramnios
Excess amniotic fluid present during gestation. This can lead to poor perinatal outcomes.

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Box 1.

Criteria for fetal surgery, adapted from Harrison, et al. [1], Deprest et al. [2], and Adzick, et al [3].

- The disease must be diagnosable *in utero* and have no effective post-natal therapy.

- *In utero* disease staging criteria must be established to ensure that only severely affected fetuses undergo fetal surgery but also that surgery is not performed on fetuses too severely affected to benefit from intervention.

- Mothers and fetuses should be free of co-morbidities including fetal karyotype abnormalities.

- There must be proof in form of a clinical trial, or animal study evidence supporting a reasonable cause to assume (in case of pre-trial case studies), that the benefits of the therapy outweigh the risks of the procedure.

- Timing of the procedure must be optimized to provide maximum benefit to the fetus while decreasing the risk of preterm labor before the gestational limit of viability.

- Surgery and delivery should be performed at a specialty center with established ethical protocols, informed consent of parents, and an experienced multi-specialty team.

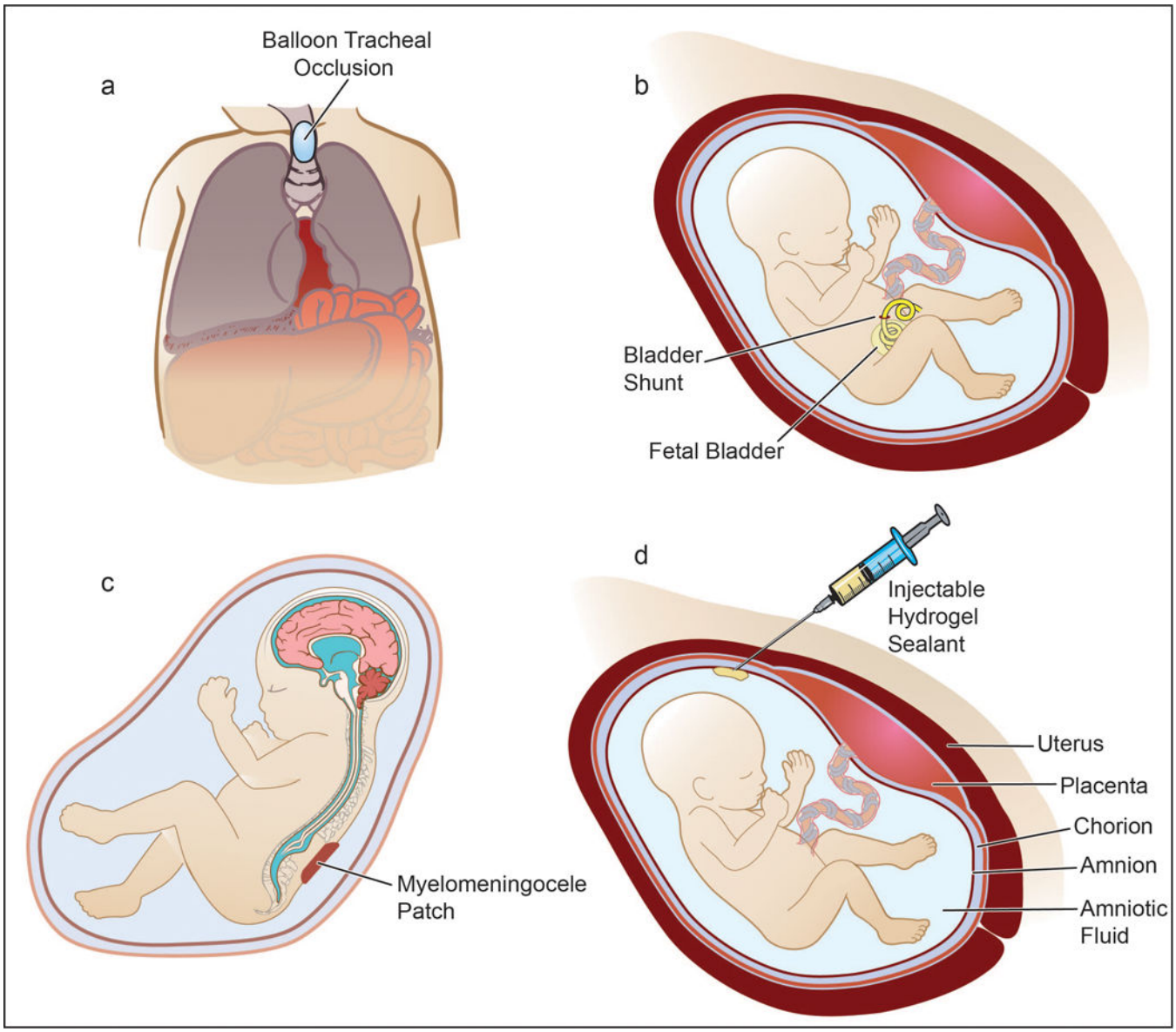

Figure 1.

Examples of biomaterials in fetal surgery. (**A**) In cases of congenital diaphragmatic hernia, *in utero* occlusion of the trachea with a silicone balloon allows lungs to fill with fluid and expand, pushing abdominal organs out of the pleural cavity. (**B**) *In utero* shunting can be used to drain fluid from swollen organs into the amniotic sac. For example, in cases of lower urinary obstruction, double-pigtail shunts can be inserted to drain the bladder. (**C**) Biomaterial patches can prevent amniotic fluid enzymes from degrading abnormally exposed tissues *in utero*, for example, in covering exposed neural tissue in myelomeningocele. (**D**) Materials to seal the fetal membranes (chorion and amnion) and reduce the risk of membrane rupture following fetal surgery are currently in development. These injectable hydrogels can seal between the uterus and membranes (called presealing) or inside the amniotic sac (as shown).

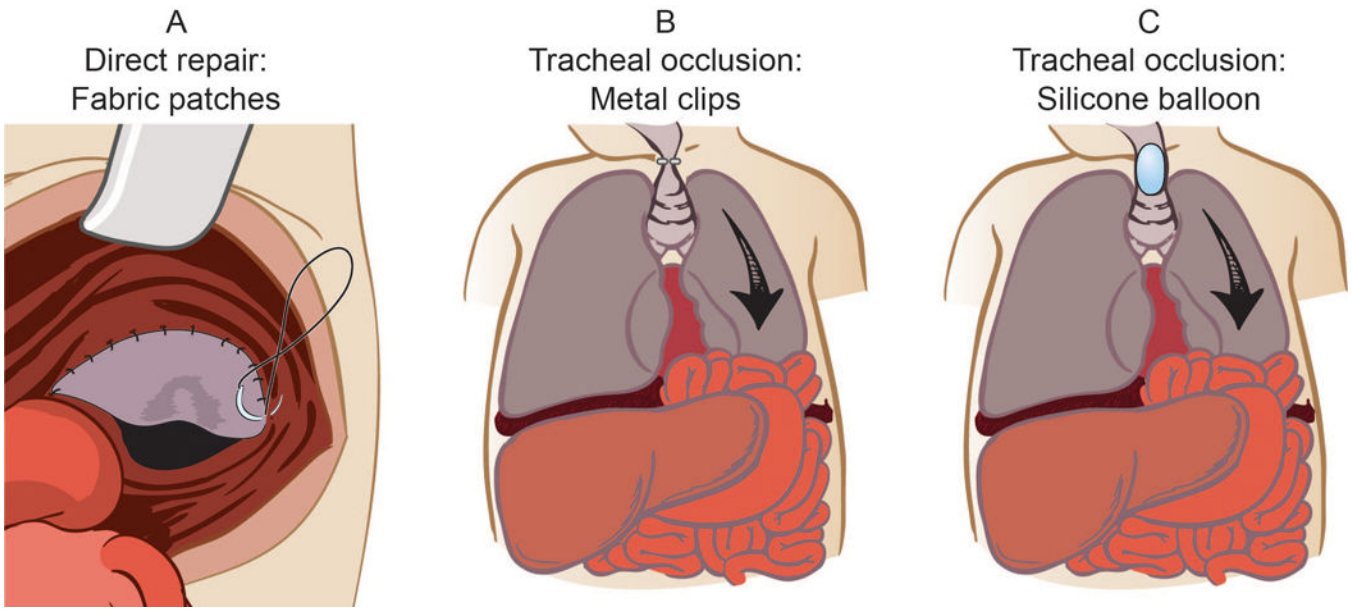

Figure 2.

Biomaterials methods to address congenital diaphragmatic hernia *in utero*. (A) In early fetal surgeries, Gore-Tex patches were used to repair the diaphragm defect and to patch the abdomen. (B) In later attempts, fetal tracheal occlusion was achieved by clamping the fetal trachea with a metal clip to occlude it and allow lung volume to expand. (C) Currently, tracheal occlusion is achieved by inserting a silicone balloon into the fetal trachea and inflating it with saline to occlude the trachea.

Table 1:

Selected materials approaches to sealing fetal membranes after surgical puncture

Material	Status	Notes	Selected Literature	Material performance
Maternal platelets and fibrin cryoprecipitate, "amniopatch"	Human cases; mixed results	Used following fetal surgery *after iPPROM* but before onset of preterm labor. Slurry of platelets and cryoprecipitate injected into amniotic fluid, through FM at site distal to initial intervention hole. In some cases, transvaginal fluid leakage ceased, but FM seal at defect site hard to confirm. One series reported fetal or neonatal death of ≥1 fetus in 11 of 21 cases [38]. Some intrauterine fetal deaths attributed to platelet overactivation.	**Quintero** et al., 1999 [50]: n = 7 cases. 3 healthy infants. **Quintero**, 2001 [38]: n = 21. 11 pregnancies with ≥1 healthy infant. **O'Brien** et al., 2002 [51]: n = 1 case, amniopatch + gelatin sponge. Healthy infant **Young** et al., 2004 [26]: n = 8 cases. 6 with no evidence of AF leakage from puncture site. **Richter**, et al. 2013 [52]: n = 24. 58% amniopatch success rate; 55% survival to discharge.	Formation of sealing plug at defect site difficult to document; mechanical properties akin to blood clot, not robust. Amniopatch method utilized only after onset of iPPROM; does not decrease incidence of membrane rupture.
Collagen or gelatin plug. For example decellularized amnion [41] or porcine-skin derived gelatin	Some in-human use; no improvement relative to the standard of care (no treatment)	As laparoscopic instruments are removed from the amniotic cavity, a small gelatin or collagen plug is left behind in the membrane defect, like a tampon.	**Chang**, et al., 2006 [37]: n = 27 TTTS laser coagulation cases. PPROM rate 4.2% attributed to "meticulous technique and atraumatic insertion and removal of ports." **Engels**, et al., 2014 [49]: n = 54 with plug; n = 87 without plug. No evidence that collagen reduces risk of PPROM after minimally invasive CDH repair. **Papanna** et al., 2010 [22]: n = 79 TTTS laser coagulation cases. PPROM rate = 34%.	Plug rapidly swells with amniotic fluid to occlude the defect site but does not form a water-tight seal.
Commercially available surgical glues				
Fibrin glues (e.g., Tisseal)	**Benchtop evaluations and animal studies; some in-human use for other applications**	Several groups have attempted to study the performance of commercially available surgical glues to seal the FM following surgical puncture. While some have been evaluated in animal or human trials and show promise, others were eliminated during phases of benchtop testing due to their poor biological or mechanical properties.	**Bilic**, et al., 2009 [19]: Compared biological and adhesive properties of surgical glues for FM sealing. **Burke**, et al., 2007 [53]: Compared adhesive properties of fibrin and mussel-inspired tissue adhesives. **Haller**, et al., 2012 [54]: Evaluated FM tissue sealing properties of glues using burst device. **Devaud**, et al., 2019 [55]: Comparative studies using novel delivery device to apply sealants to *ex vivo* human fetal membranes in benchtop uterine models.	Poor adhesion to wet tissues.
Cyanoacrylate (Dermabond, Histoacryl)			**Bilic**, et al., 2009 [19]. **Devaud**, et al., 2019 [55].	Dermabond: poor cytocompatibility, not for application to wet wounds (per manufacturer). Histoacryl: cytocompatible, adheres to tissues.
BioGlue (2-component bovine serum albumin/ glutaraldehyde glue)			**Azandani**, et al., 2009 [56]: Comparison of mechanical properties of vascular glues. **Bures**, et al., 2015 [57]: *In vitro* evaluation of BioGlue for sealing lung defects	Mismatch of mechanical properties relative to FM. When cured, BioGlue elastic modulus is 3.1 ± 1.6 MPa [56]
SprayGel (2-component multi-			**Bilic**, et al., 2009 [19]	Poor adhesion to wet tissues

Material	Status	Notes	Selected Literature	Material performance
arm PEG modified with NHS ester and lysine)				
CoSeal (2-component multi-arm PEG with NHS esters and thiols)			**Spotnitz & Burks**, 2008 [58]	Swelling up to 400%; cannot be used in confined spaces such as the FM-uterus interface. Skin sensitization issues in animals.
Duraseal (2-component solution of PEG ester and trilysine amine)			**Spotnitz & Burks**, 2008 [58]	Swelling *in vivo* up to 50%; potential for wound-site infections.
Adhesives designed specifically for fetal membrane sealing				
Catechol-PEG (cPEG)	Promising animal data	Multi-arm PEG modified with mussel-inspired catechol groups	**Bilic**, et al., 2009 [19]. **Haller**, et al., 2012 [54]: cPEG improved fetal survival in a rabbit model of fetal membrane sealing. **Kivelio**, et al., 2013 [59]. **Devaud**, et al., 2019 [55].	Catechol-mediated wet adhesion superior to other injectable glues. Biocompatibility and material cohesion could be improved
Nanosilica coacervate glue + decellularized amnion (DAm)	Studied in porcine FM sealing model	Nanosilica coacervate glue was used to adhere sheets of DAm to seal swine FM defects, but no significant difference was found between treatment and control groups.	**Mann**, et al., 2012 [41]: Benchtop evaluation of coacervate glue. **Papanna**, et al, 2015 [60]: Mini-swine FM sealing study; inconclusive as swine membranes healed spontaneously.	Further work needed to identify the properties of this adhesive system and validate in a non-self-healing animal fetal membrane model
Tissue engineering and other approaches				
Laser welding	Not suitable for FM sealing	Laser welding with albumin solders was attempted *in vitro* to seal a FM defect. This method was not effective in sealing membrane defects	**Petratos**, et al., 2002 [42].	Laser welding produces worse adhesion than either sutures or polymeric sealants.
Membrane-mimetic sheets	Preliminary benchtop studies, some animal studies	Non-adhesive sheets are sutured, glued, or placed in or on membrane defects. Cell infiltration and sealing ability is assessed.	**Roman**, et al., 2016 [61]: Electrospum polymer bi-layer with elastic properties similar to the fetal membranes. Phase: Benchtop testing. **Ochsenbein-Kölble**, et al., 2006 [44]: Comparing decellularized amnion sheets to polyesterurethane sheets in rabbit model of FM puncture. **Pensabene**, et al., 2015 [62]: Ultrathin poly-L-lactic acid film adheres to uterus and exposed FM following puncture in rabbit model. Adhesion mechanism unclear.	Most materials are non-adhesive, but approach is promising for both iatrogenic and spontaneous PPROM
Precipitated egg white	Bench top studies	Precipitated egg whites were assessed for ability to plug fluid leaks human FM in a benchtop model	**Mendez-Figueroa**, et al., 2010 [63].	Translation potential unclear as unvalidated in animal work.
Tissue engineering *de novo* FM from hPSCs	Preliminary / basic science	**Shao,** et al., 2017 [64]: Protocol to differentiate human pluripotent stem cells (hPSCs) into amnion cells. In the future, this could be expanded to create implantable FM tissues for FM repair.		

Table 2:

Materials approaches for defect repair in MMC and gastroschisis.

Material	Status	Selected Literature	Material performance
Surrounding tissue stretched to cover defect	Standard of care in fetal surgery to correct MMC; used postnatally to cover gastroschisis & omphalocele defects	**Adzick** et al., 2011 [3]: Repairing MMC defect in utero via open fetal surgery superior to post-natal repair in large human randomized controlled trial. **Stephenson**, et al., 2010 [84]: Gastrochisis repair successful in 2/2 fetal sheep via open surgery.	Surrounding tissue can successfully be used to cover MMC or gastroschisis defects, but *in utero*, this approach likely necessitates an open surgery approach. Also, in some gastroschisis and omphalocele cases, surrounding tissue is not large enough to stretch across the defect.
Gelatin/collagen sponges laced with bFGF and adhered to defect with cyanoacrylate adhesive	Successful rat and sheep studies	**Watanabe,** et al., 2010 [74]: Successful repair of MMC defect in fetal rat model using gelatin sheet/gelatin sponge combination, adhered to tissue with cyanoacrylate and laced with bFGF. Epithelial and vascular cell ingrowth into sponges. **Watanabe,** et al., 2016 [83]: Successful repair of MMC defect in ovine model using gelatin/collagen sponges laced with bFGF and with or without gelatin sheet covering. Histology revealed epithelial layers covering the defect as well as neovascularization.	Promising. Further work needed to fully characterize materials properties of sponge, including mechanical properties and cellular response to biomaterial, and to investigate if these findings could be reproduced using laparoscopic surgery. Materials did not cause inflammation of MMC defect site.
Biocellulose film	Sheep studies	**Sanchez e Oliveira**, et al., 2007 [85]: In sheep model, biocellulose films were placed atop exposed spinal tissue before skin was closed around the defect *in utero.* Film used to prevent cord tethering sometimes associated with MMC repair. **Papanna,** et al., 2016 (1) [86]: In sheep model, biocellulose films were attached with sandcastle worm-inspired sealants [41] that were cured with 532 nm laser light at 200 mW for 10 s/cm^2. Films dislodged, and no defect repair was seen.	Biocellulose films are still candidate materials, but attachment method is important. This sandcastle-worm inspired adhesive seems unsuitable for this application.
Cryopreserved human umbilical cord (HUC) + sutures	Sheep studies promising and ongoing; early human case reports successful	**Papanna,** et al., 2016 (1) [86]: In sheep model, HUC was used to patch MMC defect *in utero*. Repair was excellent, including almost full skin coverage and layered tissue regeneration. **Papanna,** et al., 2016 (2) [87]: Case report in 2 human patients. Promising results. Hindbrain herniation was reversed and minimal cord tethering was found at birth.	Promising. Further studies to validate the method and compare to *in utero* repair without patches are needed.
Placenta-derived mesenchymal stromal cells seeded onto porcine small intestine submucosa-derived ECM	Fetal rat study yielded promising results	**Chen** et al., 2018 [88]: In rat MMC model, decreased spinal cord deformity and apoptosis seen in placental mesenchymal stromal cell-seeded ECM compared to ECM-only scaffold repair in fetal rats.	Promising. More work needed in larger animal models.