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Complex gastroschisis: a new indication for fetal surgery?

Authors

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ABSTRACT

Gastroschisis (GS) is a congenital abdominal wall defect in which the bowel eviscerates from the abdominal cavity. It is a non-lethal isolated anomaly and its pathogenesis is hypothesized to occur as a result of two hits, i.e. primary rupture of the 'physiological' umbilical hernia (congenital anomaly) followed by progressive damage of the eviscerated bowel (secondary injury). This second hit is thought to be caused by a combination of mesenteric ischemia from constriction in the abdominal wall defect and prolonged amniotic fluid exposure with resultant inflammatory damage, both eventually leading to bowel dysfunction and complications. GS can be classified as either simple or complex, the latter being complicated by combinations of intestinal atresia, stenosis, perforation, volvulus, and/or necrosis. Complex GS requires multiple neonatal surgeries and has a significantly greater postnatal morbidity and mortality than simple GS. The intra-uterine reduction of eviscerated bowel before irreversible damage and subsequent defect closure may diminish or potentially prevent the bowel and other fetal and neonatal complications and risks associated with this condition. Serial prenatal amnio-exchange has been studied but never adopted because of its unproven benefit in terms of survival, bowel and lung function. We believe that recent advances in prenatal diagnosis and fetoscopic surgery now justify reconsideration of the antenatal management of complex GS under the rubric of the criteria for fetal surgery established by the International Fetal Medicine and Surgery Society. Herein we discuss how conditions for fetoscopic repair for complex GS might be favorable according to these criteria i.e. an established natural history, an accurate prenatal diagnosis, absence of fully effective perinatal treatment due to prolonged need for neonatal intensive care, experimental evidence for fetoscopic repair, and maternal-fetal safety of fetoscopy in expert fetal centers. Finally, we advance a research agenda that will help overcome barriers to progress and provide a pathway toward clinical implementation.

BACKGROUND AND RATIONALE FOR FETAL REPAIR OF COMPLEX GASTROSCHISIS

Gastroschisis (GS) is a congenital abdominal wall defect in which the intestinal structures eviscerate from the abdominal cavity. It is the most common congenital defect with a prevalence of 4.3 per 10,000 live births in the U.S and 2.6 in Europe.[1-4] For unknown reasons there was a worldwide increase in prevalence[5] between 1995 and 2012, with a 30% increase in the U.S.[1, 2] and a 25 % increase in Europe[5, 6]. Although the prevalence decreased slightly between 2012 and 2018, it remains higher than it was in 1995.[6, 7] GS may be classified as simple or complex.[8, 9] Simple GS is more common and presents with healthy bowel albeit inflamed and covered by "peel" composed of a mix of fibrinous and collagenous inflammatory material. In contrast, while accounting for about 20% of cases[10, 11], complex GS is complicated by combinations of intestinal atresia, stenosis, perforation, volvulus, and/or necrosis, including the closed GS entity leading to vanishing gut and short bowel syndrome.[10, 12-15]

The prevalence of intrauterine fetal demise (IUFD) is 4.5%, with the direct cause being largely unknown.[16] Most commonly IUFD occurs during the third trimester as an acute event without preceding indicators, and it appears to be related to umbilical cord or intestinal vascular compression (following acute intestinal dilation or volvulus) causing cardiovascular compromise and death.[16] In developed countries, the postnatal morbidity and mortality of both GS types are mainly due to postnatal intestinal dysfunction.[17] In an attempt to remedy this, fetuses with GS have been iatrogenically delivered prematurely between 34 and 37 weeks, but this approach has failed to show any obvious benefits.[18] Postnatally, a number of different surgical techniques (primary vs. staged closure using a silo) have been described.[19] These surgeries have usually been performed within the first week of life.[19] Advances in parenteral nutrition strategies, neonatal management and surgical care have reduced the overall perinatal mortality of patients with GS to less than 5% (0-4.6%).[20-23] While the perinatal mortality for simple GS has improved (0-1%)[11, 24, 25], complex GS still carries significant mortality in many U.S. (up to 11%) and European (up to 17%) centers[10, 11, 26-28]. Sepsis, which usually presents in the neonatal period, is the leading cause of death in this group. Beyond the neonatal period, liver failure (caused by sustained parenteral nutrition), and adhesive small bowel obstruction, are common causes of death. These data are consistent for the U.S. and Western Europe, but not so

for low-income countries where dramatically higher mortality rates approaching 100% have been reported.[29] Morbidity is also significant for both GS types mainly due to bowel dysfunction as detailed below.[10, 26, 30]

The U.S. Centers for Disease Control and Prevention (CDC) has stated that "Public health research is urgently needed to identify the causal factor(s) contributing to the increase in GS".[1] While identifying causal factors is a laudable long-term goal, it does not address the short-term issues associated with the management of children with GS. We therefore believe that there is a short-term need for innovative therapies aimed at preventing the complications of complex GS, and improving the core outcomes, i.e. death, sepsis, time on parenteral nutrition, liver disease, number of severe gastrointestinal complications, number of operations, growth and quality of life.[31]

In this paper we contend that complex GS is a candidate condition amenable to fetal surgery based on the five criteria promulgated by the International Fetal Medicine & Surgery Society (IFMSS; Table 1).[32-34] Minimally invasive fetal intervention may allow reversal of the bowel evisceration, reduction or prevention of secondary bowel damage and dysfunction commonly seen in complex GS, prevention of the need for multiple neonatal surgeries and general anesthesia, and in so doing minimize in the healthcare burden on patients, their families, and society in general. We also discuss how we intend to tackle the remaining challenges and determine an ethical and feasible trajectory towards clinical implementation.

ESTABLISHED NATURAL HISTORY

The pathophysiology of GS may be hypothesized to result from two consecutive "hits". The initial "hit" comprises the abdominal wall defect itself, which is a prenatal rupture (disruption) of the physiological umbilical hernia that occurs between 10 and 14 weeks of gestation.[35-38] First described by Shaw, the rupture almost always occurs on the thin right side and results in an umbilical ring, that allows the physiologically herniated midgut (distal duodenum to proximal 2/3 of transverse colon, which are vascularized by the superior mesenteric artery) to eviscerate into the amniotic cavity, where it continues to grow in an unrotated state.[37] This hypothesis is supported by a study of healthy human embryos and fetuses in whom the physiological hernia was located on the right side of

the umbilical cord, the thin "pars flaccida".[35] An experimental study in chicken embryos confirmed that the site of the GS defect is not the abdominal wall itself, but the umbilical hernia.[39] The timing of the fetal rupture, i.e. before the end of organogenesis, in fetuses with GS, is reinforced by the presence of a normally developed umbilical cord, herniated but unrotated bowel[35], and the absence of any other associated structural anomalies[40, 41]. The cause(s) of GS remains unknown but is not thought to be primarily genetic[42, 43]. Epigenetic and some multifactorial etiologies combining biological and molecular mechanisms have been suggested[36, 43]. There are many risk factors for GS, especially maternal age <20 years.[4] First-trimester exposure to teratogens (tobacco, amphetamine, cocaine and opioids), medications (aspirin and antidepressants), bacteria (chlamydia trachomatis genitourinary infection), toxins (estrogen disruptors) and radiation (X-rays) have all been suggested as possible causes.[43-46]

The second "hit" occurs over time as the eviscerated bowel is persistently exposed to mechanical and chemical stimuli, leading to ischemic and inflammatory injuries.[17, 47, 48] These are respectively a chronic mesenteric lymphovascular constriction of the eviscerated bowel at the level of the umbilical ring which occurs from 10 weeks[35] onwards, and exposure to amniotic fluid which contains increasingly elevated levels of toxic digestive compounds after 30 weeks[17, 47]. First simulated in fetal lambs by Langer et al., the ischemic injury is believed to cause the intestinal volvulus, atresia, stenosis, necrosis and perforation seen in complex GS.[49] This was recently confirmed by Anderson et al. who surgically induced a model of complex GS with bowel atresia or volvulus at birth (term, 145 days).[50] At midgestation (75 days), they made a 1.5cm horizontal incision of the abdominal wall, eviscerated the small bowel, placed a 1.5cm diameter silicon ring around the bowel and secured the ring to the abdominal wall. Bowel complications were directly caused by mesenteric lymphovascular constriction of the eviscerated bowel at the level of the ring. This is in relative contrast to the localized vascular accident of part(s) of the small bowel that is the cause of congenital intestinal atresia.[51] The inflammatory injury, as demonstrated by Tibboel et al. in human embryos and fetuses, is thought to result in the extra-luminal fibrous coating on the eviscerated bowel after 30 weeks referred to as bowel peel.[17] A positive correlation was found between digestive compounds (bile acids) and amniotic fluid inflammatory markers (ferritin and interleukin 1b).[47] These injuries

collectively are likely to be responsible for progressive intestinal dysmotility and intraperitoneal adhesions. This premise has been extensively supported in the literature.[52] We hypothesize that the bowel damage in complex GS is mainly ischemic, and not inflammatory, due to the chronic mesenteric lymphovascular constriction of the eviscerated bowel at the level of the umbilical ring.

ACCURATE PRENATAL DIAGNOSIS

Prenatal ultrasound screening allows to diagnose GS as early as the first trimester and certainly by the early second trimester in almost all cases (Figure 1).[19, 28] Much research has been done to try and distinguish simple vs. complex GS prenatally. The most commonly cited and reliable diagnostic marker for distinguishing complex from simple GS is intra-abdominal bowel dilation (IABD) on prenatal ultrasound.[19, 28] A meta-analysis showed that fetuses with IABD on ultrasound have a higher risk of bowel atresia diagnosed at the time of surgery (OR=5.48, 95% CI=3.1–9.8).[19] Additionally, retrospective studies have attempted to determine the optimal IABD cutoffs (range 6-25 mm) to accurately predict complex GS during the second and third trimesters.[28, 53, 54] Ultimately, based on individual data, a recent longitudinal prospective multicenter study on 104 patients showed that the presence of a single IABD measurement at ≥10 mm between 20 and 22 weeks is predictive of complex GS with a clinically acceptable specificity (100%), positive predictive value (100%) and negative predictive value (77%).[25] This is comparable to that relied upon with other diagnostic tests for other prenatal conditions. For example, in congenital diaphragmatic hernia (CDH), the observed-to-expected Lung-to-Head-circumference-Ratio with an optimal cut-off value of 40% has a 70% specificity for predicting neonatal survival.[55] This marker is currently used as an inclusion criterion for fetoscopic endoluminal tracheal balloon occlusion to improve the postnatal outcome in moderate and severe CDH.[56, 57] Despite the fact that CDH has a different morbidity and mortality, we believe that is not unreasonable to consider IABD ≥10 mm at 20-22 weeks as a predictive marker for complex GS and to identify patients who may benefit from fetal repair. Our own institutional retrospective data is suggestive of this cut-off and we are conducting a prospective clinical study to corroborate it. We have also performed and submitted a systematic review and meta-analysis which

confirms these findings. Future directions in prenatal diagnosis could assess amniotic fluid and/or serological biomarkers for bowel ischemia - such as intestinal fatty acid binding protein, ischemia modified albumin and citrulline[58, 59] - to improve patient stratification and determine the optimal time window for fetal repair when bowel damage is still reversible.

ABSENCE OF FULLY EFFECTIVE GOLD STANDARD POSTNATAL THERAPY

Although intestinal inflammation improves after postnatal repair, patients with complex GS are subject to significant mortality and morbidity.[10] Short- and medium-term intestinal complications are related to the ongoing bowel dysfunction and the subsequent need for total parenteral nutrition.[21, 26, 30] Patients with complex GS have a higher prevalence of short bowel syndrome, necrotizing enterocolitis and sepsis, as well as a three times longer length-of-stay and duration of parenteral nutrition (around 4 months) as compared to simple GS (Table 2).[10, 11, 60, 61] Short bowel syndrome and abdominal compartment syndrome require repeated surgeries including emergent laparotomy, silo placement and staged delayed closure with a prosthetic patch.[61] The consequences of these are protracted or recurring hospitalizations often with parenteral nutrition and central venous line dependence, all of which are associated with an increase in complications including recurrent sepsis, cholestasis, liver failure, and even death.[10, 30, 61]

Furthermore, children with GS are prone to medium- and long-term complications which are often overlooked and likely underestimated.[21, 24] Gastrointestinal complications encompass chronic constipation, abdominal pain or bloating, gastroesophageal reflux disease, nutrition deficits, adhesive bowel obstruction and need for additional surgery.[10, 21, 62, 63] From a neurodevelopmental viewpoint, GS patients are at risk for behavioral and emotional disorders.[21] While children with complex GS are at increased risk for mental and motor delay[64], children with either GS type display increased risk for difficulties with executive functioning despite having normal intellectual quotient[65].

ABSENCE OF EFFECTIVE EXPERIMENTAL PRENATAL THERAPY

Although a variety of prenatal interventions have been proposed for GS, to date none have been shown to improve postnatal outcome.[52, 66] These efforts have been focused

on reducing intestinal exposure to the amniotic fluid and on promoting fetal anti-inflammatory responses. A randomized trial comparing serial percutaneous amnio-exchange with saline every two weeks from 30 weeks, did not show efficacy in the improvement of survival or of bowel and lung function.[47] A recent randomized trial of expectant management of pregnancies complicated by GS versus elective preterm delivery at 34 weeks not only showed no benefit but suggested that iatrogenic preterm birth was harmful to neonates with GS because of late-onset sepsis.[18] Moreover, other prenatal interventions, including administration of maternal antenatal corticosteroids, have not shown improvement in neonatal outcomes.[67]

Our rationale for fetal surgery in complex GS is an extension of the exemplary experimental research pathway from which the fetal surgical approach for another non-lethal condition (spina bifida aperta, SBA)[68, 69] was developed. Clearly, a definitive, safe and effective prenatal treatment to protect the intestines and improve both fetal and neonatal outcomes would be an important addition to our armamentarium.[1] We hypothesize that fetal anatomical repair of complex GS between 20 and 26 weeks will improve or reverse the natural history, i.e. reduce or prevent the occurrence of bowel complications and improve gastrointestinal health at birth mainly by preventing ongoing and irreversible ischemic bowel injury, and also by reducing toxic exposure of exposed bowel. This therapeutic window occurs after prenatal diagnosis is made at 20-22 weeks and before the later part of the third trimester when the incidence of IABD significantly increases[25] and intrauterine fetal demise takes place[16].

EXPERIMENTAL EVIDENCE FOR FETAL GS REPAIR

Experimental models are critical in the introduction of any innovative technique.[70] Surgical innovations are best researched in an animal model prior to clinical implementation. Historically, the fetal lamb has been the primary animal model used in the development of fetal surgical techniques. This is due to anatomical similarity and high surgical fidelity despite the facts that maternal physiology in the pregnant ewe, reaction to anesthesia, and type of placentation do not perfectly mimic the physiologic conditions present during human fetal surgery.[71, 72] Several teams have used the fetal lamb model of GS to study therapy options.[48, 49, 73, 74] When the small bowel is exteriorized at mid-gestation (75-80

days where term is 145 days) by laparotomy, and the lambs are assessed at term, their bowel shows inflammation, thickening and a peel as well as necrosis and stenosis, closely resembling the human condition.[50] A recent systematic review summarized all prenatal interventions performed in animal models, encompassing open fetal and fetoscopic repairs, anti-inflammatory therapies and stem cell therapy.[52] Studies of fetal bowel reduction and defect closure (via either open[75, 76] or a 3-port fetoscopic[77-79] approach) in sheep confirm reduced histologic bowel inflammation at delivery. Simply covering the exposed bowel and the fetal abdominal defect with a collagen scaffold or a silastic sheet, showed similar results.[75, 80] A feasibility study in fetal lambs also showed that open fetal GS repair might increase feeding tolerance and gastrointestinal motility.[50] Despite these findings, we acknowledge that the therapeutic window for fetal repair of complex GS remains unestablished in the fetal lamb model. Moreover it is unknown whether open or fetoscopic GS repair involving bowel reduction and defect closure, will improve bowel function in neonatal lambs. We believe that these are the next research questions that need to be answered.

FETAL MINIMALLY INVASIVE SURGERY IN MULTIDISCIPLINARY FETAL CENTERS

The IFMSS guidelines recommend that fetal surgery is performed in an established fetal center with a dedicated training program by a multidisciplinary team.[34, 81, 82] Authors of this opinion are working at fetal centers that follow these guidelines and have significant preclinical and clinical experience in both of the open and fetoscopic approaches currently used in the management of a variety of congenital anomalies.[32, 81, 83] This includes the antenatal management of SBA. The randomized Management Of Myelomeningocele Study (MOMS) trial provided evidence that fetal repair of SBA by maternal laparotomy and hysterotomy is safe and effective for the fetus.[22, 84, 85] However, the hysterotomy can induce complications such as premature rupture of membranes (PPROM), prematurity, and hysterotomy scar dehiscence/rupture in the index and subsequent pregnancy.[86] Cesarean delivery is therefore mandated in order to reduce the risk of uterine rupture. Patients are also advised to wait for at least two years after an open hysterotomy repair before attempting another pregnancy.[22, 85, 87-90]

The maternal, obstetric and neonatal risk profile of open fetal repair of SBA through a large hysterotomy has prompted the development of alternate minimally invasive approaches.[91] Laparotomy-assisted fetoscopy has minimized the risk of open fetal surgery by decreasing maternal obstetric and perinatal morbidity, while maintaining the benefits of the surgery for the fetus.[83, 92, 93] Compared with open fetal repair, fetoscopic surgery reduces the need for maternal blood transfusion at delivery (0% vs. 9%) and essentially removes the risk of uterine dehiscence (0% vs. 35%) in the index pregnancy and potentially the risk of uterine rupture in any subsequent pregnancy.[22, 83, 85, 86, 92] Moreover it is unique in resolving the Achilles' heel of fetal surgery, preterm delivery.[94] Laparotomy-assisted fetoscopy rarely causes PPROM at less than 30 weeks, has a low prematurity rate (mean gestational age at birth: 37.6 vs. 32.4 weeks for percutaneous fetoscopy[95, 96] vs. 34.0 for open repair[85]) and allows term and planned vaginal delivery in 71% and 47% of cases respectively[83]. This technique has been safely developed (n=95, Houston, U.S.) [93] and we were able to duplicate this (n=3, Leuven, Belgium) following completion of our learning curve for open fetal surgery defined as 35 consecutive cases (n=45 in Houston; n=90 in Leuven)[81, 97], and using a multi-step training program consisting of inanimate and animal models and on and off site mentoring[98-100]. These results have led us to speculate that the laparotomy-assisted two-port fetoscopic approach between 20 and 26 weeks may be safely and effectively applied to the fetal repair of complex GS under partial amniotic insufflation with heated and humidified carbon dioxide without significant risk of extreme prematurity.[101-103]

ADVANCES IN TRANSLATIONAL MODELING AND RESEARCH AGENDA

In order to improve outcomes in complex GS, we intend to test the hypothesis that fetoscopic repair of complex GS is feasible, safe, and effective. Intra-uterine reduction of eviscerated bowel and subsequent defect closure may diminish or potentially prevent the mesenteric constriction before irreversible damage occurs. If this is the case, prenatal surgery may diminish or prevent the bowel damage and the fetal and neonatal complications and risks associated with this condition. Our consortium has taken advantage of specific skills and experience, as well as the availability of established preclinical skills-labs and experimental surgery facilities to develop an incremental

approach ideally suited to tackle this issue.[99, 100] We have first shown the feasibility of a standardized, stepwise fetoscopic procedure to repair GS in utero and are training fetal laparoscopic surgeons using (i) silicone 3D printed simulators, and (ii) two separate animal models (rabbit and fetal lamb) previously used in training for fetal SBA repair (Figure 2).[99, 100] We are now performing a study in the fetal lamb to assess the safety and efficacy of open and fetoscopic repair of complex GS focusing on neonatal bowel function as the primary outcome. In a meta-analysis and a clinical study, we are concomitantly determining whether IABD ≥10 mm as measured by prenatal ultrasound is predictive of complex GS and its complications. Our novel research and training program follows the IDEAL (Idea, Development, Exploration, Assessment, Long-term) recommendations for surgical innovation and evaluation, which state that preclinical studies, including simulators and valid animal models, are "essential before first-in-human trials of an innovation" under institutional review board and U.S. Federal Drug Agency (FDA) and European Medicines Agency (EMA) oversight.[70, 104]

SUMMARY

Gastroschisis is still a significant source of neonatal morbidity and mortality. Herein we discuss the rationale for the fetoscopic repair of complex GS to improve outcomes, based on the five IFMSS criteria. First, GS has an established pre- and postnatal natural history. It is a progressive disease, with a two-hit pathophysiology that progressively worsens in-utero i.e. a primary rupture of the physiological umbilical hernia followed by secondary bowel damage from chronic lymphovascular mesenteric constriction and exposure to amniotic fluid toxins. In 1 out of 5 cases the constriction leads to mesenteric ischemia which we believe is responsible for the significant morbidity and mortality seen in complex GS. Second, complex GS can be accurately diagnosed prenatally using IABD ≥10 mm measured during a second-trimester ultrasound scan as a predictive marker. Third, despite advanced perinatal medical and surgical management, children with complex GS suffer significant morbidity and mortality, far greater than that seen in simple GS. To date, clinical trials of early preterm delivery and prenatal management by amnio-exchange have failed to show any benefit. Fourth, based on experimental studies in the fetal lamb model, we hypothesize that fetal anatomical repair of complex GS may mitigate the

adverse effects of mesenteric constriction and improve fetal-neonatal outcomes by protecting the intestines from injury. Technically, bowel reduction and defect closure can now be performed via laparotomy-assisted, two-port fetoscopy in rabbit and fetal lamb models. Fifth, the latter fetoscopic approach in the repair of SBA has been shown to be safe and effective in an established large volume fetal center. Before undertaking this paradigm shifting surgery in human GS fetuses, the feasibility, safety, and efficacy of this innovative procedure need to be confirmed. We propose that this can be done using the established fetal lamb model of complex GS. In addition, the capability and competency of the fetal laparoscopic surgeons who will perform these procedures need to be assured. To this end standardized training on validated and realistic simulators as well as on live animal models is deemed essential. This approach has previously been shown to benefit our teams in the implementation of successful fetoscopic SBA repair programs and follows the IDEAL recommendations for surgical innovation and evaluation.

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TABLES AND FIGURES

Figure 1 – Prenatal diagnosis of GS using high-definition ultrasound during the second trimester.

(A) Right location of the eviscerated bowel (b) as compared with the stomach (S) and umbilical cord (doppler). (B) Prenatal marker of complex GS at 22 weeks of gestation, i.e. IABD ≥6 mm. (C-D) 3D reconstructions of fetuses with GS highlighting the location of the eviscerated bowel (b) on the right side of the umbilical cord. Abbreviations: GS, gastroschisis; IABD, intra-abdominal bowel dilation. Courtesy from Pr. Luc de Catte, UZ Leuven. Copyright by UZ Leuven, Belgium.

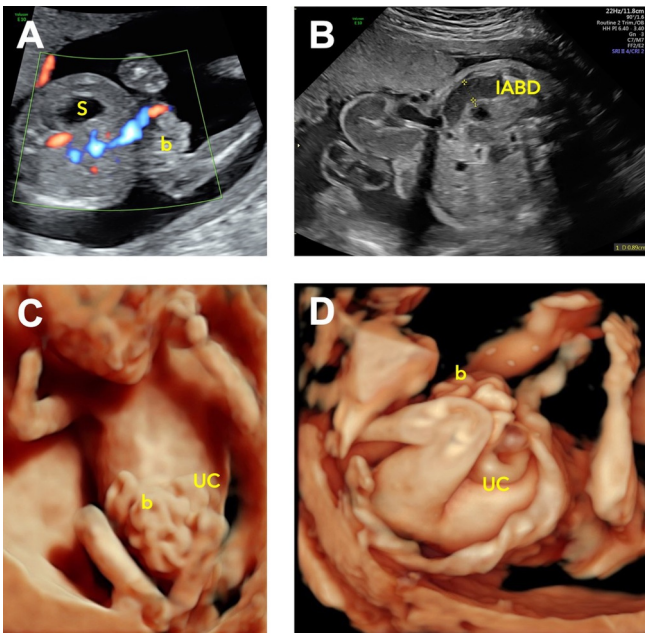
Figure 2 – GS models for training purposes and feasibility assessment (silicone and rabbit) and efficacy assessment (fetal lamb). (A-B) Silicone model simulating a fetus with GS inside the uterine cavity; the bowel (b) is located on the right side of the umbilical cord (UC). (C-D) Novel rabbit model where the abdominal cavity simulates the uterine cavity, the liver mimics the placenta, and the open stomach and 1m of small bowel simulate the fetal abdomen and the eviscerated bowel. (E-F) Fetal lamb model induced at 75 days of gestation (term; 145 days) with a 3D reconstruction of the eviscerated bowel (b); (G-H) two-port fetoscopic approach to repair a GS at 90 days of gestation. Abbreviations: GS, gastroschisis. Copyright by Texas Children's Hospital, Houston, TX, U.S. and UZ Leuven, Belgium.

Table 1 - Criterion check for fetal surgery in gastroschisis adding an extra criterion for a safe and effective prenatal approach.

IFMSS criteria	Meets criteria for complex gastroschisis
Accurate prenatal diagnosis	Yes
Established natural history	Yes
No fully effective postnatal or prenatal therapy	Yes
Experimental evidence of feasibility, safety and efficacy	No
Intervention in multidisciplinary fetal centers	Yes (collaboration of established fetal centers)
Safe and effective prenatal surgical approach for the mother	Yes (laparotomy-assisted fetoscopy)

Table 2 - Gastroschisis Mortality and Morbidity based on the core outcomes set. Abbreviations: GS, gastroschisis; WG, weeks of gestation; PN, parenteral nutrition; LOS, length of stay; RR, relative risk; MD, mean difference. Extracted data from Bradnock et al. 2011, Bergholz et al. 2014; D'Antonio et al. 2015; 2016 MMWR Report; Wright et al. 2018; Laje et al. 2018 ; Allin et al. 2019; Lap et al. 2020; De Bie et al. 2020 and Dekonenko et al. 2021.

Gastroschisis	**Both types**	**Simple GS**	**Complex GS**		**P Value**	**RR or MD (+)**
Proportion		80-83%	17-20%			
GA at birth (WG)		36.3	35.5		< 0.001	-0.75
Mortality						
US	<3%	0 %	≤ 11%		< 0.001	5.4
Europe	<5%	≤ 2.2%	≤ 17%			
Thailand	6-8%					
Turkey	36%					
Iran	80%					
Sub-Saharan Africa	75-100%					
Morbidity						
LOS (days)	58	40	117		< 0.001	+ 72-77 days
Time on PN (days)	51	30	112		< 0.001	+ 82-102 days
Sepsis		20.6%	51.3%		< 0.001	2.3
Abdominal Compartment Syndrome		0.6%	2.7%		0.19	3.3
Short Bowel Syndrome		2.3%	28.2%		< 0.001	12.0
Necrotizing Enterocolitis		9.0%	20.3%		0.03	2.0
Bowel obstruction		8.4%	18.4%		0.002	2.2



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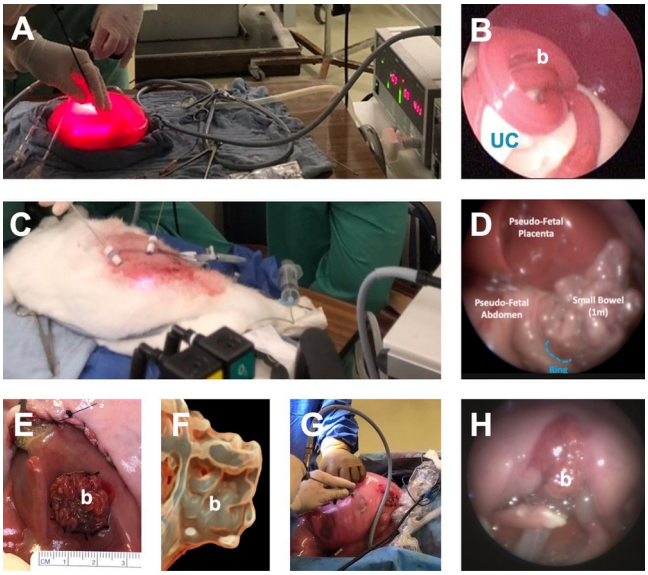

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