Advancements in Fetal Medicine and Intervention

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Objectives

- To review the history of fetal “therapy” and discuss the technological breakthroughs that have moved the needle with respect to newborn outcomes.
- To review some of the available fetal therapies and interventions for common and less common fetal conditions.
- To briefly review open neural tube defects – their diagnosis, etiopathogenesis, typical management and prognosis
- To review options for treatment of open neural tube defects, including in utero fetal repair
- To discuss the pre- and post-surgical evaluation and management of the fetal and maternal patient undergoing fetal intervention/surgery for various fetal anomalies.
- To outline the use of technology for the improvement of fetal care.

Disclosures

- I have no financial or other conflicts of interest to disclose

Early Fetal Intervention

- Antenatal Corticosteroids
  - Arguably the greatest contribution to the improvement of health outcomes for babies born preterm in the last 50 years
  - Introduced in late 1969 in a paper by Dr. Graham Liggins, an Obstetrician working at National Women's Hospital in Auckland
  - Studying the initiation of labor in sheep
  - Hypothesized that glucocorticoids were the trigger
    - Glucocorticoids withheld -> No Labor
    - Glucocorticoids given -> Labor
  - Observed that those lambs who did not receive Glucocorticoids died, while those who did receive Glucocorticoids lived
    - Presumably due to the accelerated appearance of surfactant activity

Surfactant

Antenatal Steroids

- Dr. Liggens conducts experimental trial in 282 women and reports favorable results in 1972
  - Experiment continues until 1974 when 1142 women are enrolled, representing 1248 babies
  - Earlier beneficial findings are confirmed

- By 1981, 12 experimental trials showed that receipt of antenatal glucocorticoids by women at risk of preterm delivery reduced by ½ the risk of death and RDS in their babies
  - Also reduced risk of brain bleeds and bowel infection without increasing risk

- Majority of eligible women received the therapy in the 1980s in New Zealand and Australia
  - Only 10-20% of eligible women were receiving this therapy in the early 1990s in the United Kingdom and United States

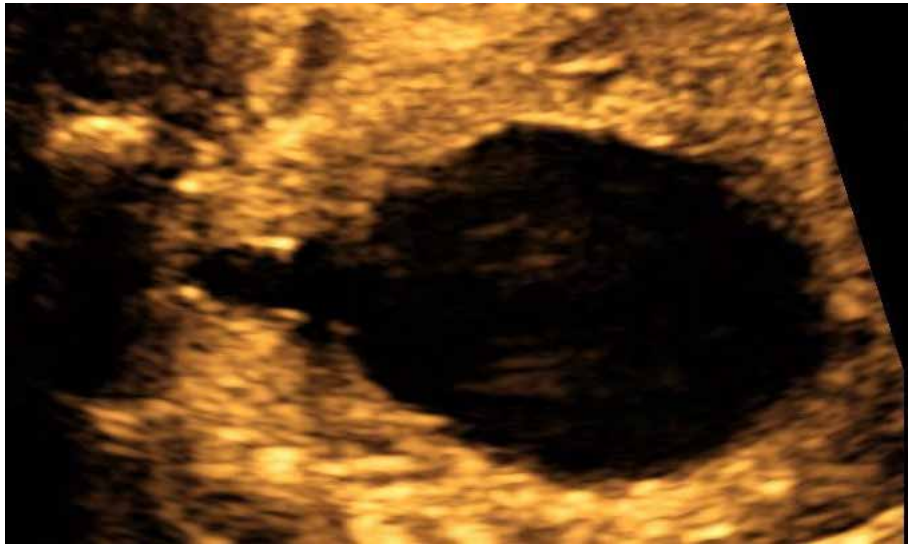
Antenatal Steroids

- NIH Consensus Statement
  - Antenatal corticosteroid therapy is indicated for women at risk of premature delivery with few exceptions and will result in a substantial decrease in neonatal morbidity and mortality, as well as substantial savings in healthcare costs
  - Usage rose around the world in women prior to 34 weeks gestation

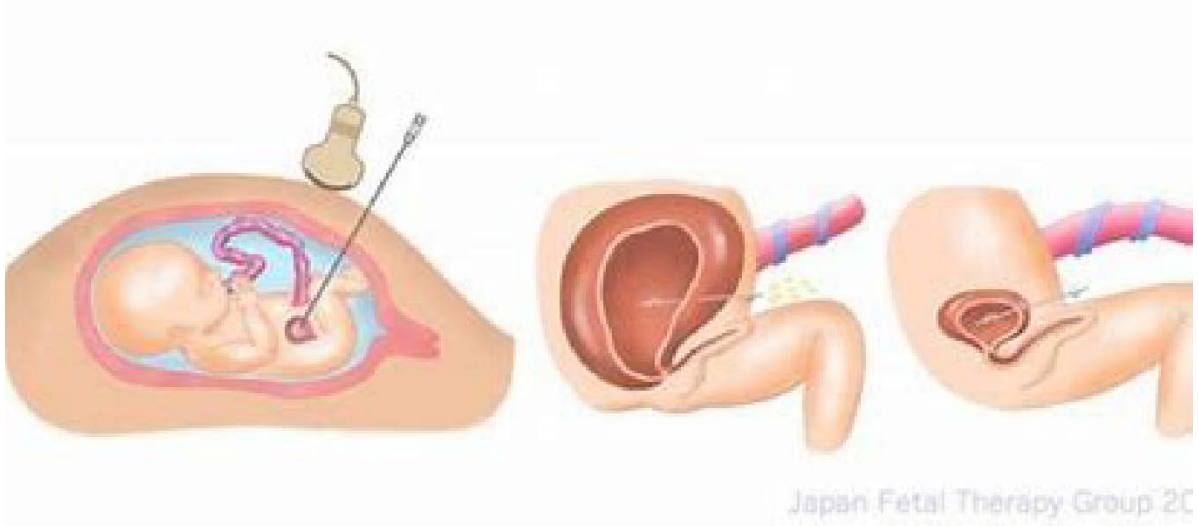
- Rescue Course

- Administration until 37 weeks gestation

Lower Urinary Tract Obstruction



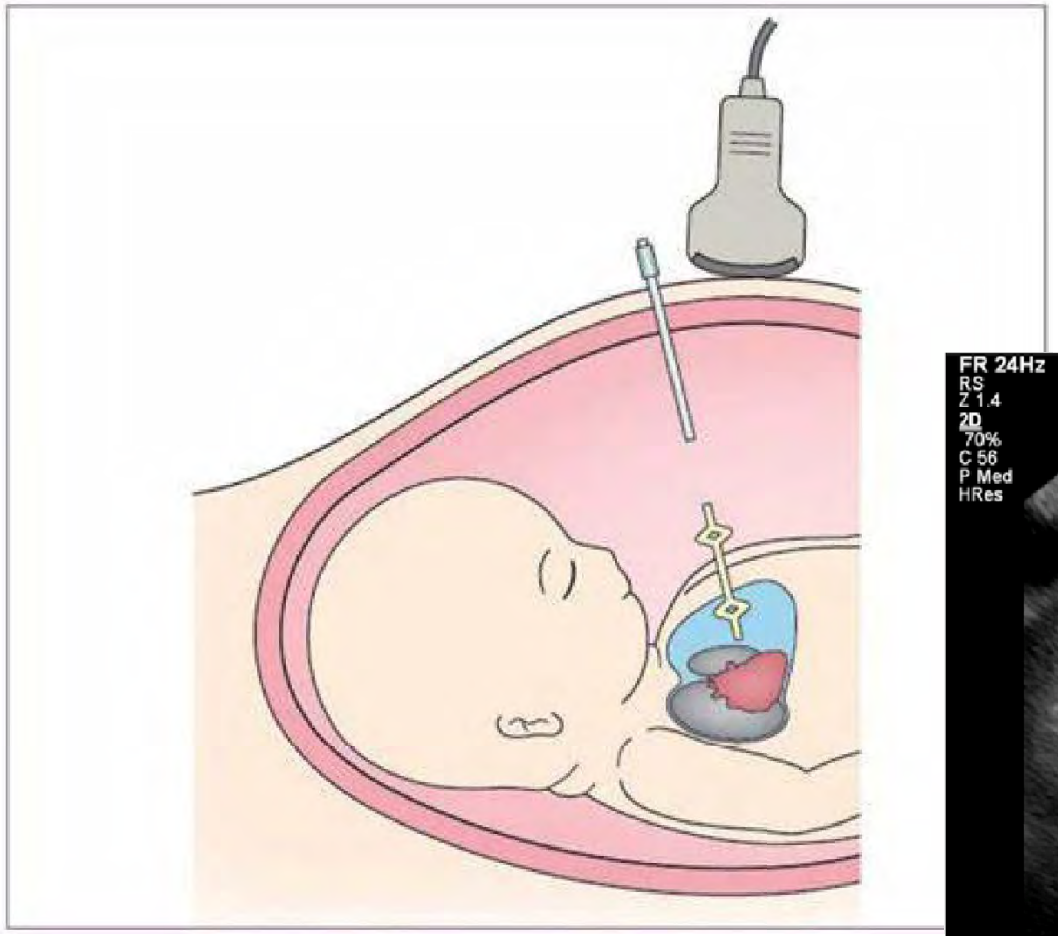
Bladder Stent

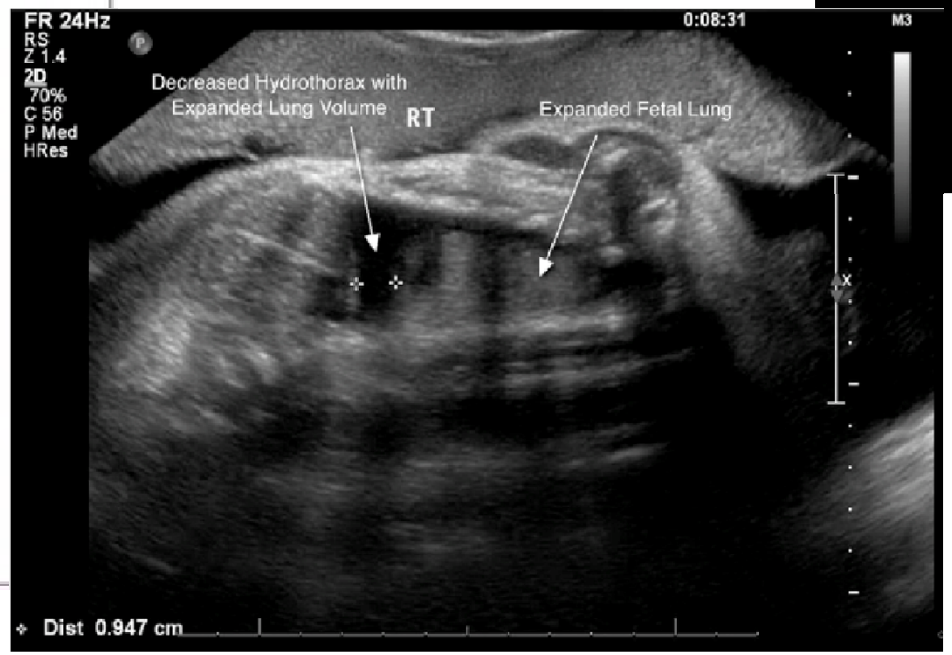


Fetal Bladder Catheter

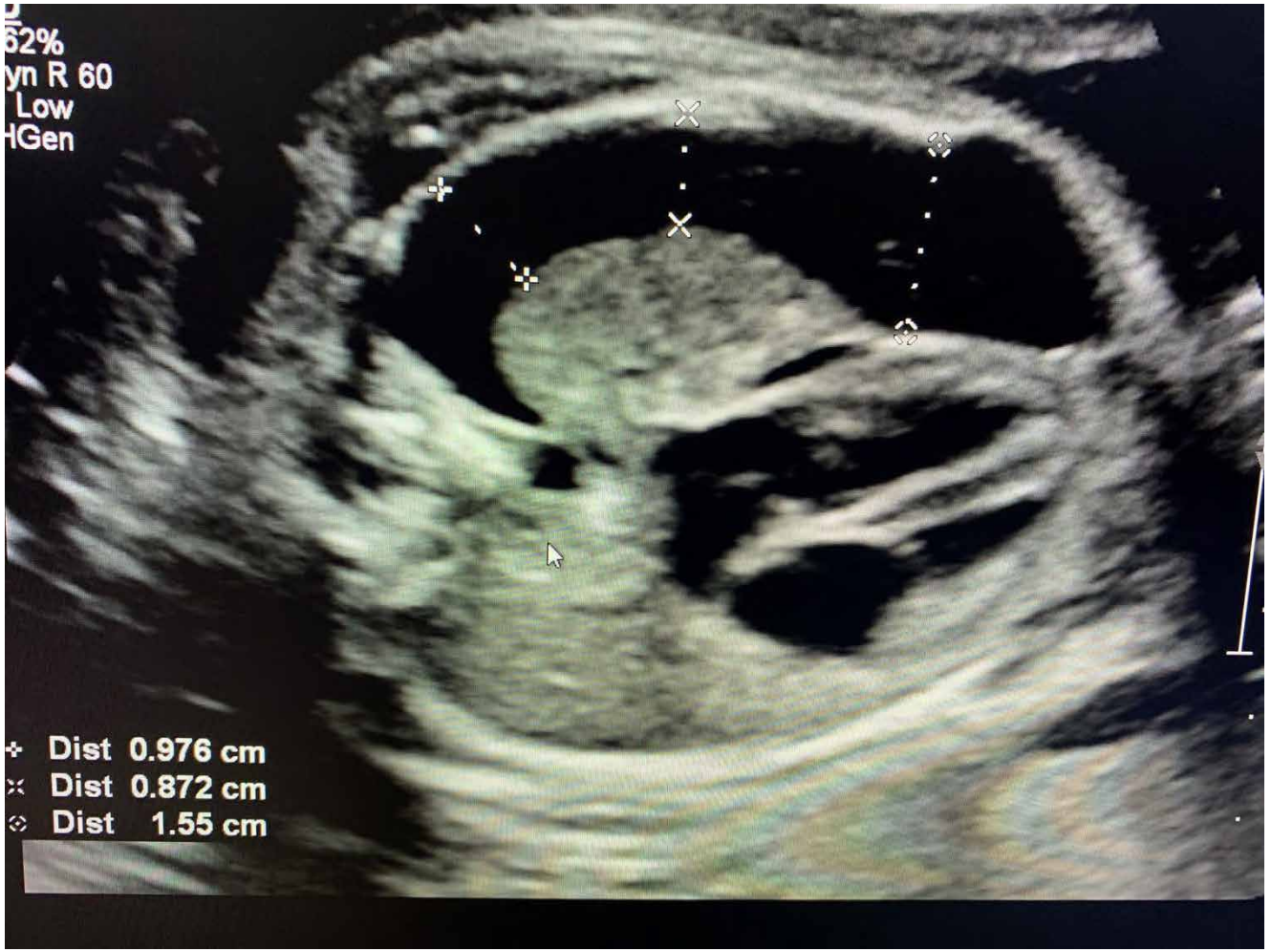
Pleural Effusion

Pleural Shunt





Pleural Effusion



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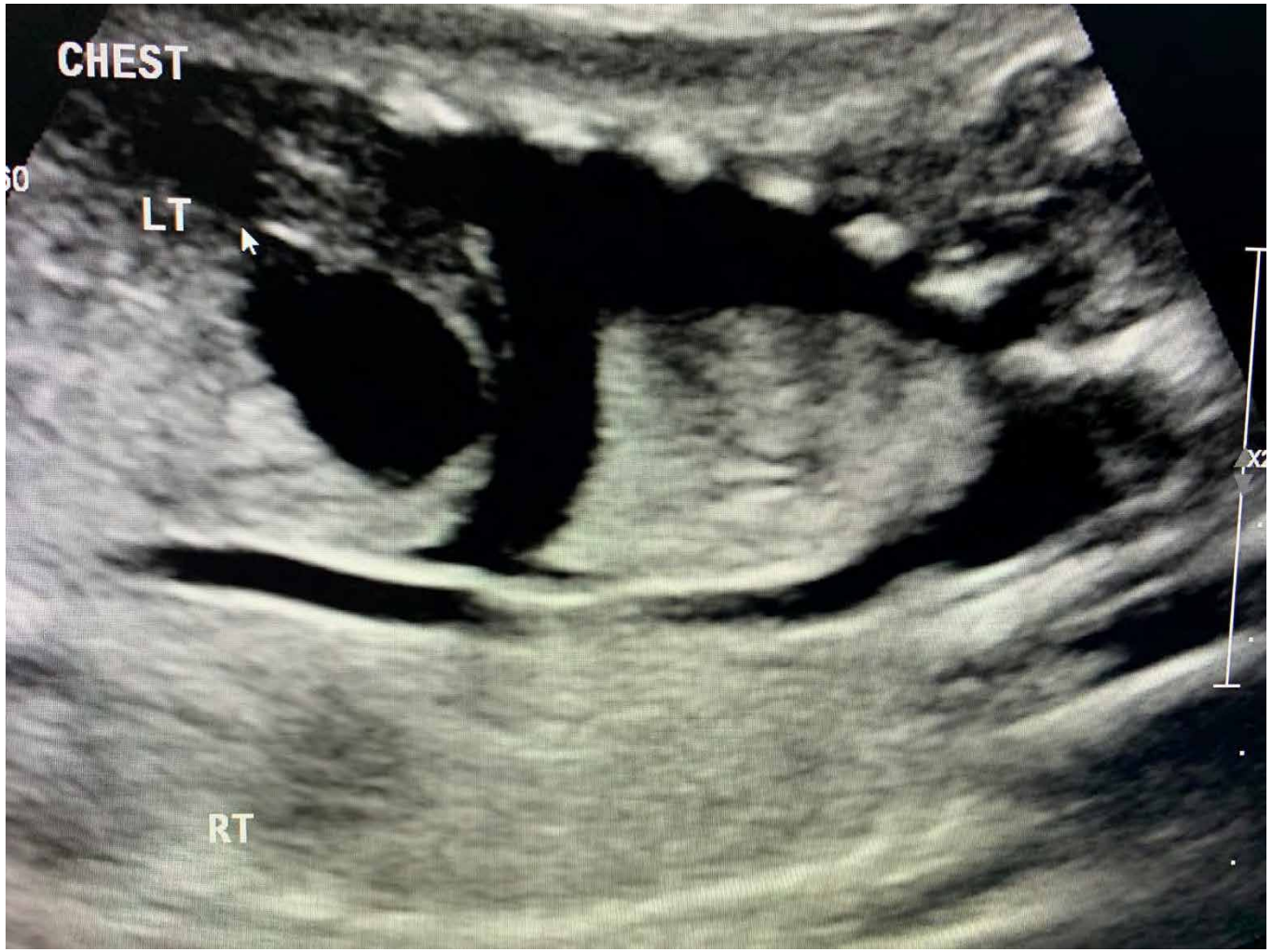

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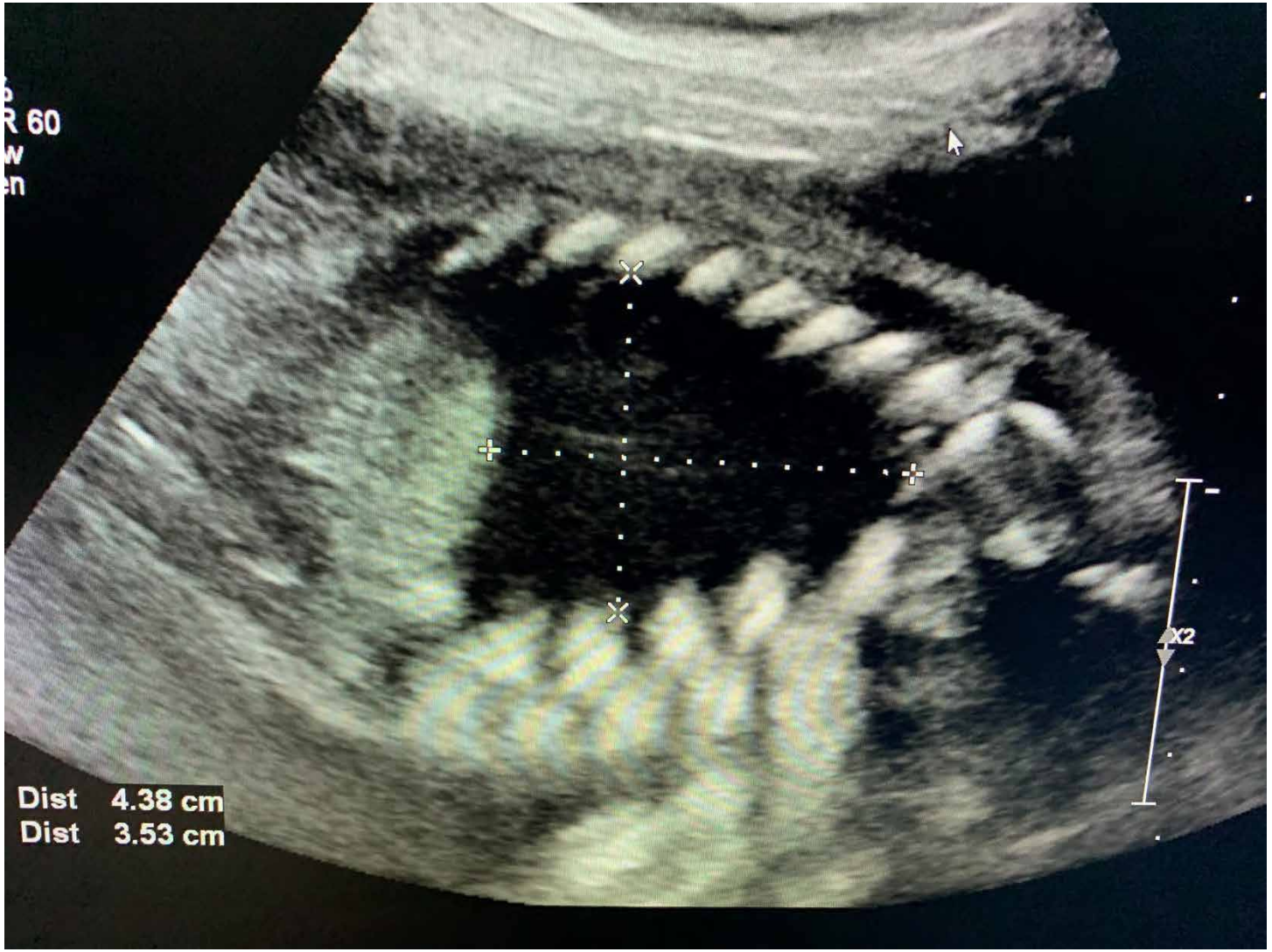
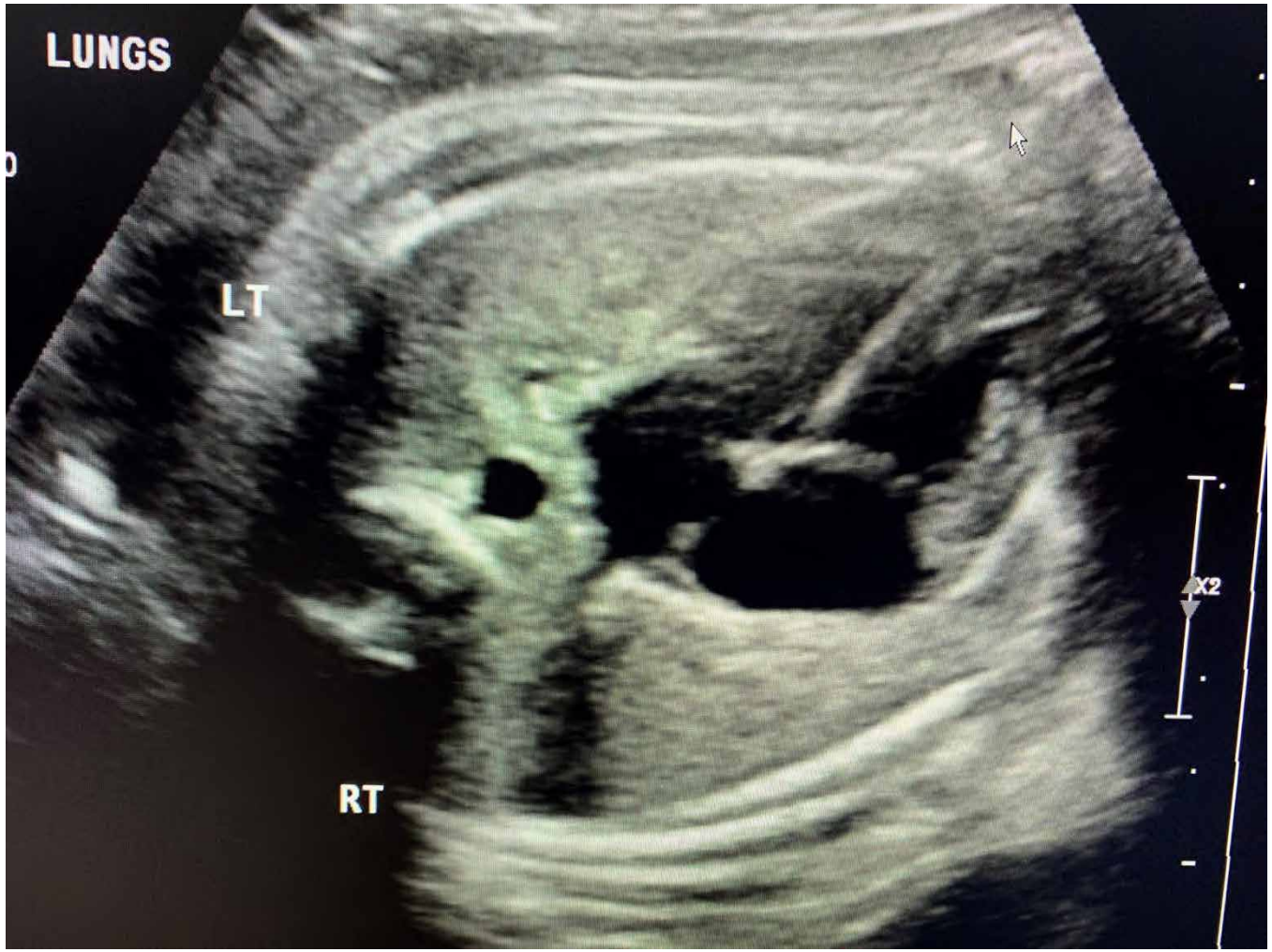


Pleural Shunt Placement



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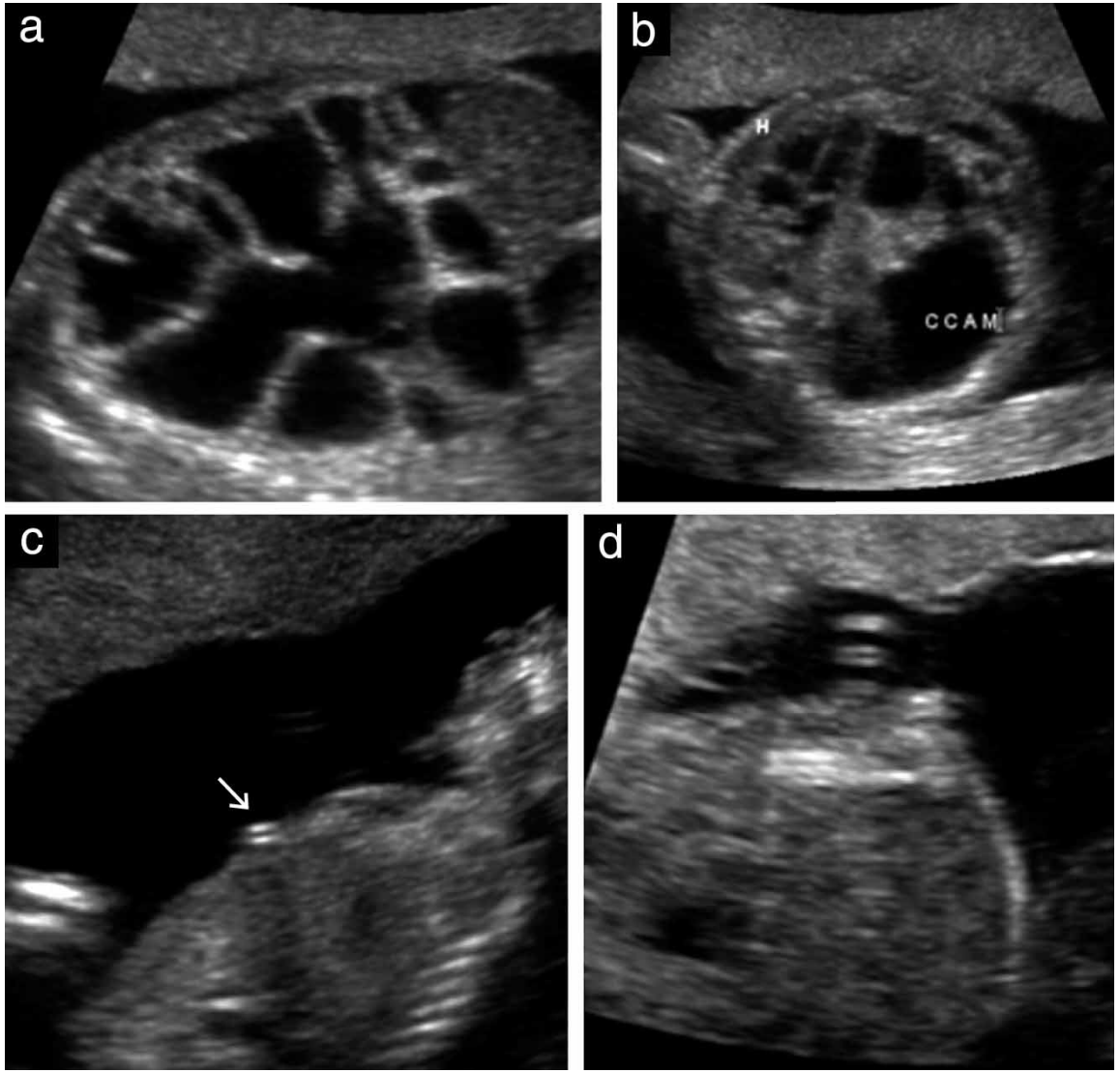
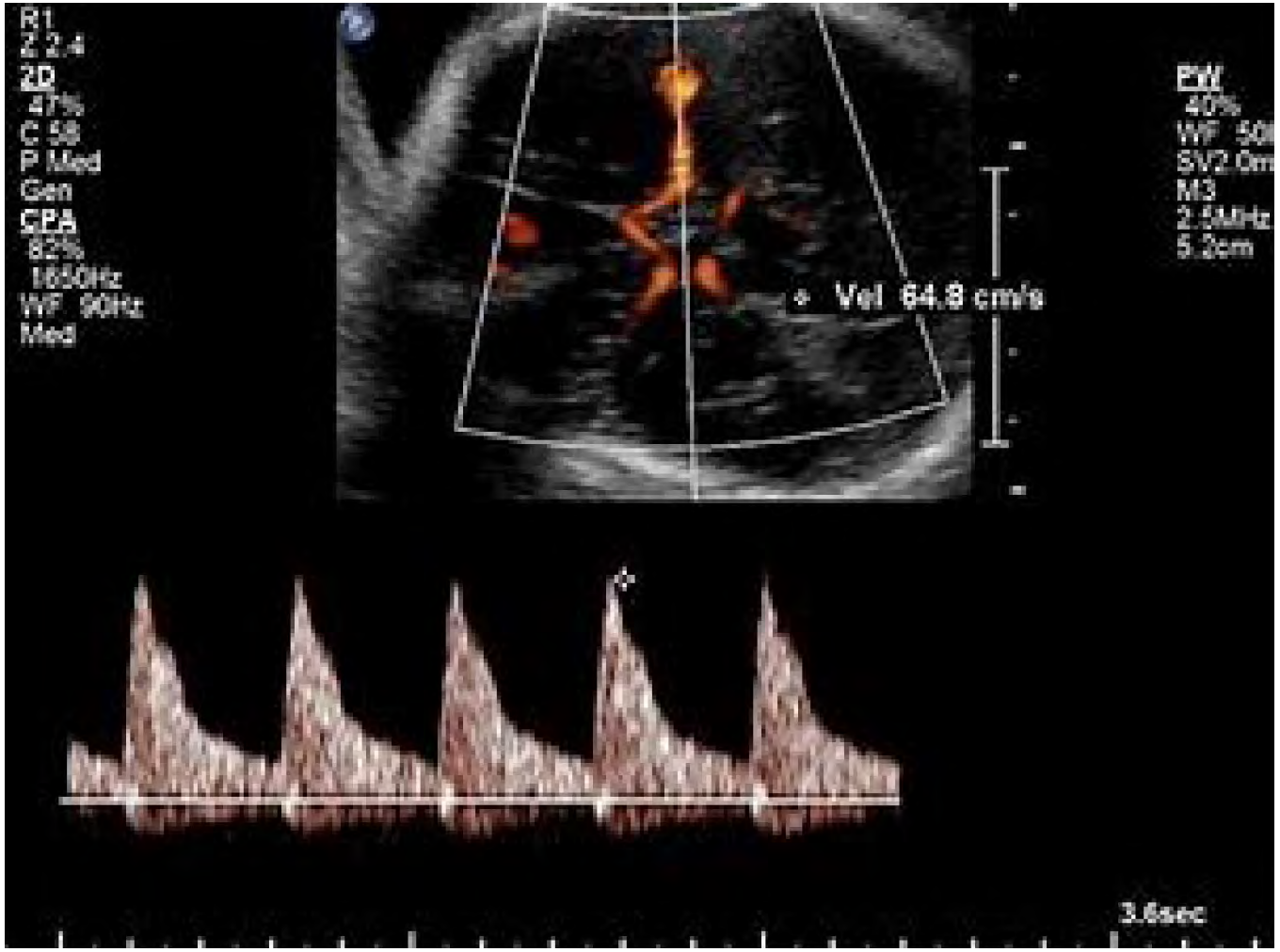
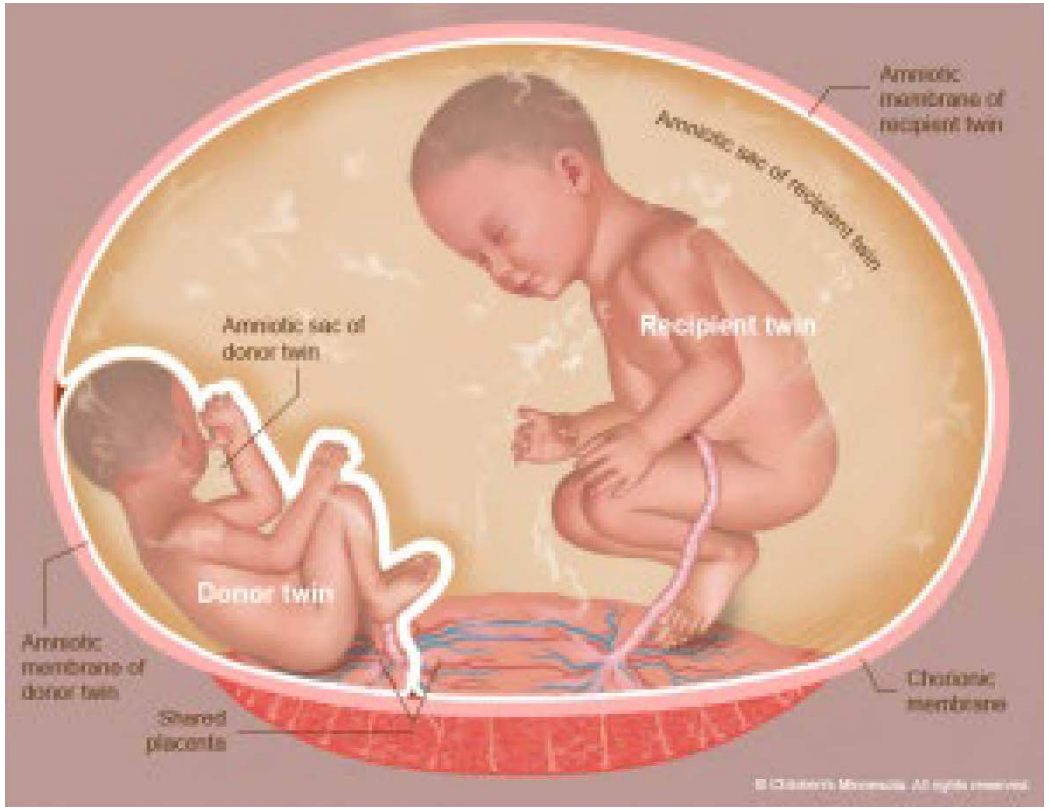


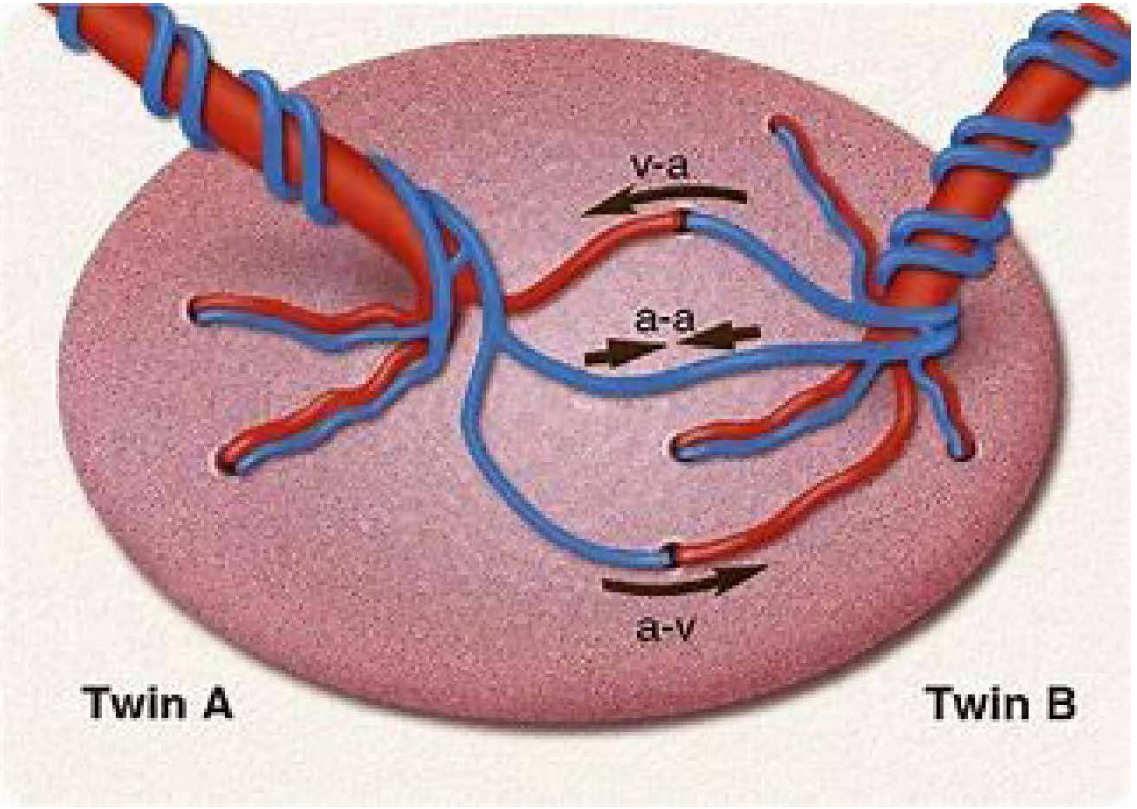
Fetal Anemia



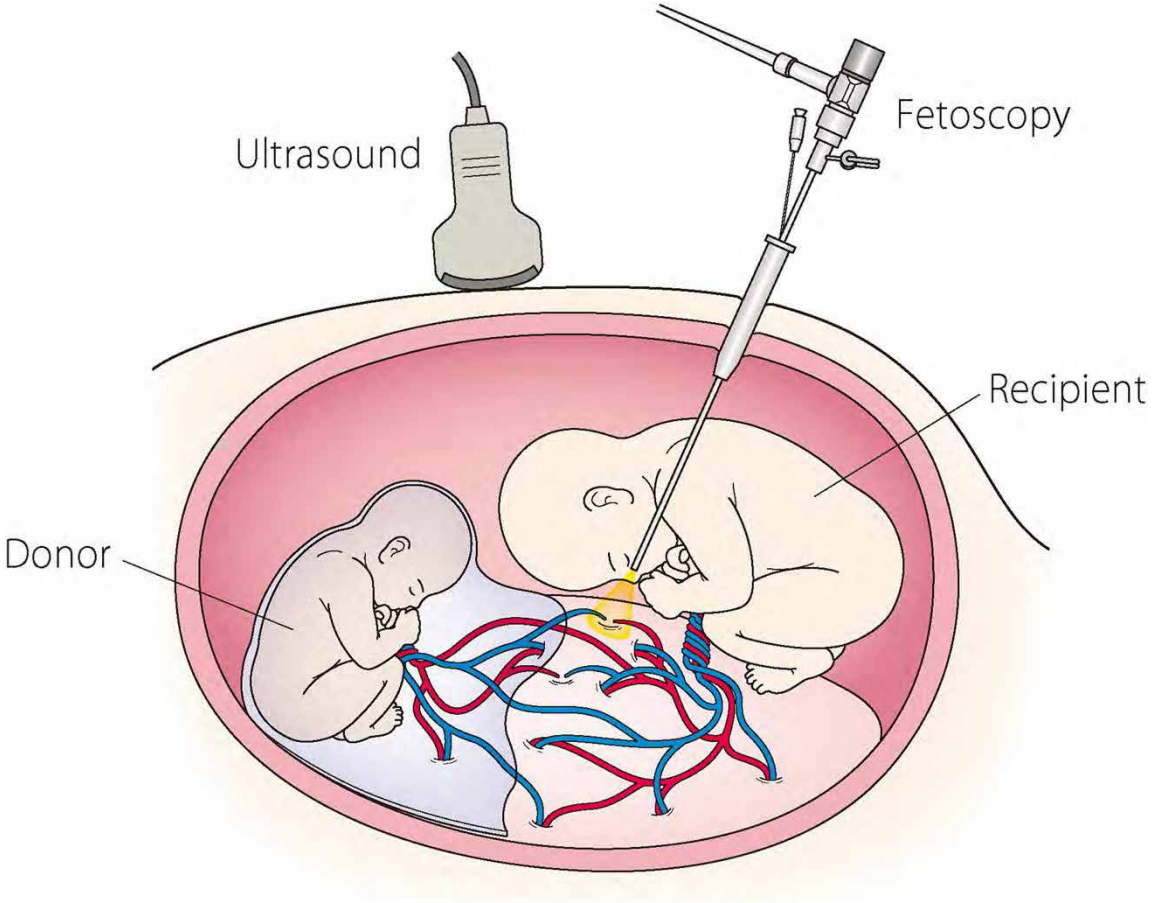
Twins!!

Monochorionic Twin Gestations and Twin to Twin Transfusion Syndrome (TTTS)

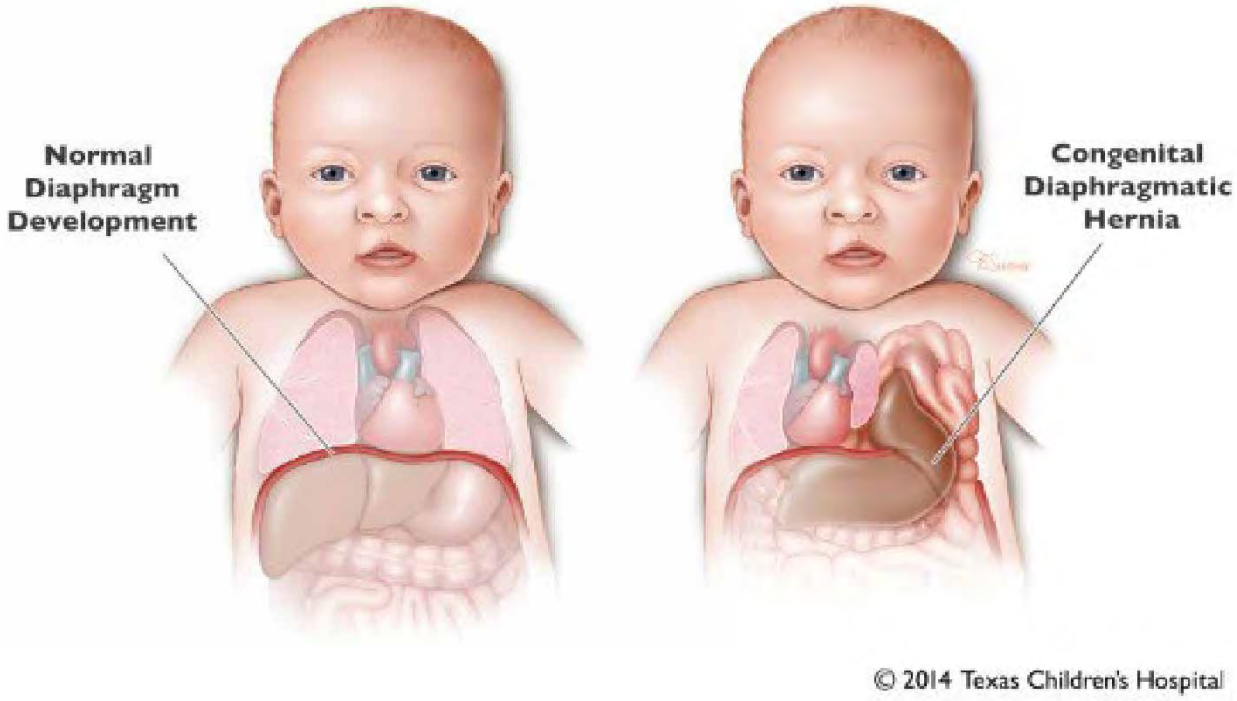


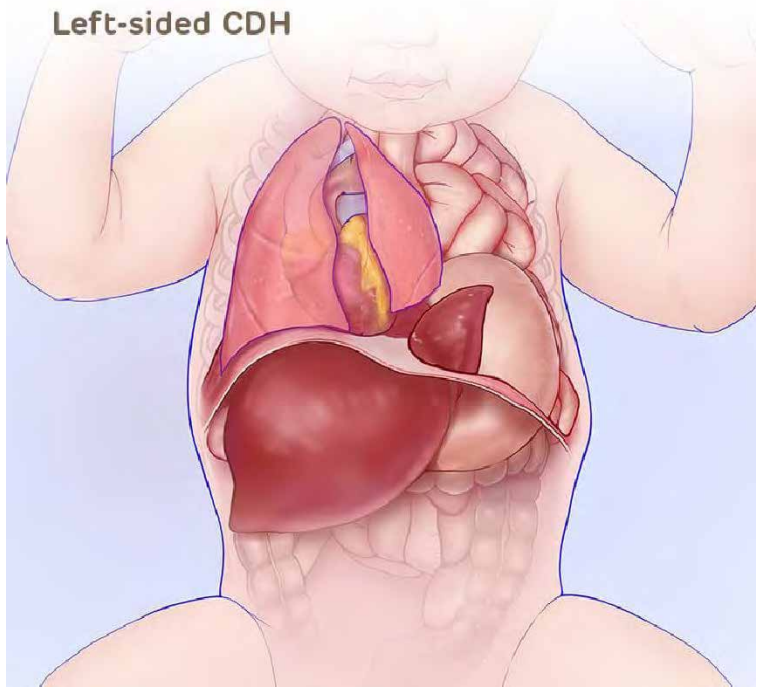


Fetoscopic Laser Ablation



Congenital Diaphragmatic Hernia





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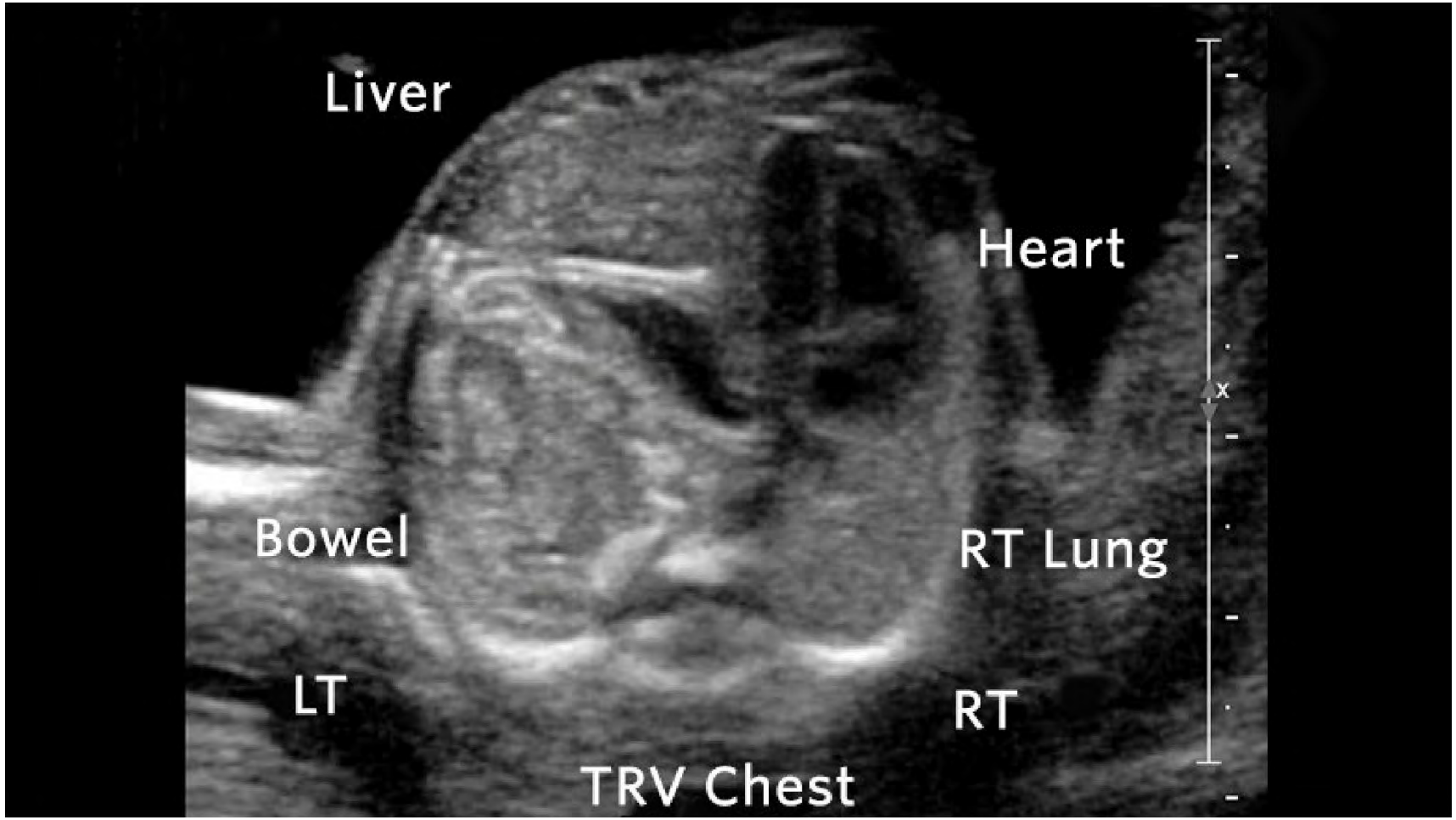
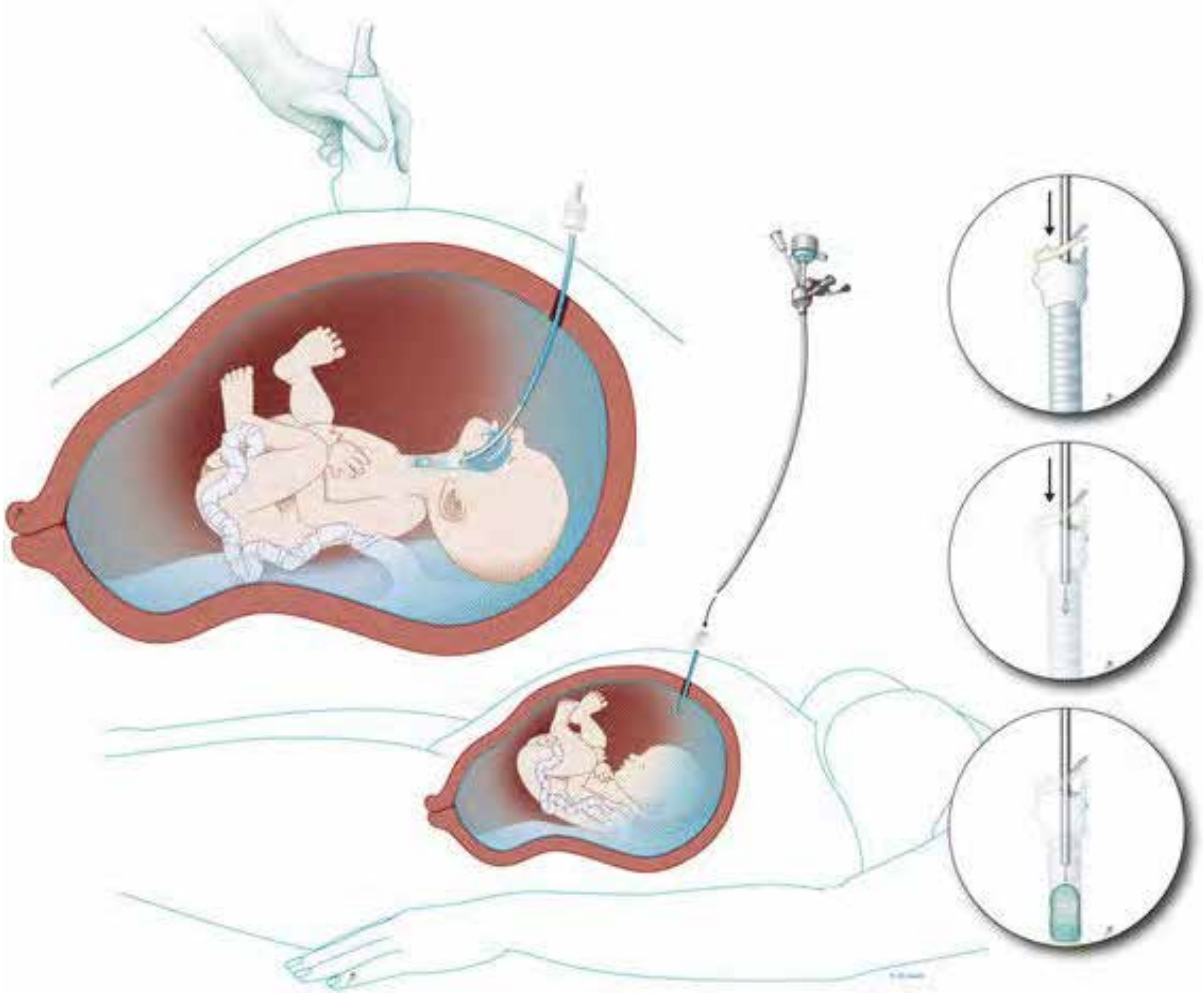


Fetoscopic Endoluminal Tracheal Occlusion (FETO)



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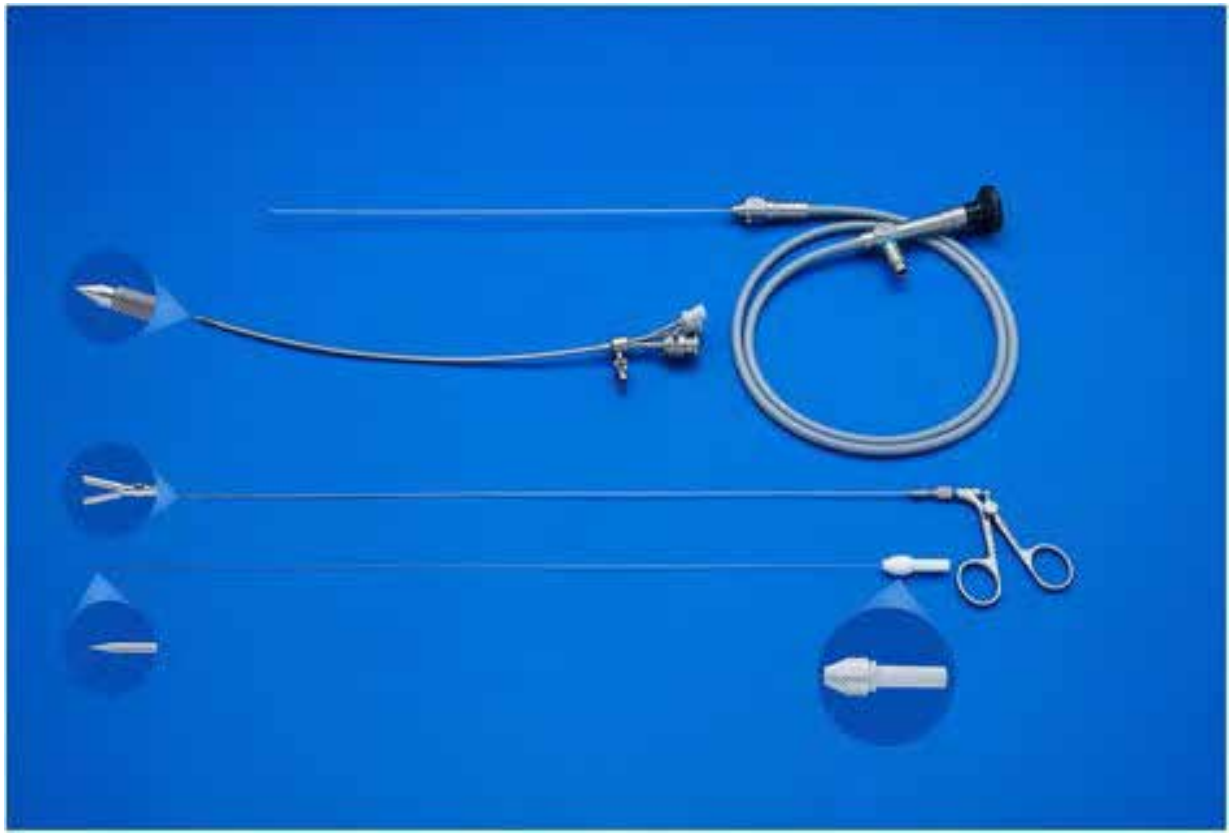

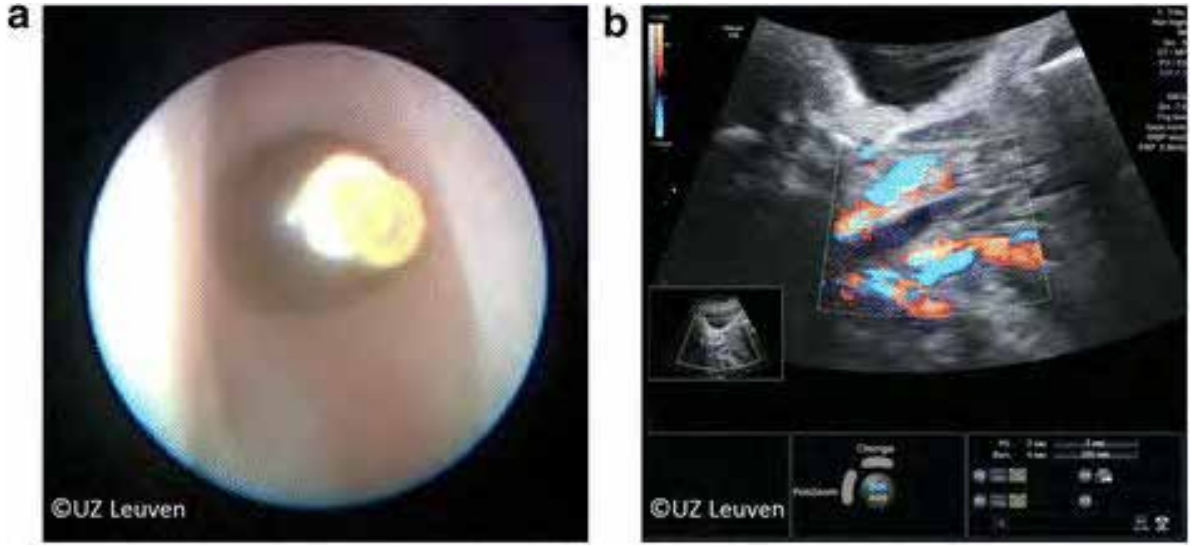

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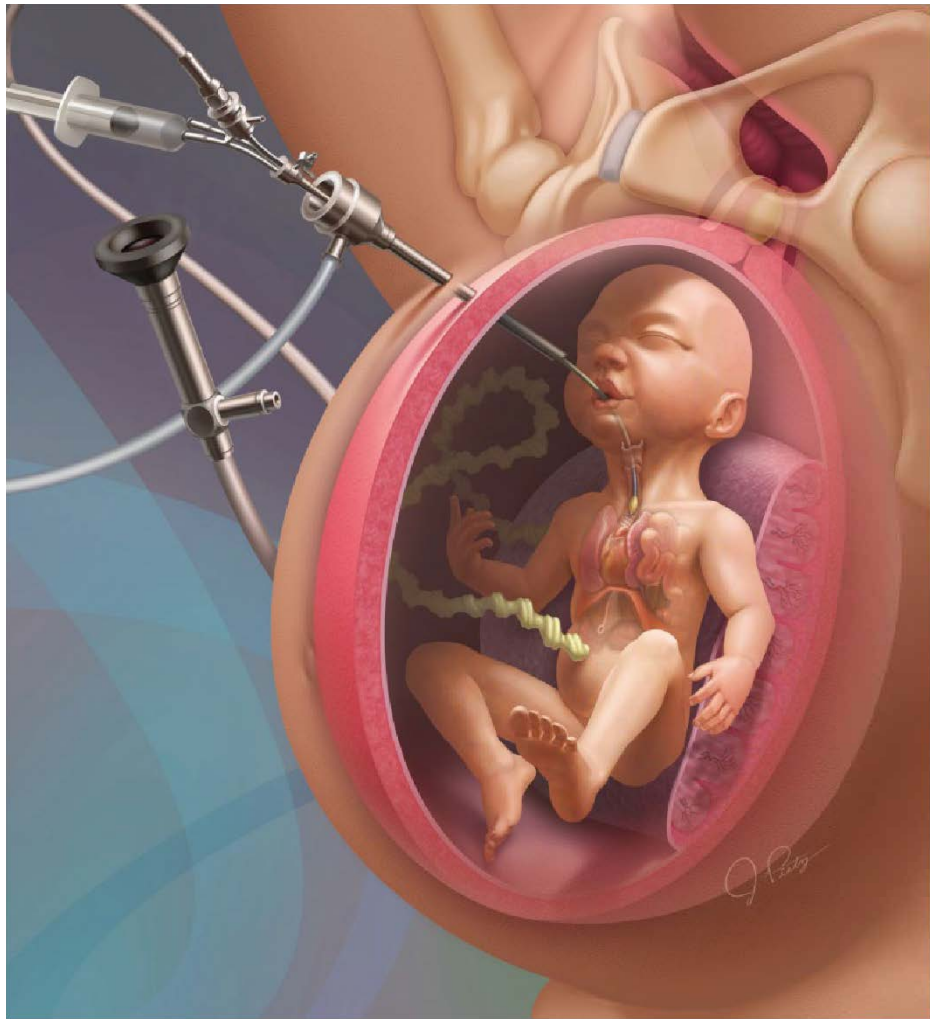

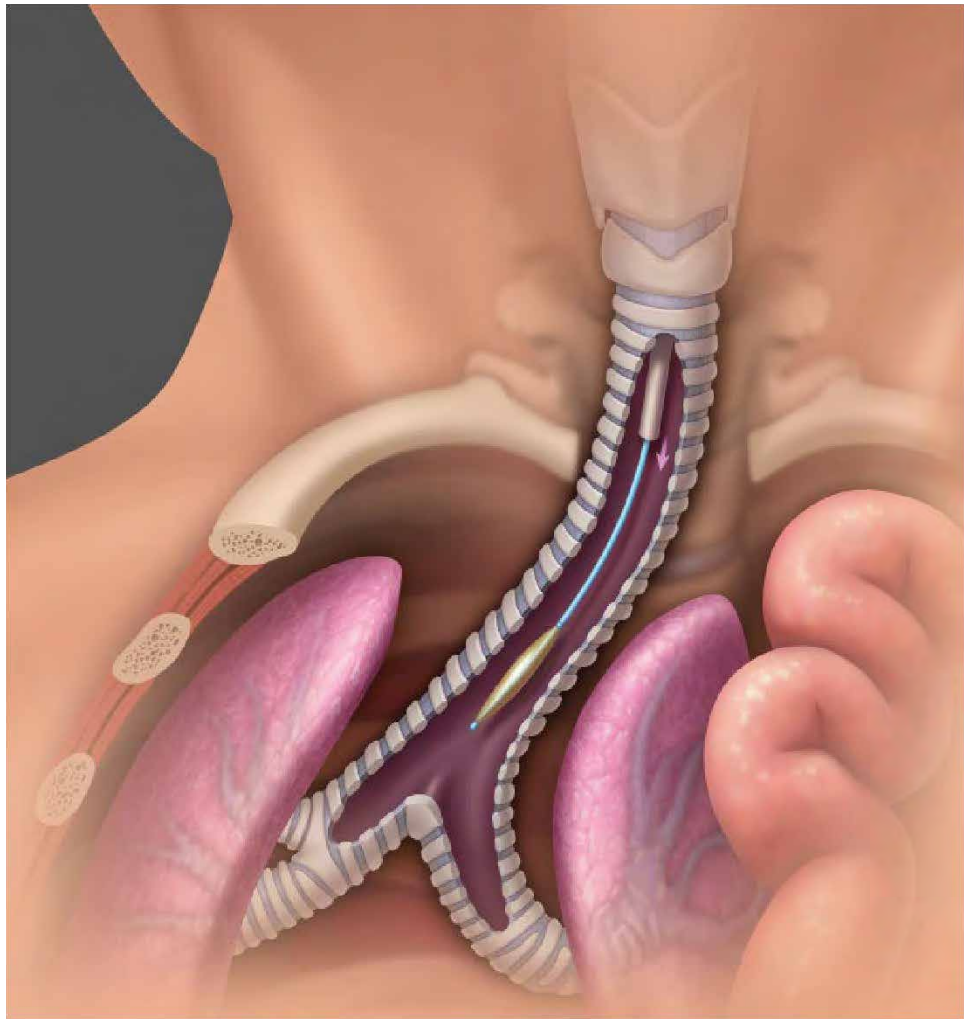

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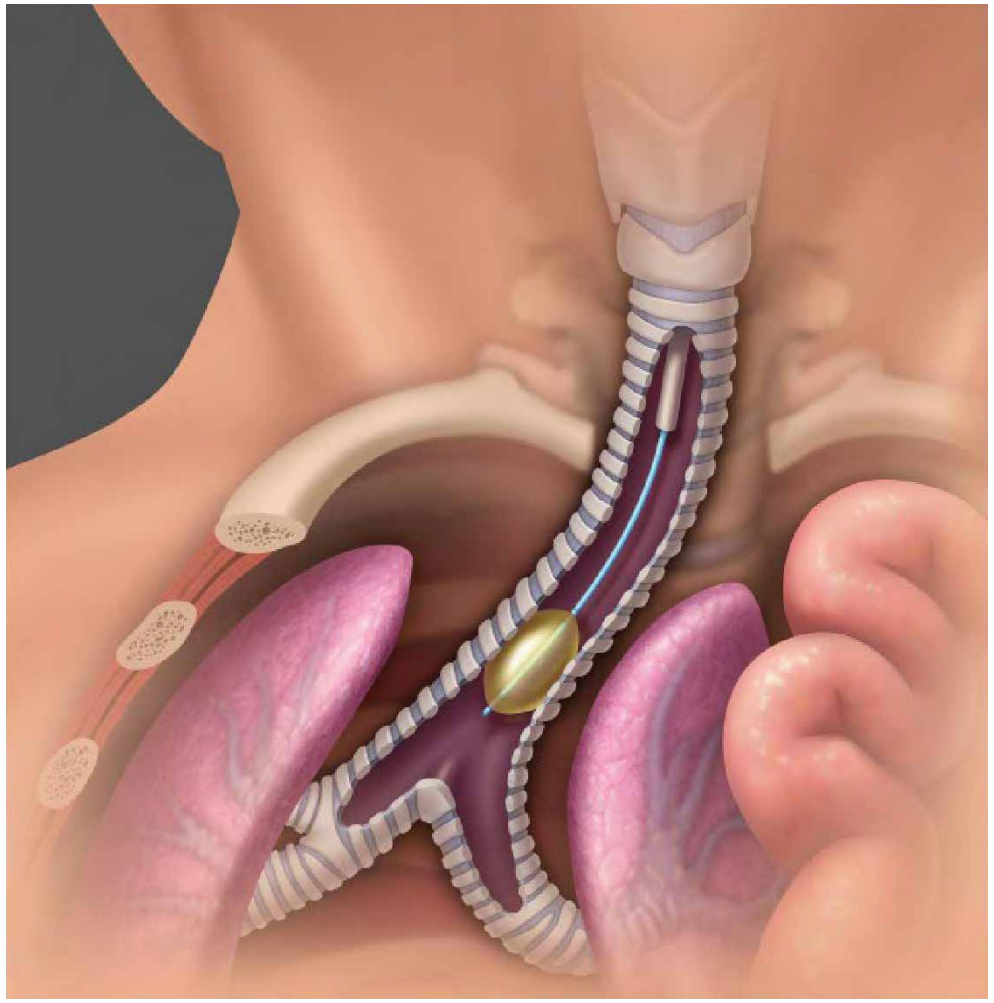

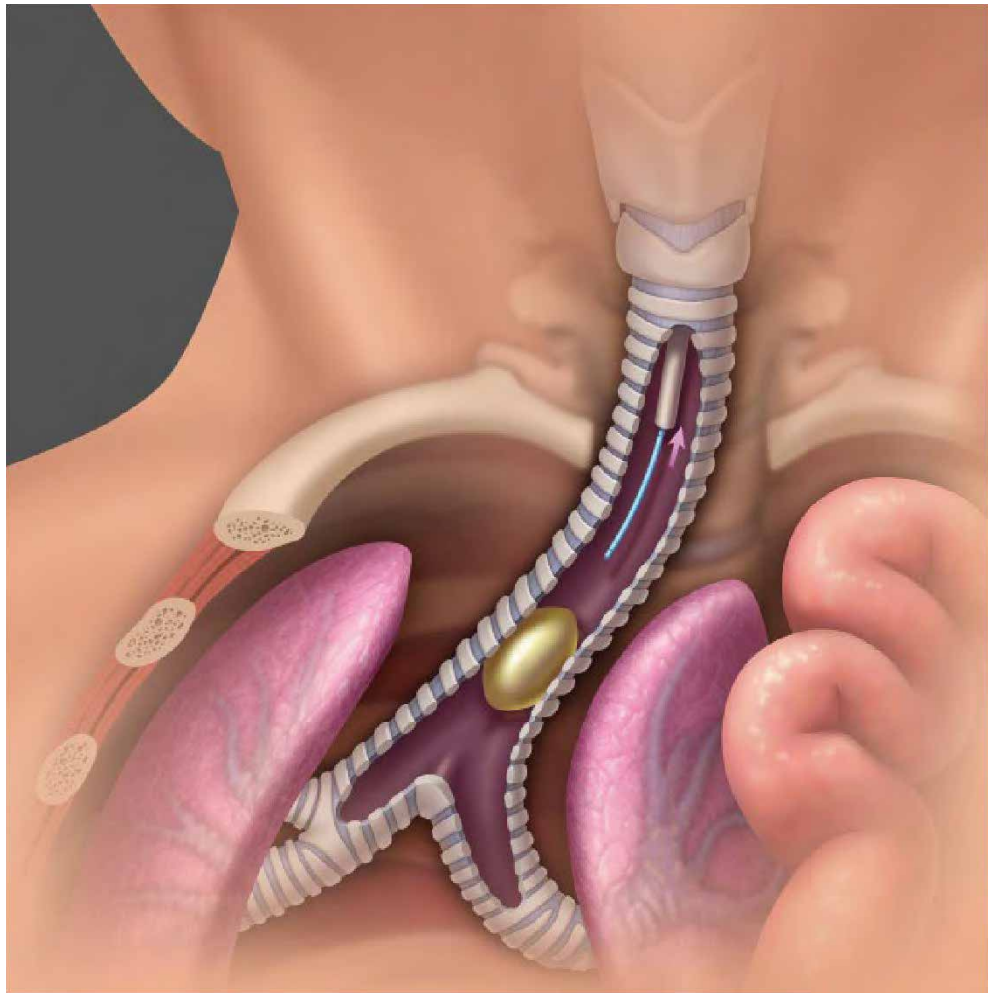

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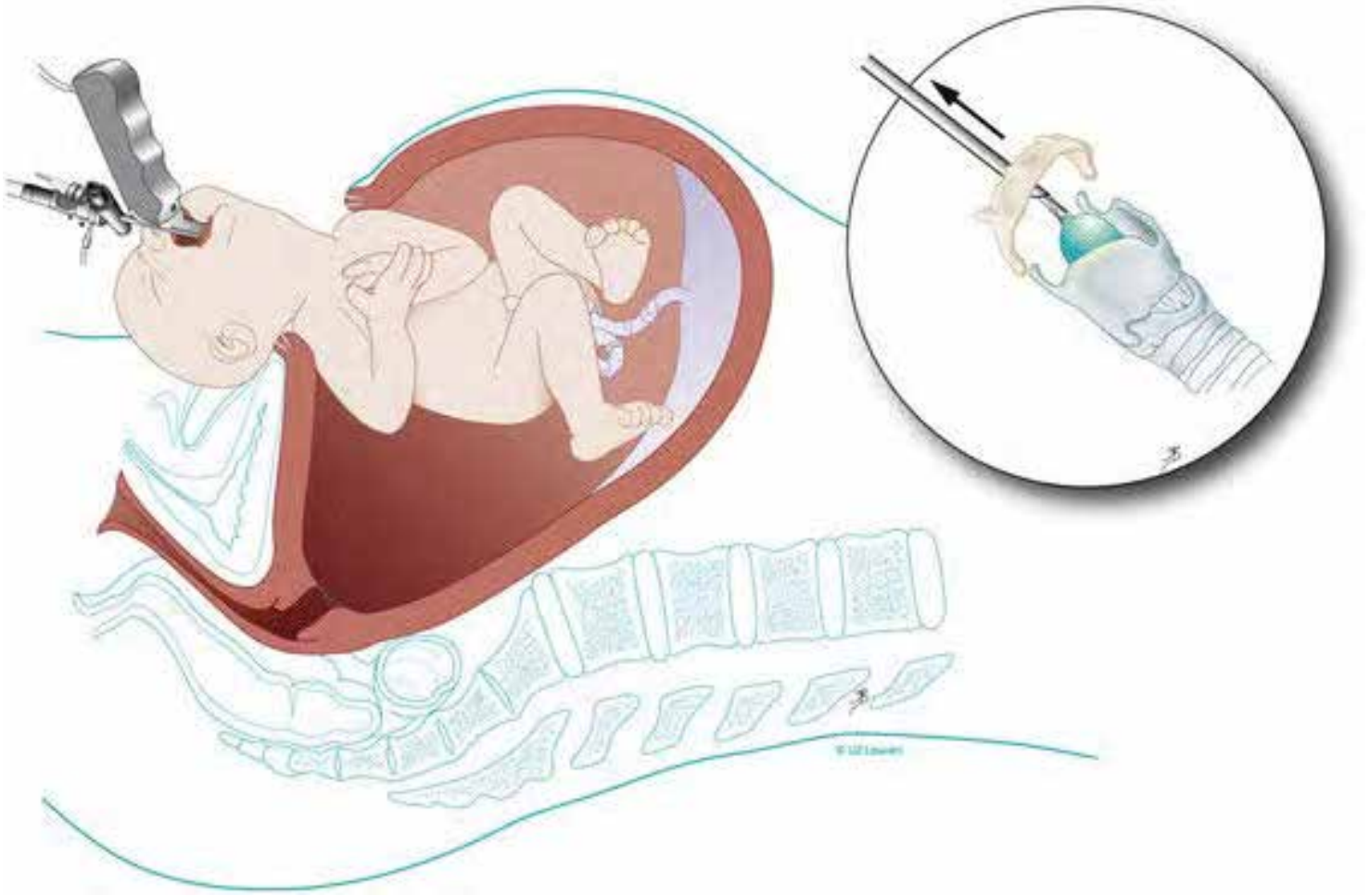
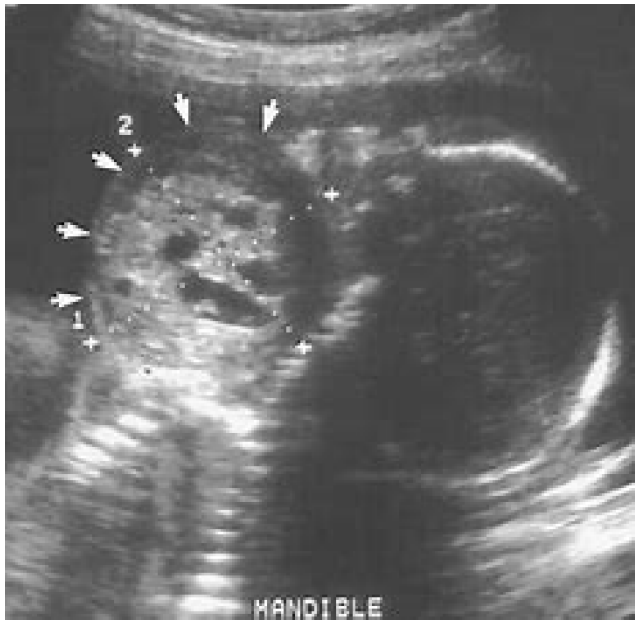


Ex Utero Intrapartum Treatment (EXIT)

- Procedure designed to maintain fetus on “placental bypass” while airway is secured
  - Initially only head/neck are typically delivered to allow exposure
- Can be used in cases of obstructive upper airway mass or compression caused by neck masses (lymphangiomas, cervical teratomas, etc.)
- Requires multidisciplinary team to manage the maternal condition while the uterus is kept open and placental circulation is maintained during the procurement of a suitable airway for the fetus/neonate
- Once ventilation is ensured, delivery of the remainder of the baby occurs

Ex Utero Intrapartum Treatment (EXIT)



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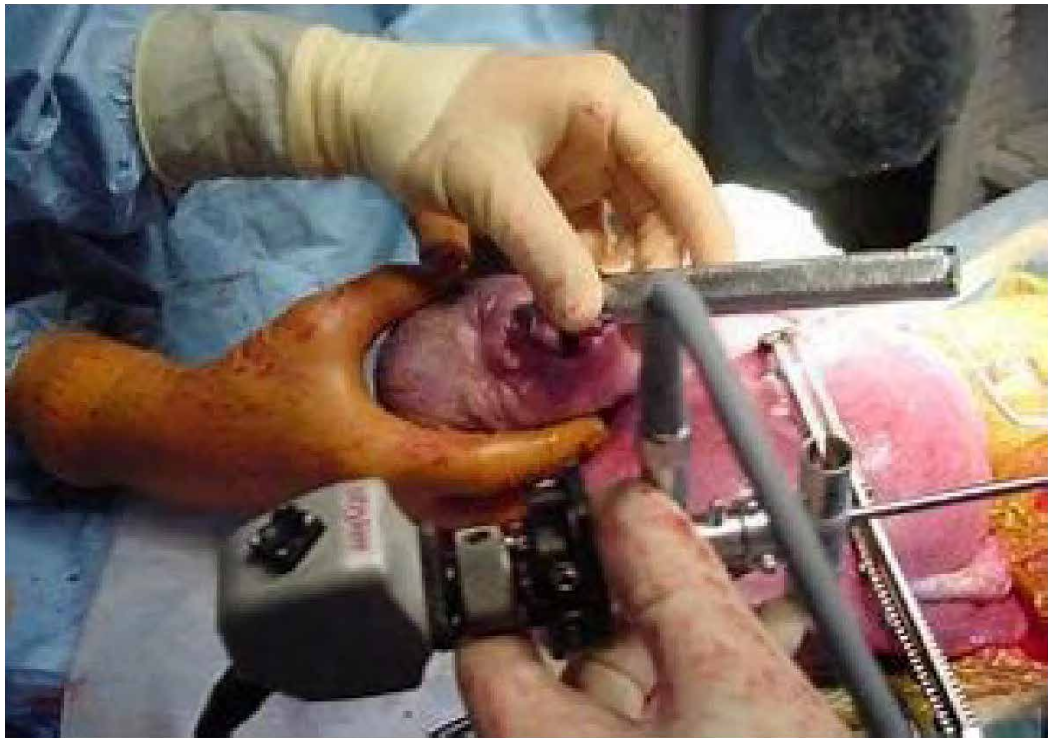
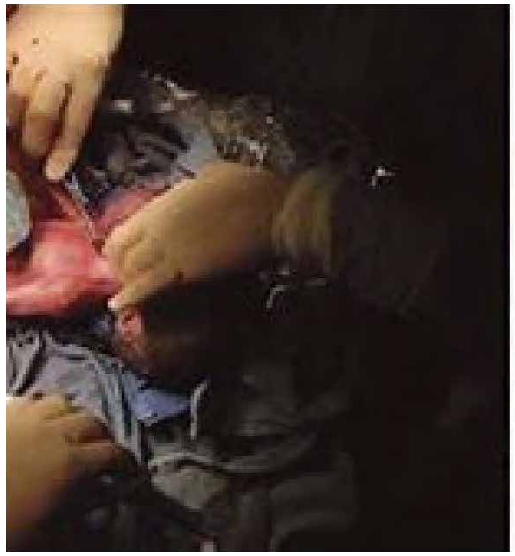


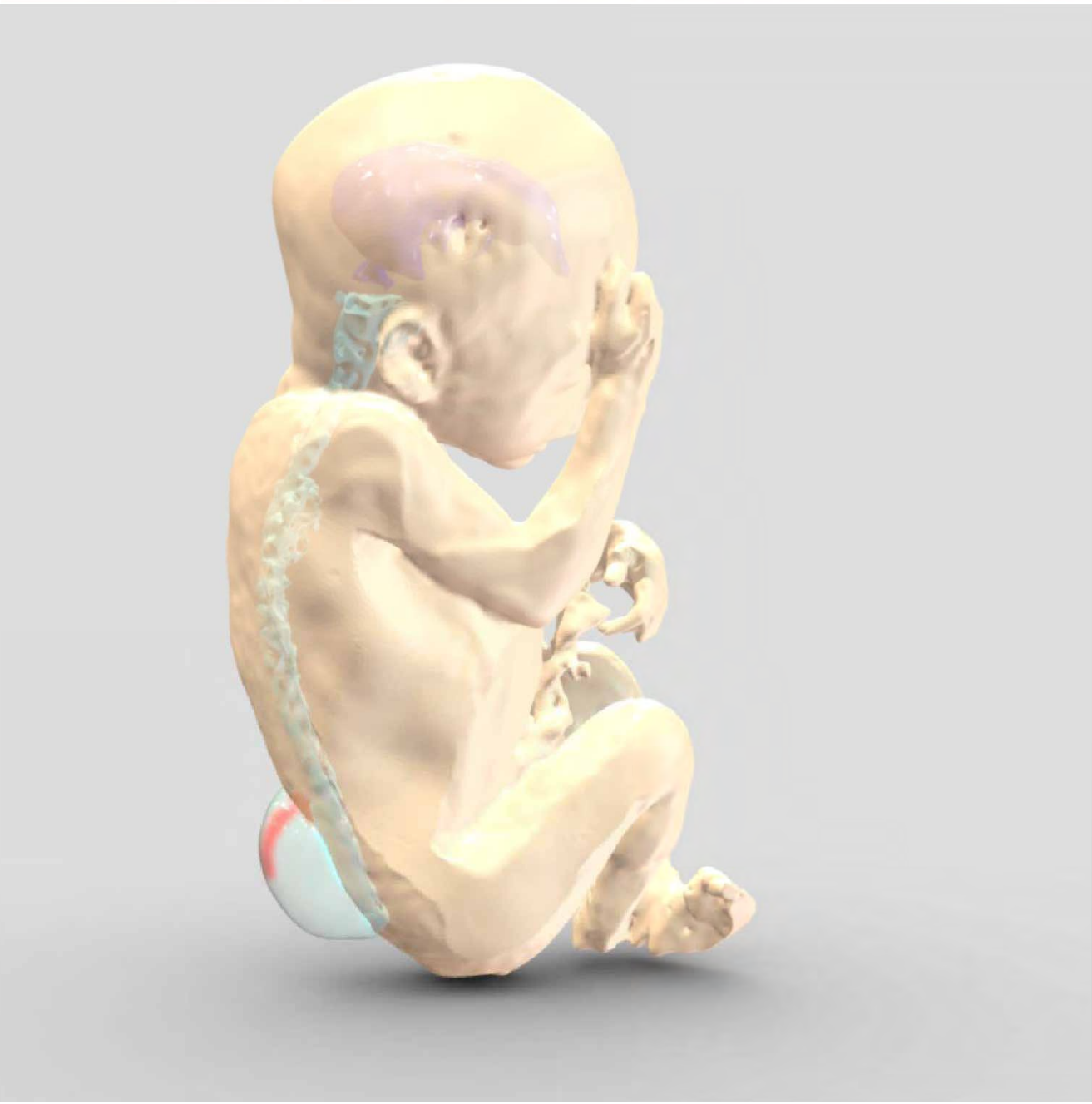


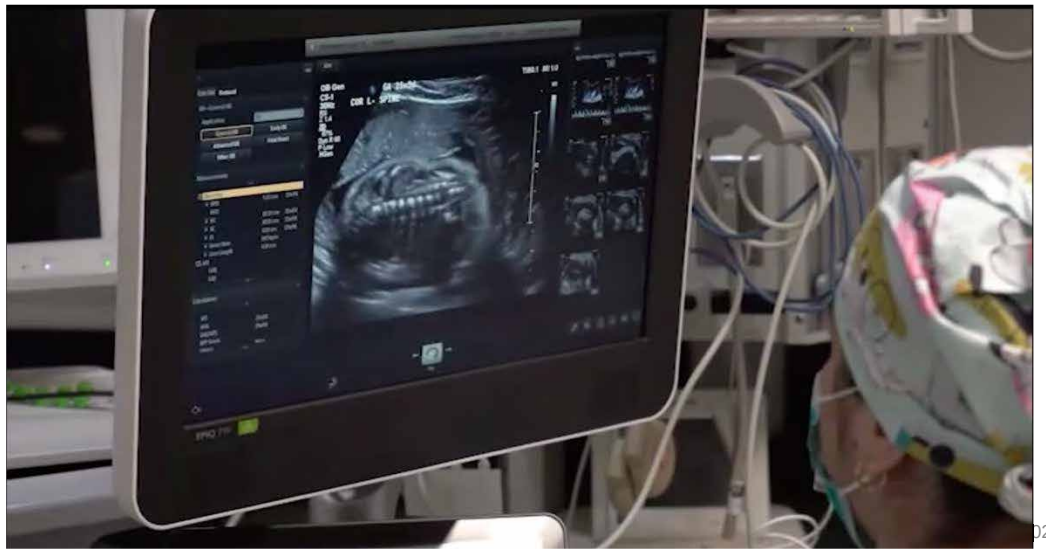
NERDS!!

3D Printing for Spina Bifida Repair – Fetal Surgery

DASH – Orlando Health's 3D Printing Partner

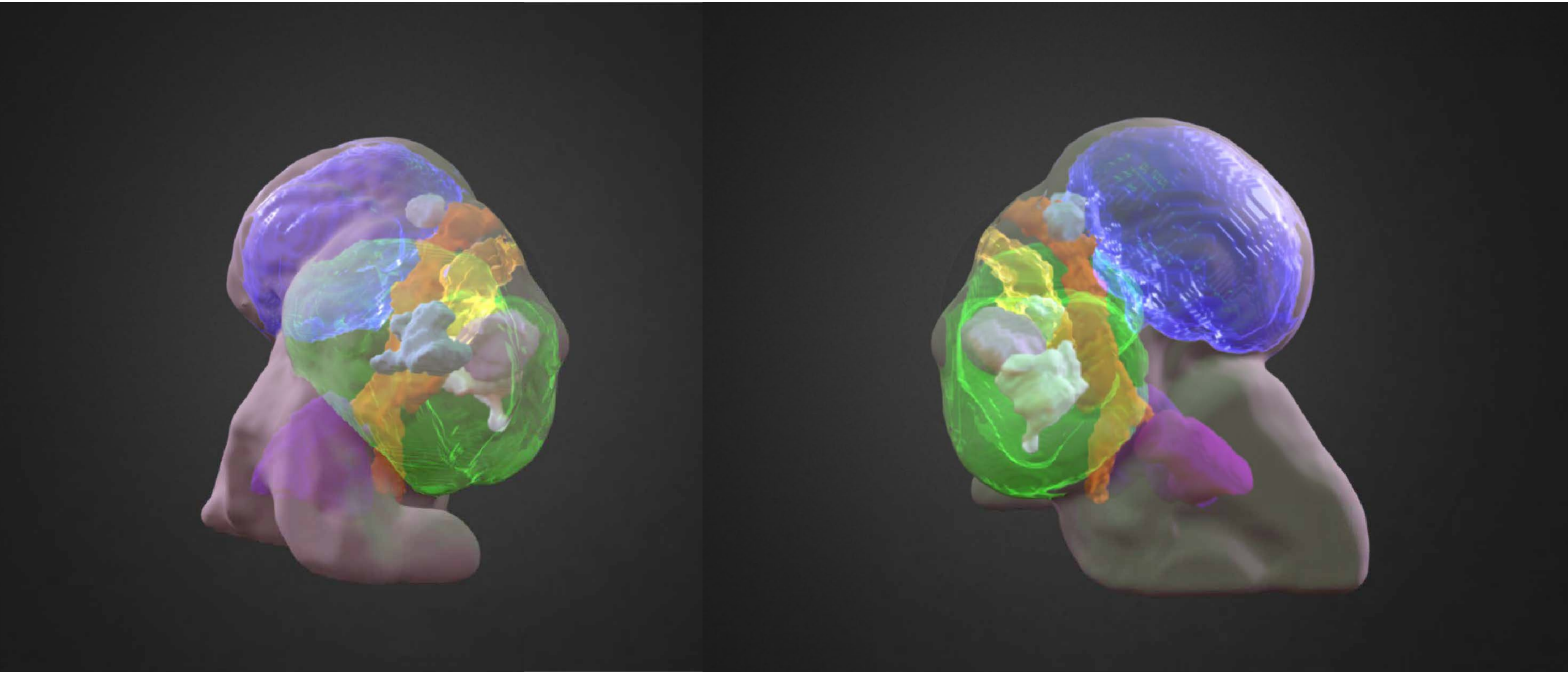
DASH





3D Visualization – Fetal Airway

3D Renderings for Airway Evaluation Before Delivery



Open Fetal Surgery to Improve Outcome…

…Everywhere

Thank You!

Open Fetal Repair of Spina Bifida in the Post MOMS Trial Era – Considerations for the Obstetrician/Perinatologist

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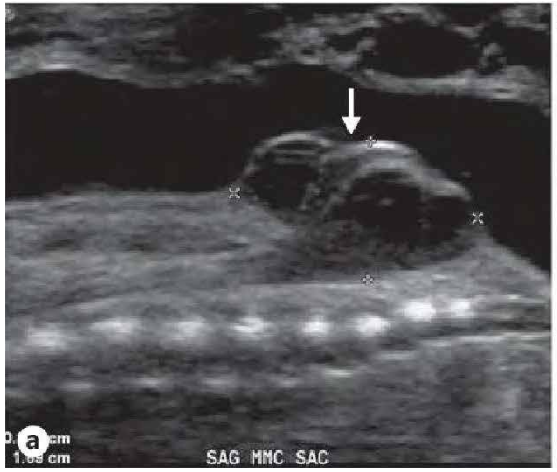
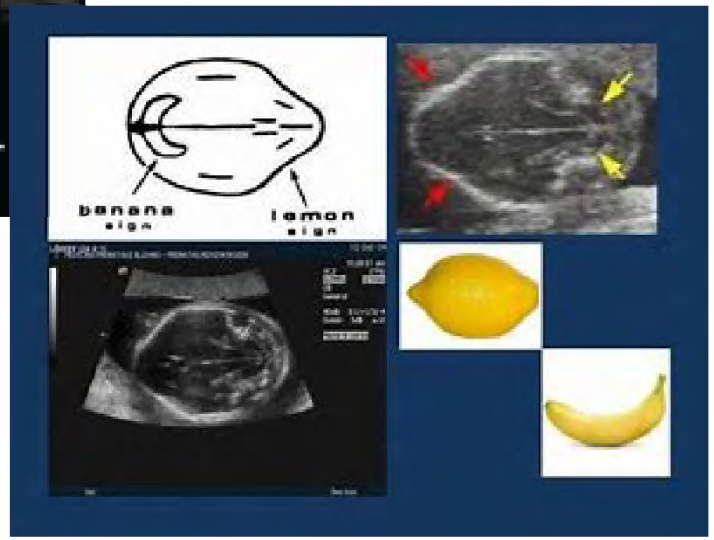
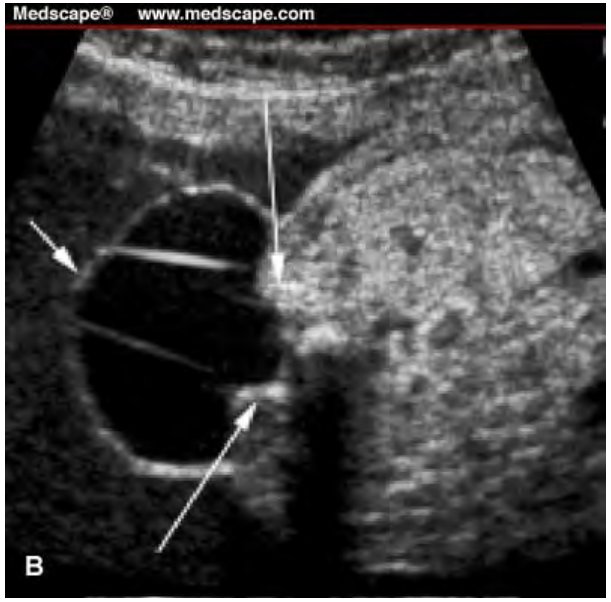
13 August 2023

Open Neural Tube Defects







Open Neural Tube Defects (Spina Bifida)

- Neural tube closure is completed 28 days from conception. The preventative effect of Folic Acid is not effective after that time period.
- Spina Bifida occurs during the first month of pregnancy when the spinal cord does not develop or close properly.
- In its most severe form, myelomeningocele, the defect leaves a section of the spinal cord and nerves exposed in a sac (or without a sac in the case of myeloschisis) on the baby's back.
- Neural tube defects need to be repaired either postnatally or antenatally.
  - There is evidence to suggest that in utero fetal repair alters the pathophysiology of the disease process and can improve outcome

Pathophysiology of Myelomeningocele/Myeloschisis

- Impact of Myelomeningocele/Myeloschisis (Intracranial)
  - Primary failure of neurulation
  - Failure of skin closure at the level of the defect
  - Negative pressure created by a loss of cerebrospinal fluid across the defect allows shifting of the brain in the cranium
  - Resulting shifting of the brain leads to hindbrain herniation – Chiari II Malformation
  - Chiari II Malformation prevents normal circulation of cerebrospinal fluid
  - ”Trapped” CSF within the ventricles leads to ventriculomegaly/hydrocephalus

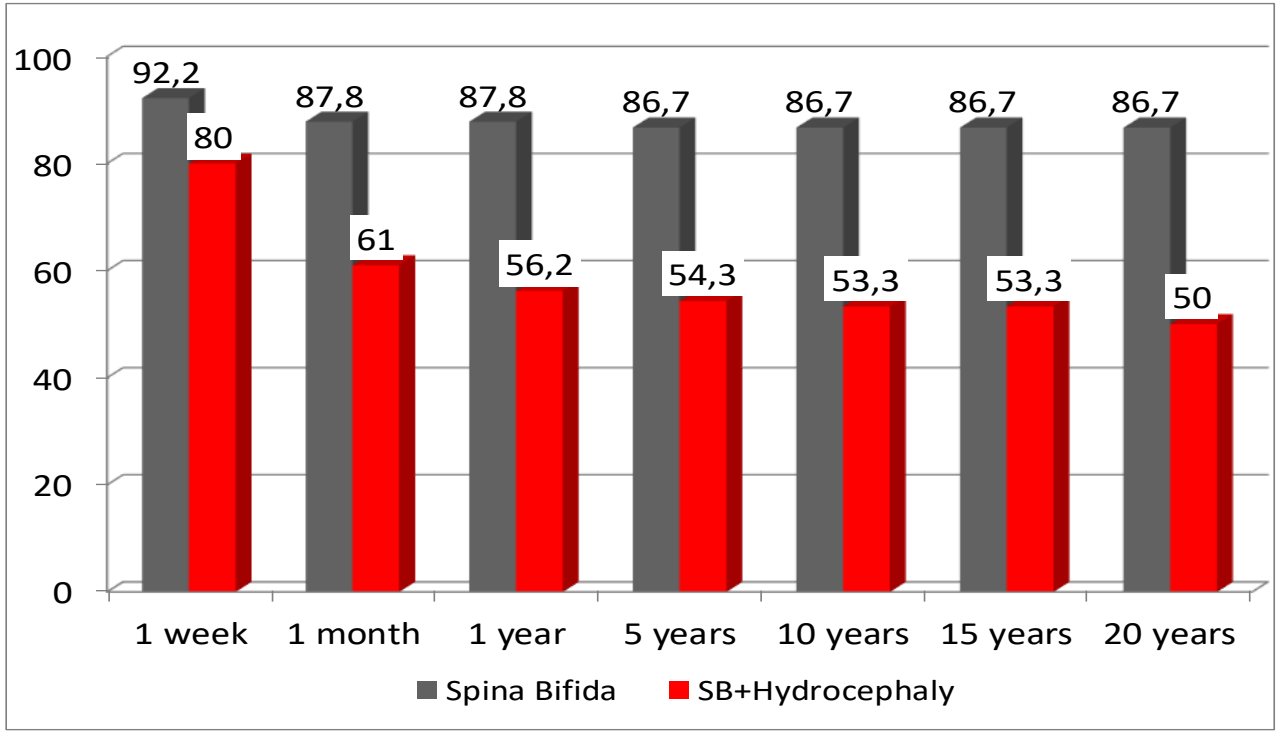
- Impact of Myelomeningocele/Myeloschisis (Extracranial)
  - Exposure of neural tissue to amniotic fluid can be damaging
  - Mechanical trauma
  - Traction on cord at attachment to defect can exacerbate hindbrain herniation with fetal growth

Myelomeningocele and Myeloschisis Repair

- Myelomeningocele/Myeloschisis were the first non-lethal anomalies to be treated by open fetal surgery
  - Approximately 1500 babies born each year with spina bifida in the United States
  - Incidence of about 1 in 2750 live births
    - Slightly higher in the Hispanic population
      - 3.8 per 10000 live births (vs 2.7 for Black and 3.1 for Non-Hispanic White populations)
  - Hydrocephalus can result in 80-90% of cases (if untreated in utero)
    - Can lead to shunt dependence and related complications/challenges
    - Cerebellar and respiratory impairment
  - In addition to neurocognitive impact, motor, orthopedic, urinary, gastrointestinal and sexual impairment is common

Hydrocephalus and Long-Term Survival with Spina Bifida

- Presence and severity of hydrocephalus is the major determinant of long-term survival
- Fetal therapy presents the chance to improve outcome through a reduction in shunt dependent hydrocephalus



Tennant PWG et al . 20-year survival of children born with congenital anomalies. A population-based study. Lancet 2010;375:649-56

Myelomeningocele and Myeloschisis Repair

- Repair in utero is based on altering the “two hit” nature of Myelomeningocele/Myeloschisis
  - Reverse the pathophysiology of disease
  - Close the spinal defect stopping the negative pressure phenomenon
  - Reverse the hindbrain herniation and allow cerebrospinal fluid to resume flow
  - Simultaneously protect neural elements of the cord through adequate closure of the defect

Open Fetal Surgery for Myelomeningocele

- Management of Myelomeningocele Study (MOMS)
  - Randomized, controlled trial comparing prenatal and postnatal repair
  - A total of 183 eligible women underwent randomization between February 2003 and December 2010
  - Designed to assess improvement at 12 and 30 months of life
    - Reduction in hindbrain herniation and shunt dependent hydrocephalus
    - Improvement in functional neurological outcomes
  - Fetal surgery performed at three centers
    - Children's Hospital of Philadelphia
    - Vanderbilt University
    - University of California, San Francisco
  - Fetal surgery was halted elsewhere during the study window
  - **Trial was stopped early due to efficacy**

Concerns Surrounding the MOMS Trial

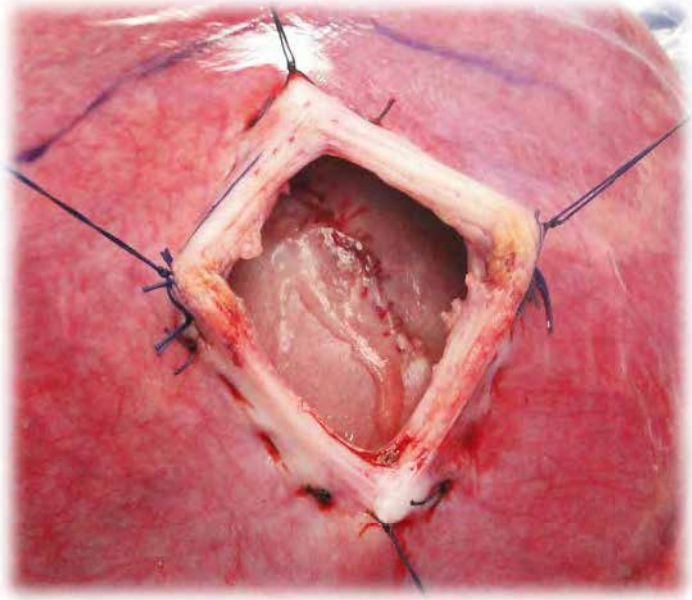
- Mean Gestational Age at Birth – 34.1 vs 37.3
- Preterm Birth – 79% vs. 15%
  - < 30 weeks – 13% vs. 0%
  - 30-34 weeks – 33% vs. 5%
  - 35-36 weeks – 33% vs. 10%
  - >/= 37 weeks – 21% vs. 85%
- Preterm Premature Rupture of Membranes – 46% vs. 8%
- Oligohydramnios – 21% vs. 4%
- Weakening or dehiscence of uterine hysterotomy
- Chorioamniotic membrane separation and placental abruption
- Perinatal Death – 2 in each arm
- No maternal deaths during study period

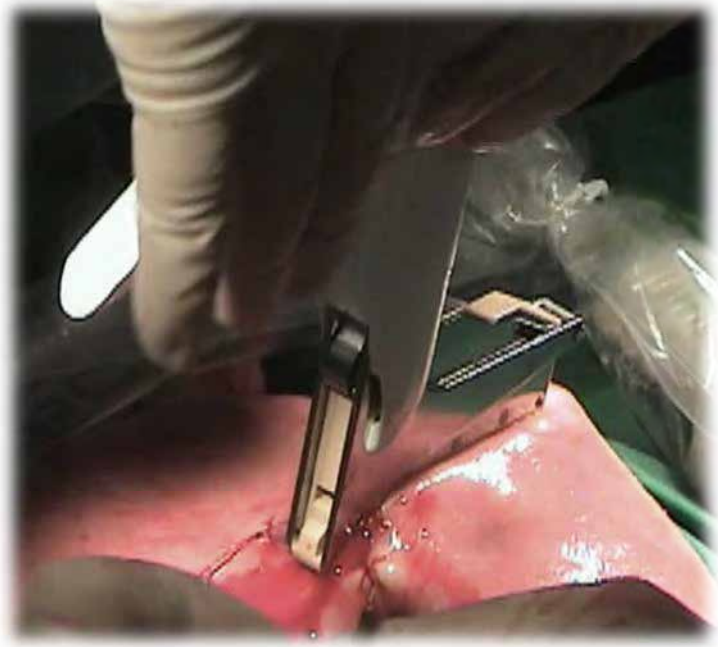
Adzick NS et al. A **R**andomized Trial of **P**renatal Versus **P**ostnatal **R**epair of **M**yelomeningocele N Engl J Med 2011; 364: 993-1004

Background in Florida

- 1500-2,000 cases per year in US
- Florida births per year: Approximately 225,000
- Evaluated 82 cases since May of 2018
  - 39 Surgeries Performed
  - 3 Currently Pregnant (late third trimester)
  - Terminations of Pregnancy
  - Exclusions / Failure to meet Inclusion Criteria

- Issues with Stapler
- Alternative methods for open fetal surgery



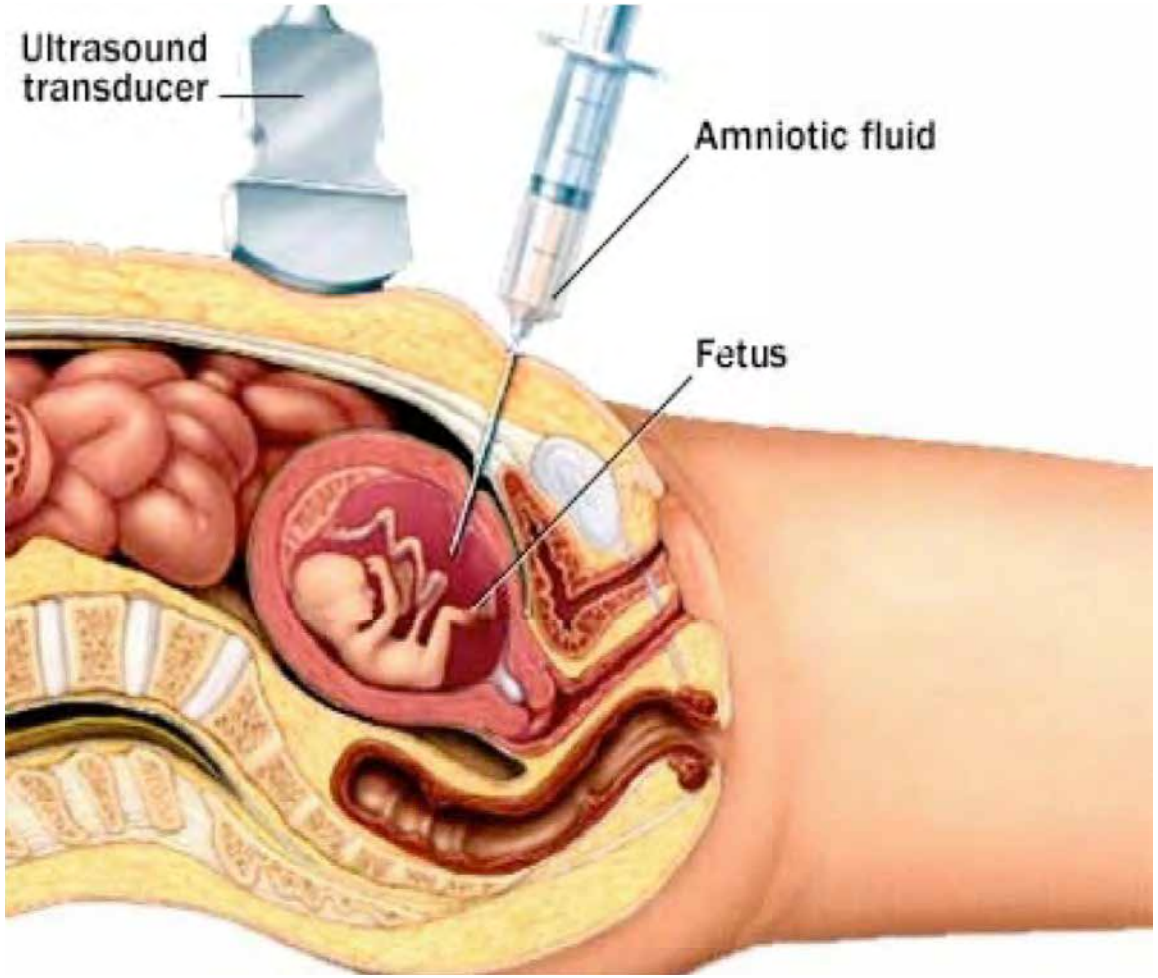


Inclusion / Exclusion Criteria

- **Inclusion criteria**
  - Singleton
  - Less than 26 weeks' gestation
  - Upper myelomeningocele boundary at T1-S1
  - Evidence of hindbrain herniation
  - Normal karyotype and no other malformations
  - BMI < 35/40
  - Low risk for preterm birth

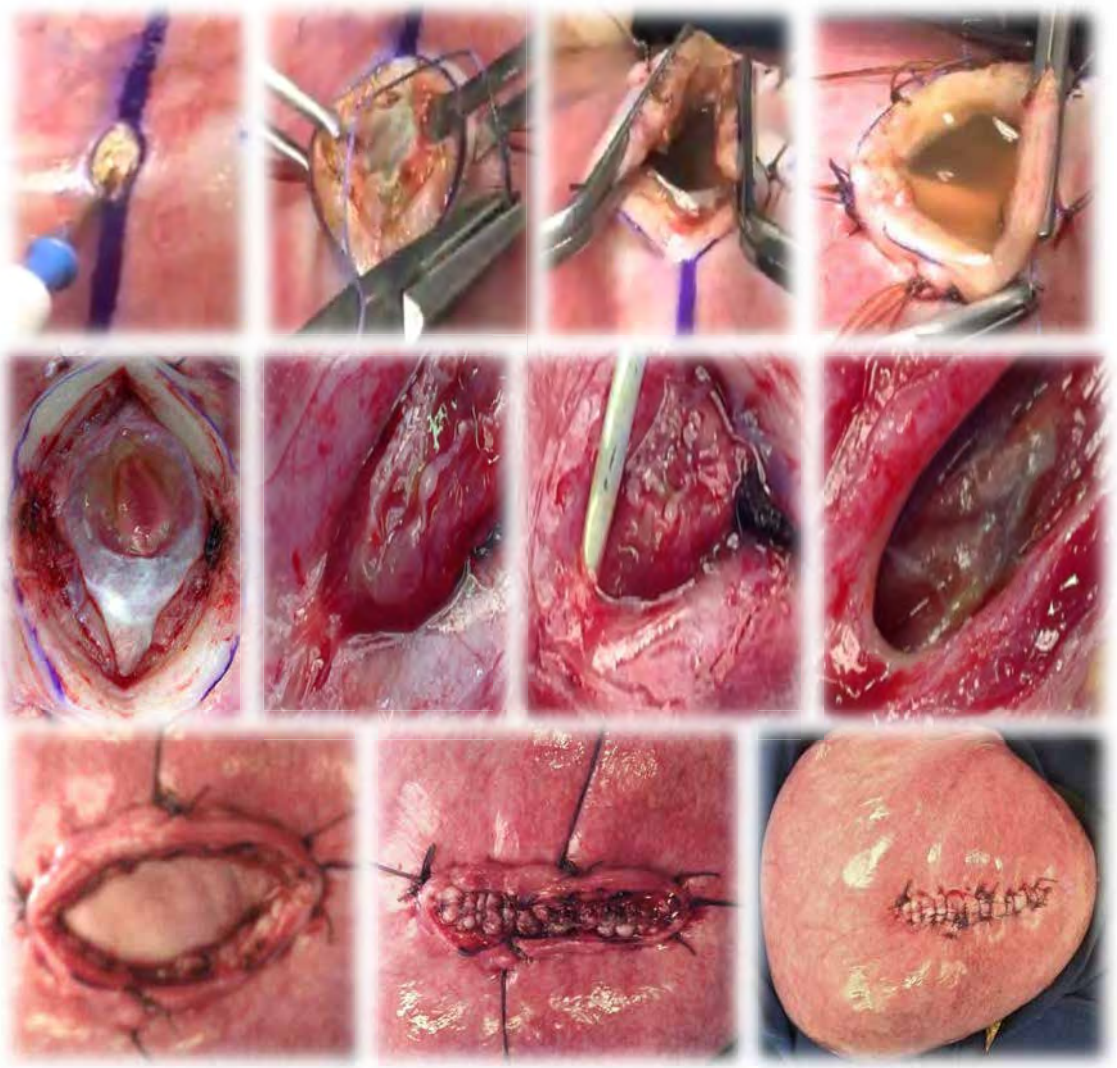
Inclusion / Exclusion Criteria

- **Exclusion Criteria**
  - Gestational age >/= 26 weeks
  - Fetal kyphosis or other associated malformation
  - Increased risk for preterm delivery
  - Maternal hypertension, diabetes, lupus, obesity, HIV, Hepatitis, Psychosocial issues.
  - Some genetic abnormalities

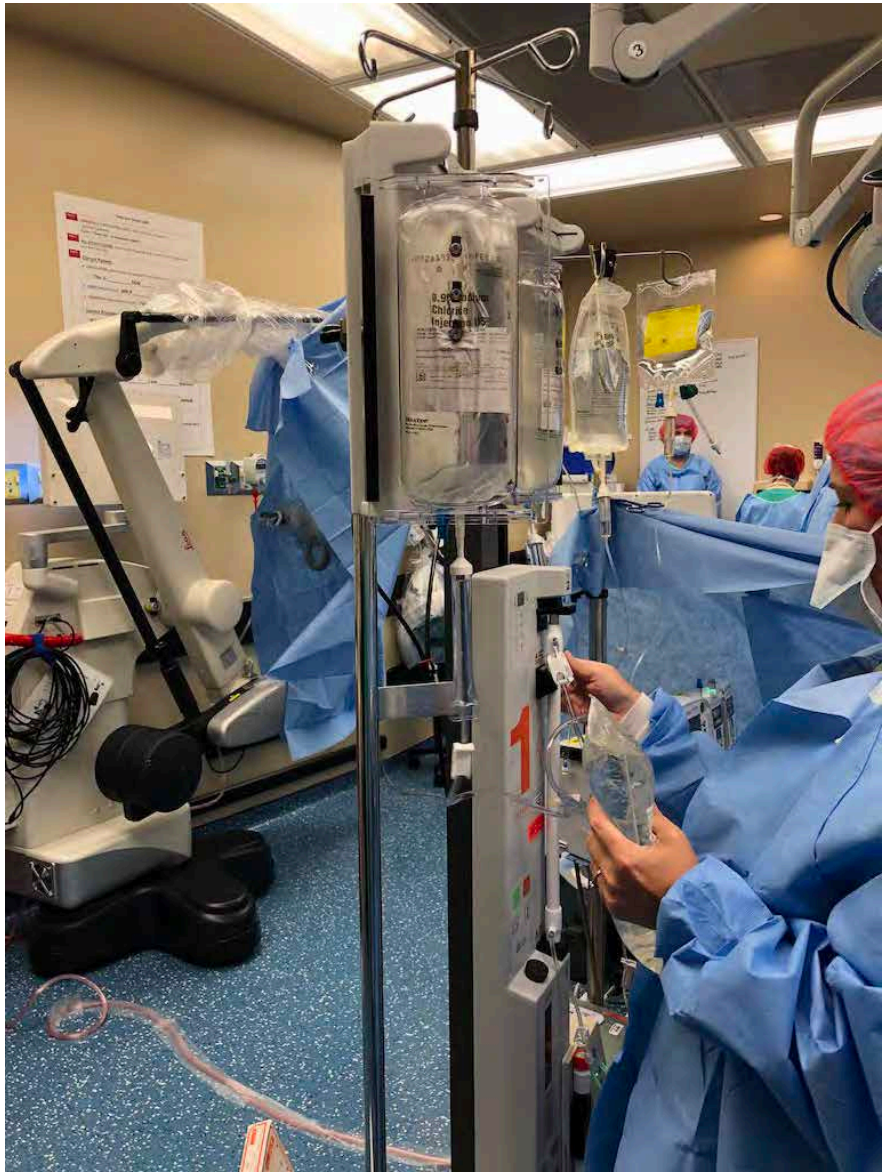


Technical Overview

- General and Regional Anesthesia
- Joel-Cohen Laparotomy
- Uterus exteriorized from abdominal cavity
- Hysterotomy
- Myelomeningocele/Myeloschisis repair
- Fetal Heart Rate Monitoring
- Hysterorrhaphy
- Return of uterus to abdominal cavity
- Closure of abdominal wall

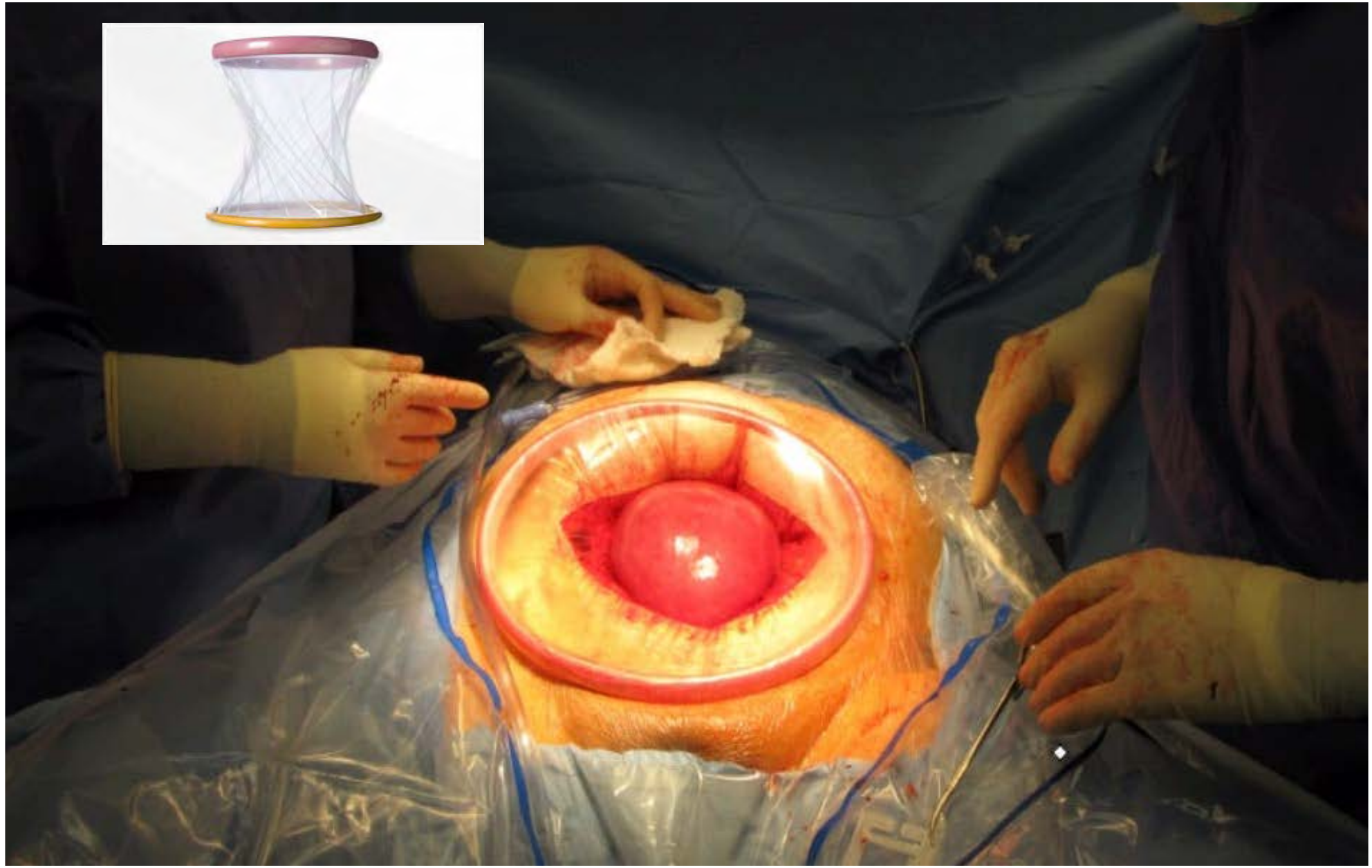


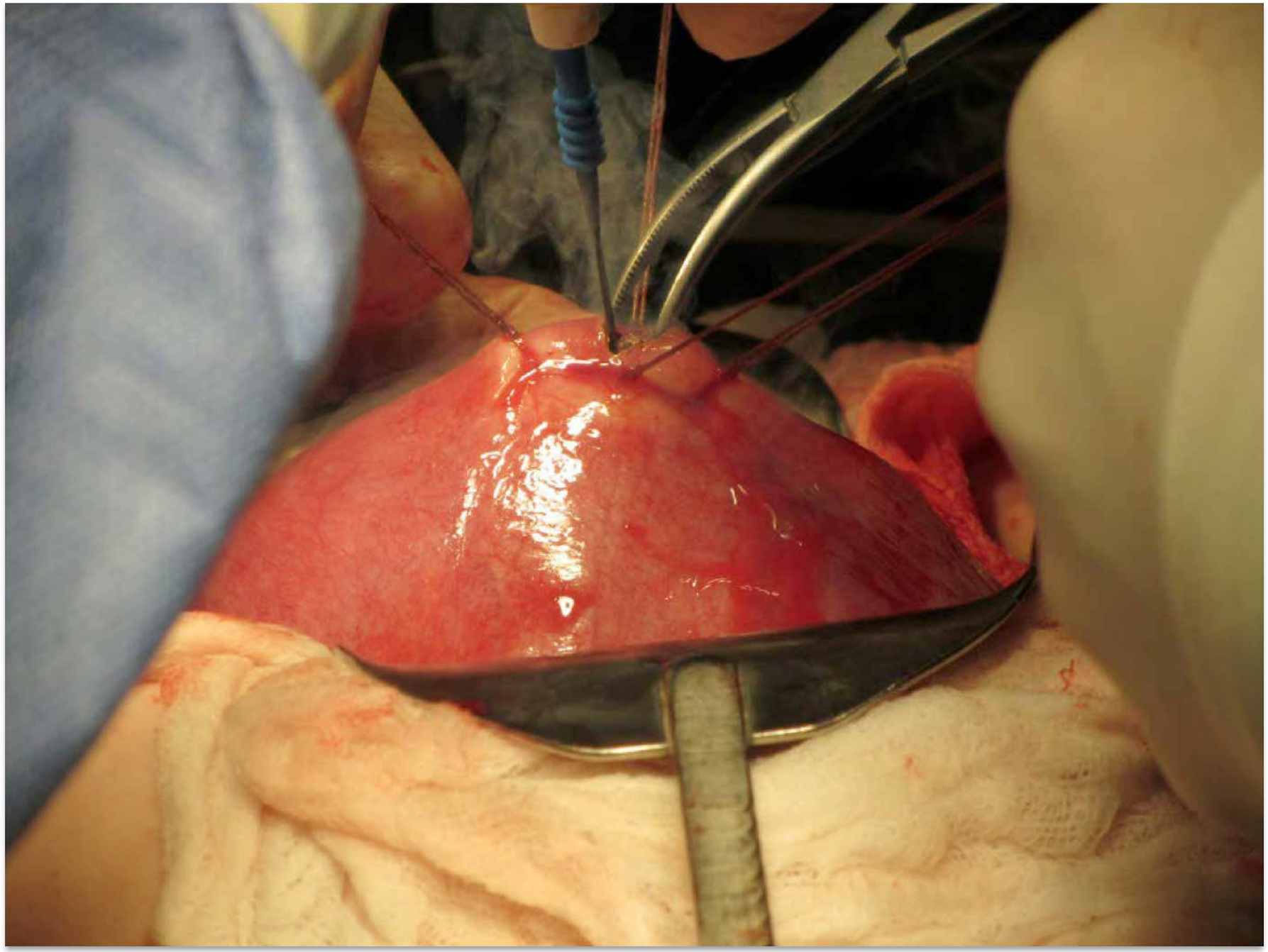
Operating Room Set-Up



Laparotomy and Hysterotomy

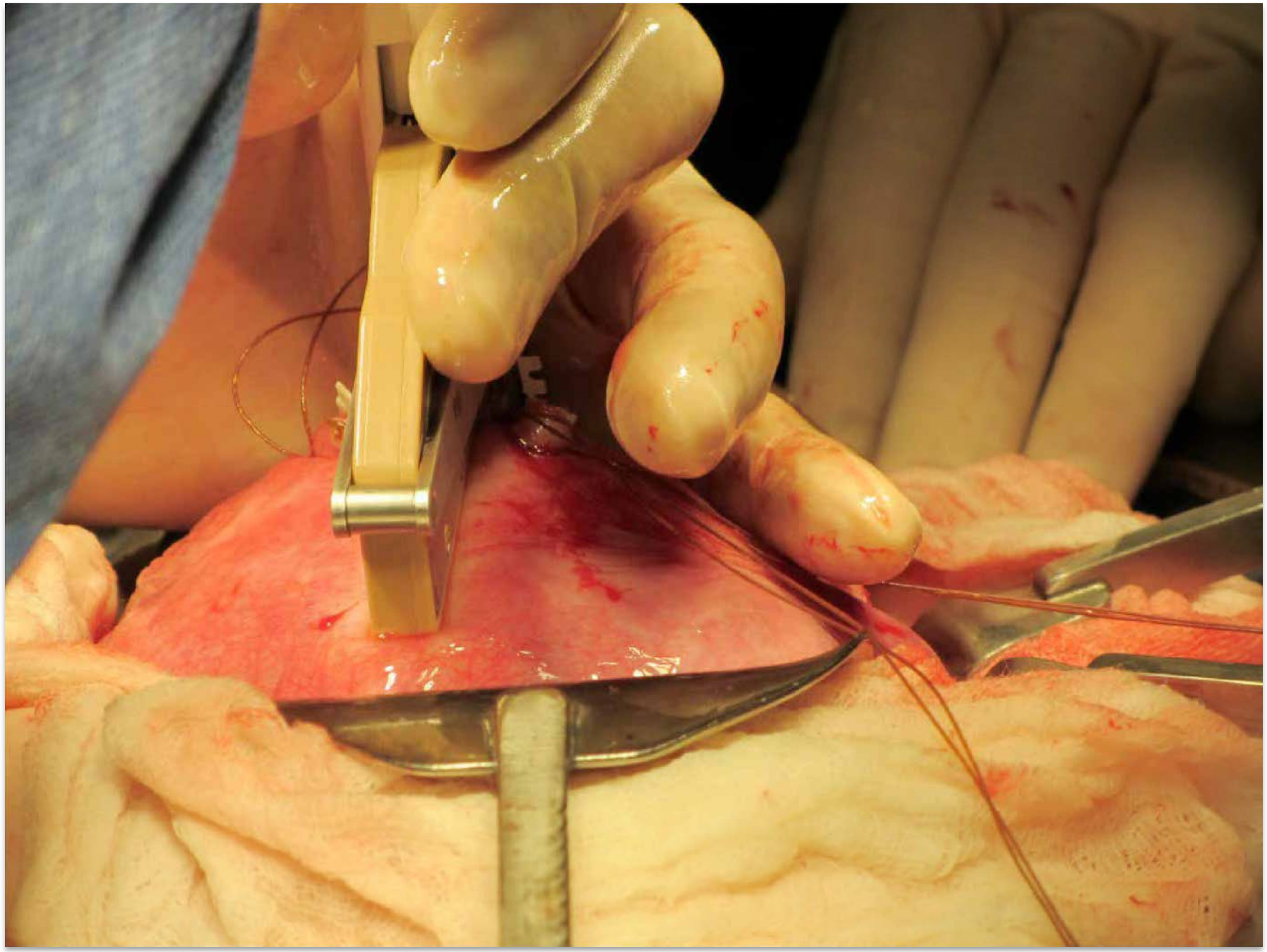
- Joel-Cohen laparotomy
  - May need to bisect rectus muscles
- Uterus removed from the abdominal cavity and positioned (based on placental location)
- Ultrasound scan performed to find the proper place to set the hysterotomy (placental mapping)
  - Use of electrocautery to define margins
- Ultrasound used to identify myelomeningocele location and position fetus for optimal entry
- Bilateral of box stitch technique in the middle to assist with creation of hemostasis at site of entry and allow for manipulation of uterine wall
- Opening of the uterine wall to expose the amniotic membranes
- Penetrate membranes and transfix to the uterine myometrium
- Secure membrane to uterine wall and address any bleeding or other membrane separation





Hysterotomy and Exposure of fetus

- Place two Masterson clamps into the opening of the myometrium and chorioamniotic membranes
- Apply compression with clamps
  - Reduces blood flow to area of compression
  - Thins tissue to allow for improved activation of uterine stapler
- Deploy stapler – address challenges
- Ensure membranes remain secure and suture as necessary
- Trim excess staple material
- Position fetus to allow visualization of myelomeningocele within hysterotomy/surgical field

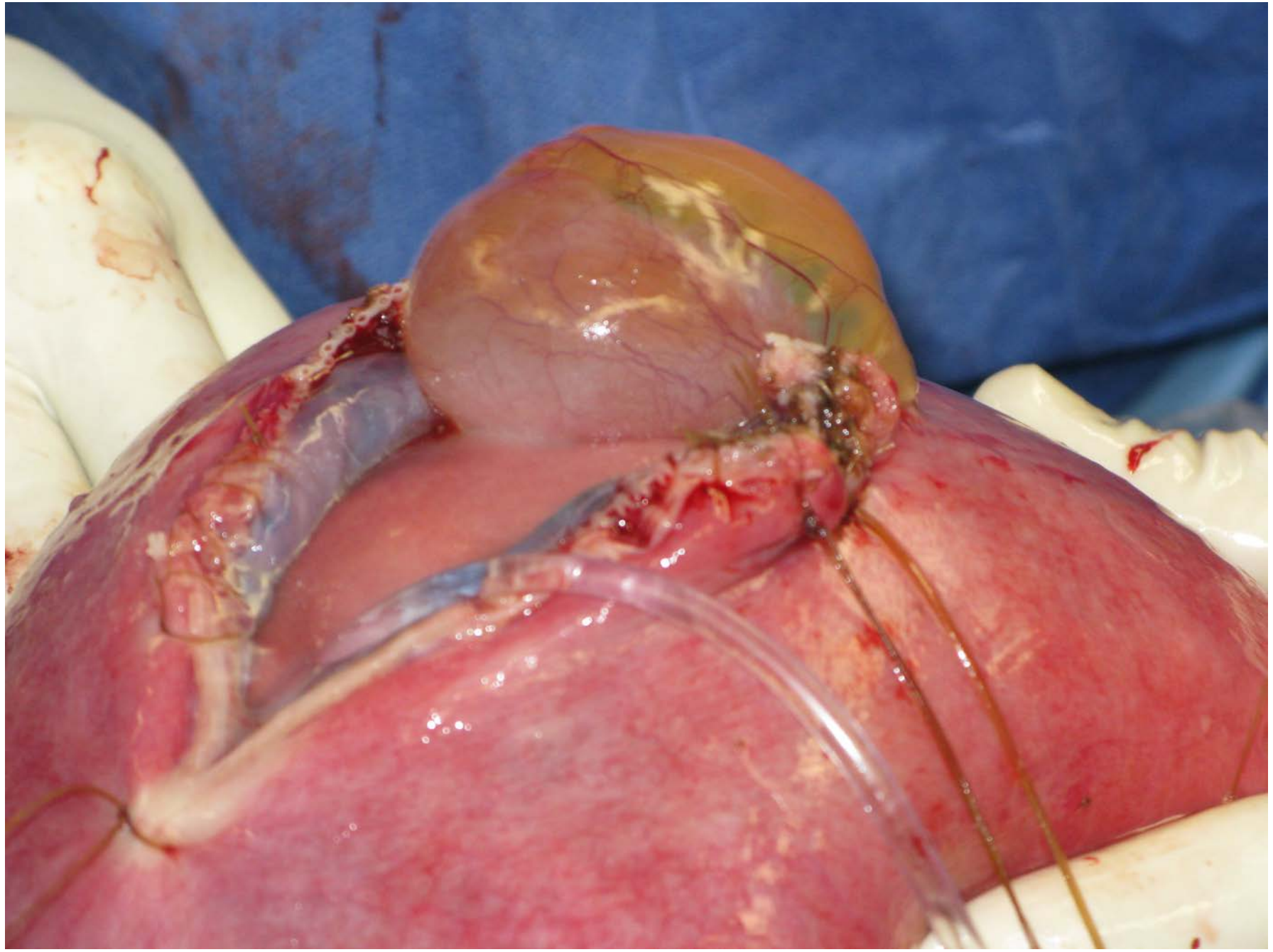


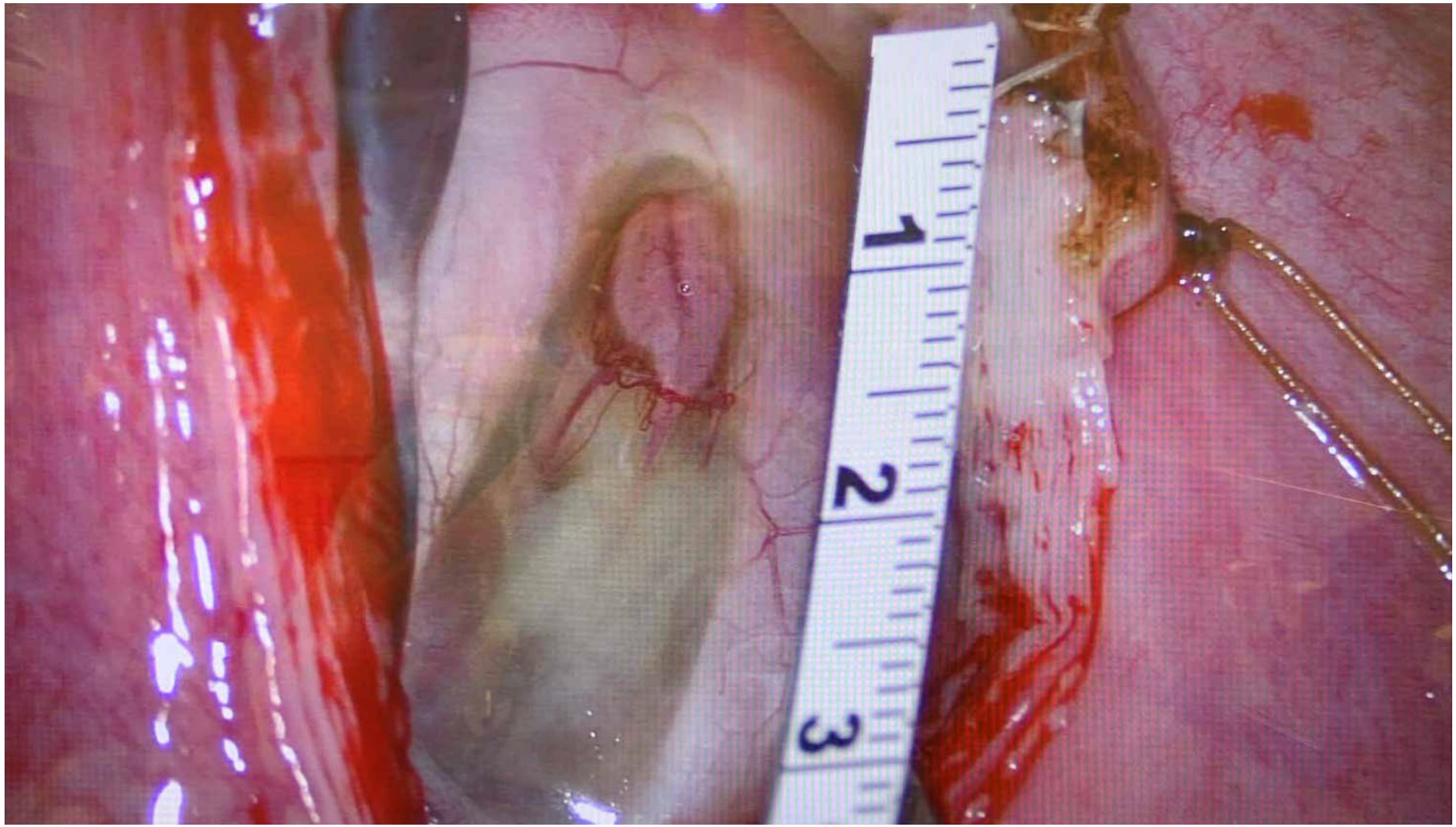
Fetal Repair

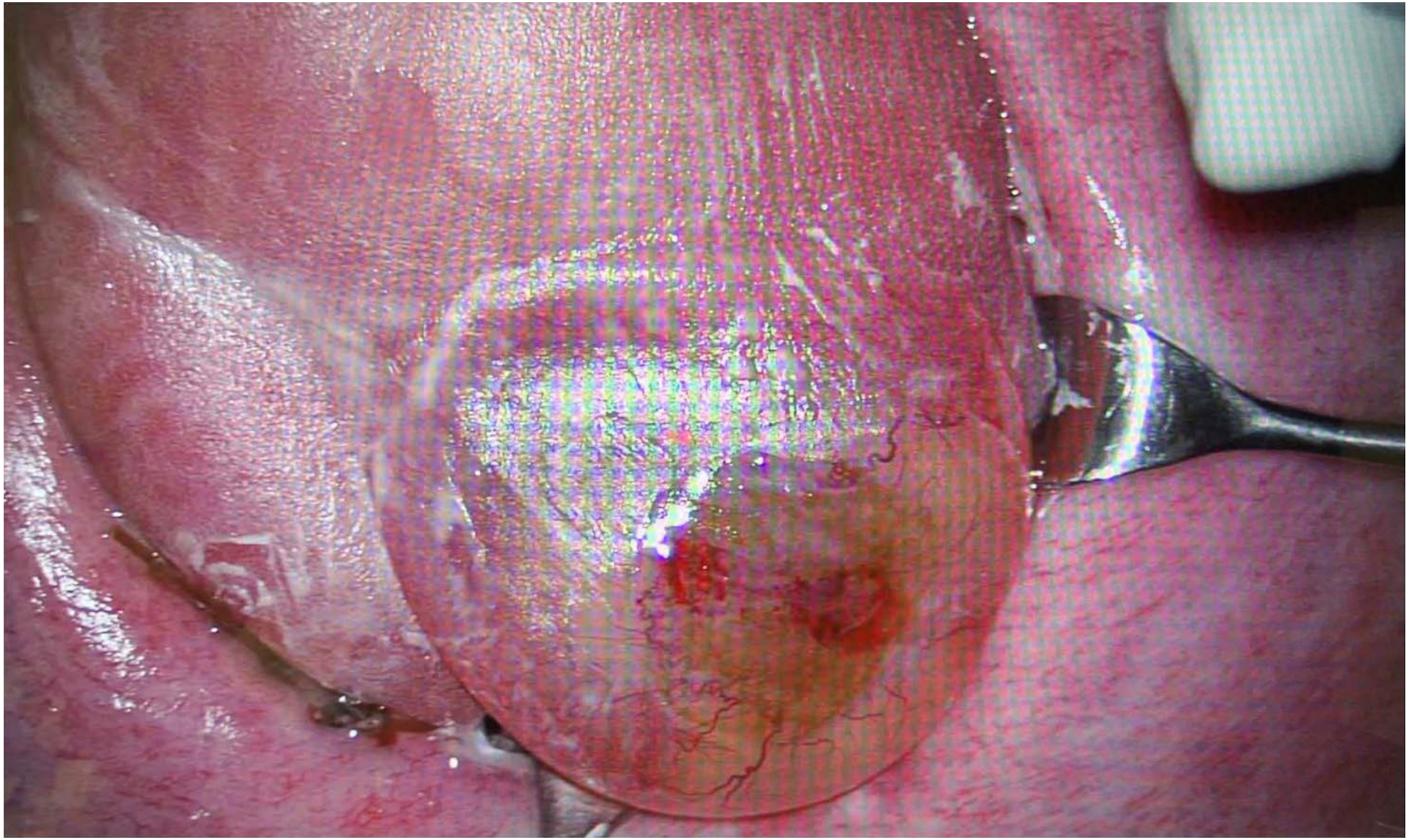
- With fetus adequately positioned
  - Administer fetal cocktail
  - Vecuronium, Atropine and Fentanyl
    - Doses calculated based on weight
  - Position myelomeningocele within hysterotomy
  - Provide visualization for neurosurgical repair
  - Stablilize fetus
  - Monitor maternal vital signs
  - Monitor fetal temperature
    - Neonatal esophageal temp. probe
  - Continuous infusion with Level 1

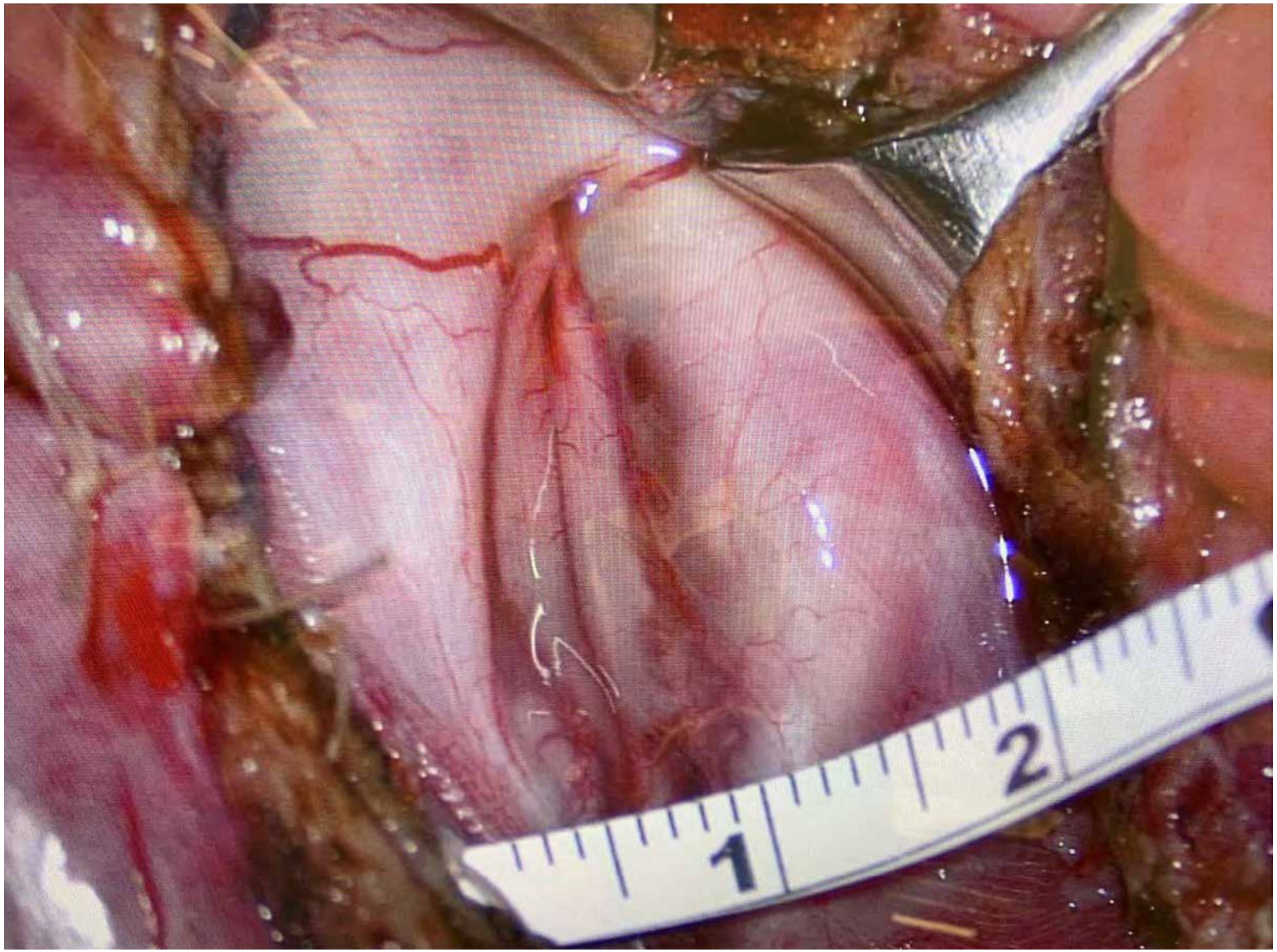
Fetal Heart Rate Monitoring

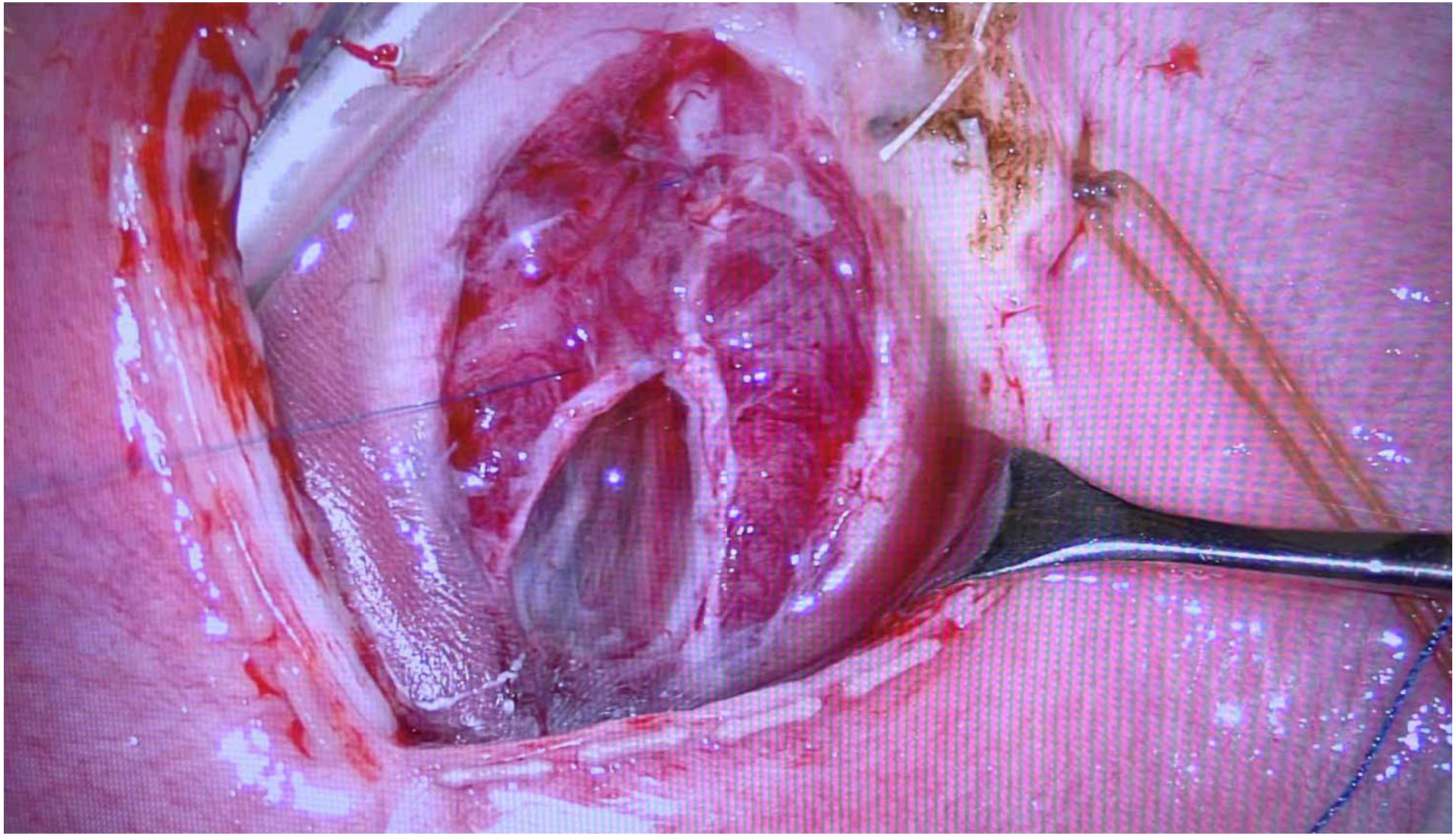
- 2 Ultrasound probes on surgical field
- Every 5 minutes while uterus is closed
- Every 3 minutes while uterus is open
- Surgical manipulation
- Stress or Pain
- Anesthesia – Fentanyl / Atropine / Epinephrine
- Fetal chest compression
- Oligohydramnios
- Hypothermia
- Surgical time

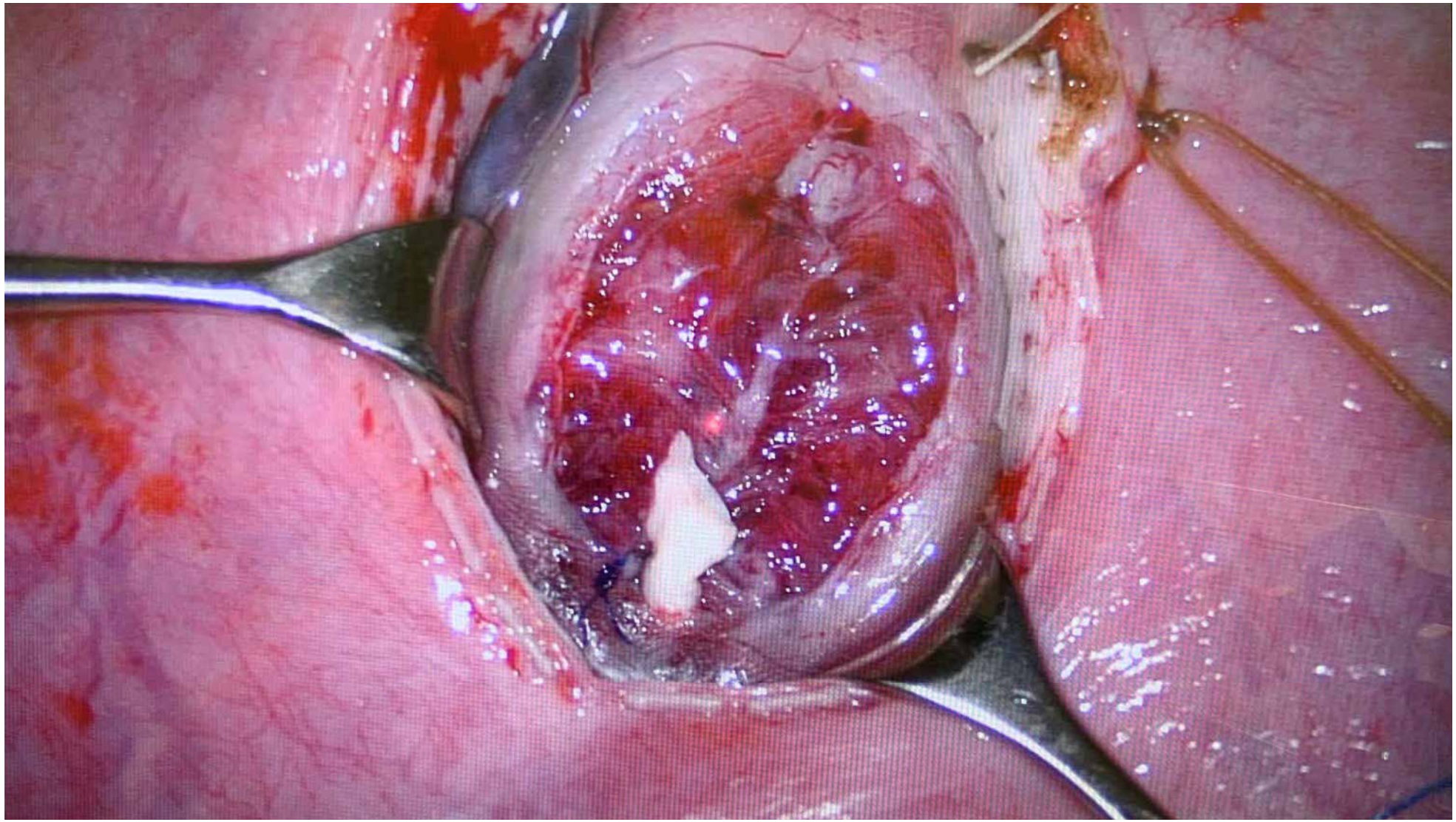


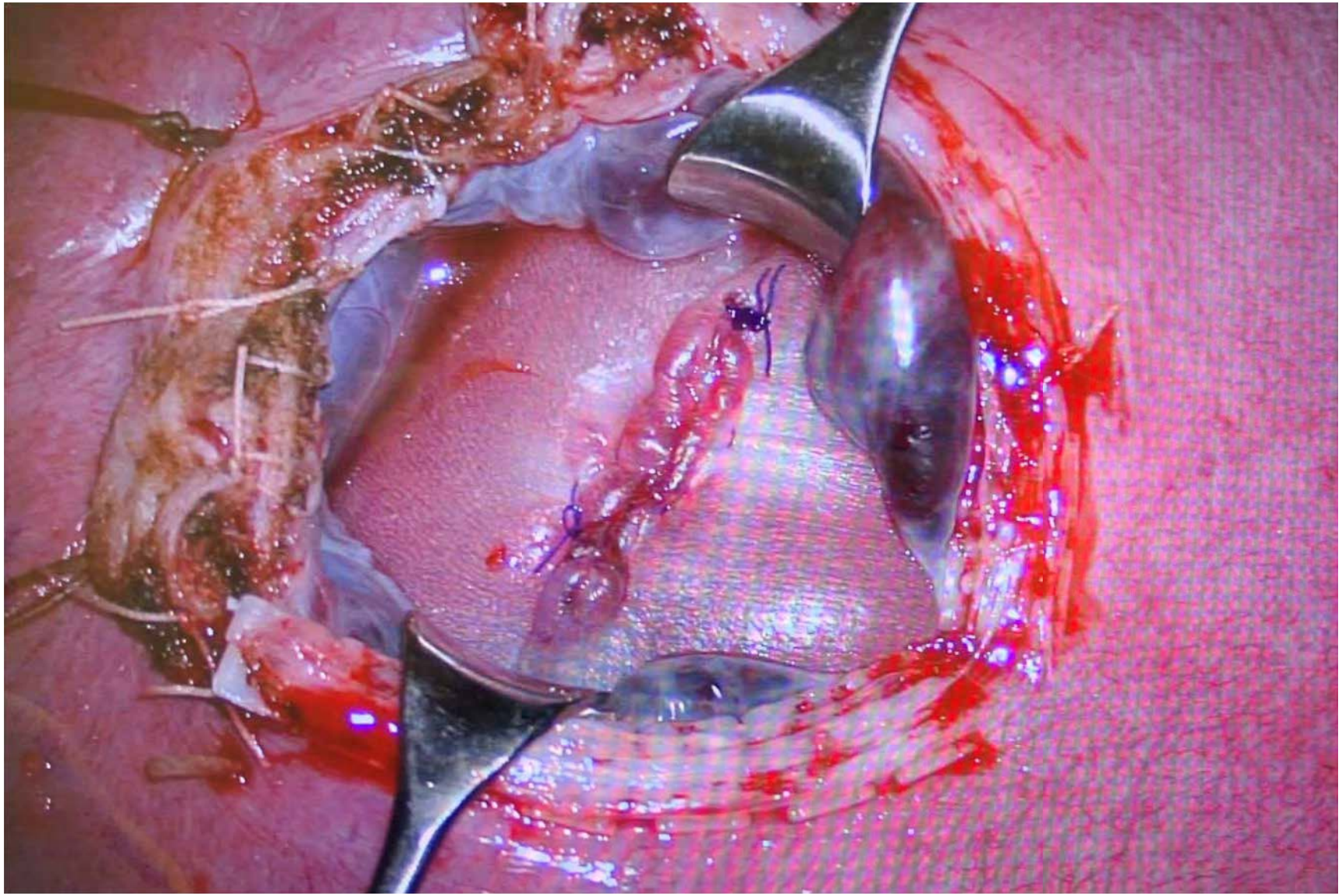












Hysterorrhaphy

- Additional stitches placed to secure membranes
  - Continuous or interrupted
- Running locking suture to close 1st layer
- Continuous stich parallel to hysterotomy for 2nd layer
  - Creates imbricating layer
- Tisseal use over suture line
- Repositioning of uterus in abdomen

Post-Operative Care

- Patients typically remain inpatient for 3-5 days
- Care is provided in WICU
  - First 24 hours, Labor and Delivery Nurse Staffing
  - Remainder of stay – WICU Nurse Staffing
- Continuous Electronic Fetal Monitoring and Tocometry throughout stay
- Encourage Incentive Spirometry Use
- Gradual ambulation
- Minimal diet restrictions
- Prevention of Wound Infection
- DVT Prophylaxis
- Supplemental Oxygen to keep saturation at/above 96%

Post-Operative Day #0

- Patient will have Epidural for 48 hours
- IV Tylenol permissible if needed
- Magnesium Sulfate at 2 grams/hour
- Continue Indomethacin for 24 hours at 50 mg dose Q 6 hours
- Use of Incentive Spirometer when possible
- Clear liquid diet – Advance as Tolerated
- Typically no ambulation Day #0
- DAY of REST

Post-Operative Day #1

- Patient will keep Epidural for 48 hours
- IV Tylenol permissible if/as needed
- Magnesium Sulfate at 1-2 grams/hour
- Continue Indomethacin for an additional 24 hours at 25 mg dose Q 6 hours
- Aggressive use of Incentive Spirometer
- Advance diet as tolerated
- Typically ambulate to chair, sit up in bed
- Day of EARLY ACTIVITY

Post-Operative Day #2

- Patient will discontinue Epidural
- Begin oral pain medication
- IV Tylenol permissible if/as needed
- Magnesium Sulfate will be discontinued
- Begin Nifedipine at dose of 10 mg Q 6 hours
- Indomethacin course is completed
- Foley Catheter out
- Continued aggressive use of Incentive Spirometer
- Advance diet as tolerated
- Typically ambulate to toilet and around room
- Day of MODEST ACTIVITY/FREEDOM

Post-Operative Day #3

- Continue oral pain medication as needed
- IV Tylenol permissible if/as needed
- Continue Nifedipine at dose of 10 mg Q 6 hours
- Continued aggressive use of Incentive Spirometer
- Regular Diet should be implemented by now
- Typically ambulate to nurse station/around unit. Patient may shower
- Day of FREEDOM to ROAM

Post-Operative Day #4/5

- Continue oral pain medication as needed
  - Patient should need minimal narcotic at this point
- IV Tylenol permissible if/as needed
- Continue Nifedipine at dose of 10 mg Q 6 hours
- Continued use of Incentive Spirometer
- Regular Diet
- Ambulate to nurse station/around unit. Patient may shower
- Day(s) to prepare for discharge

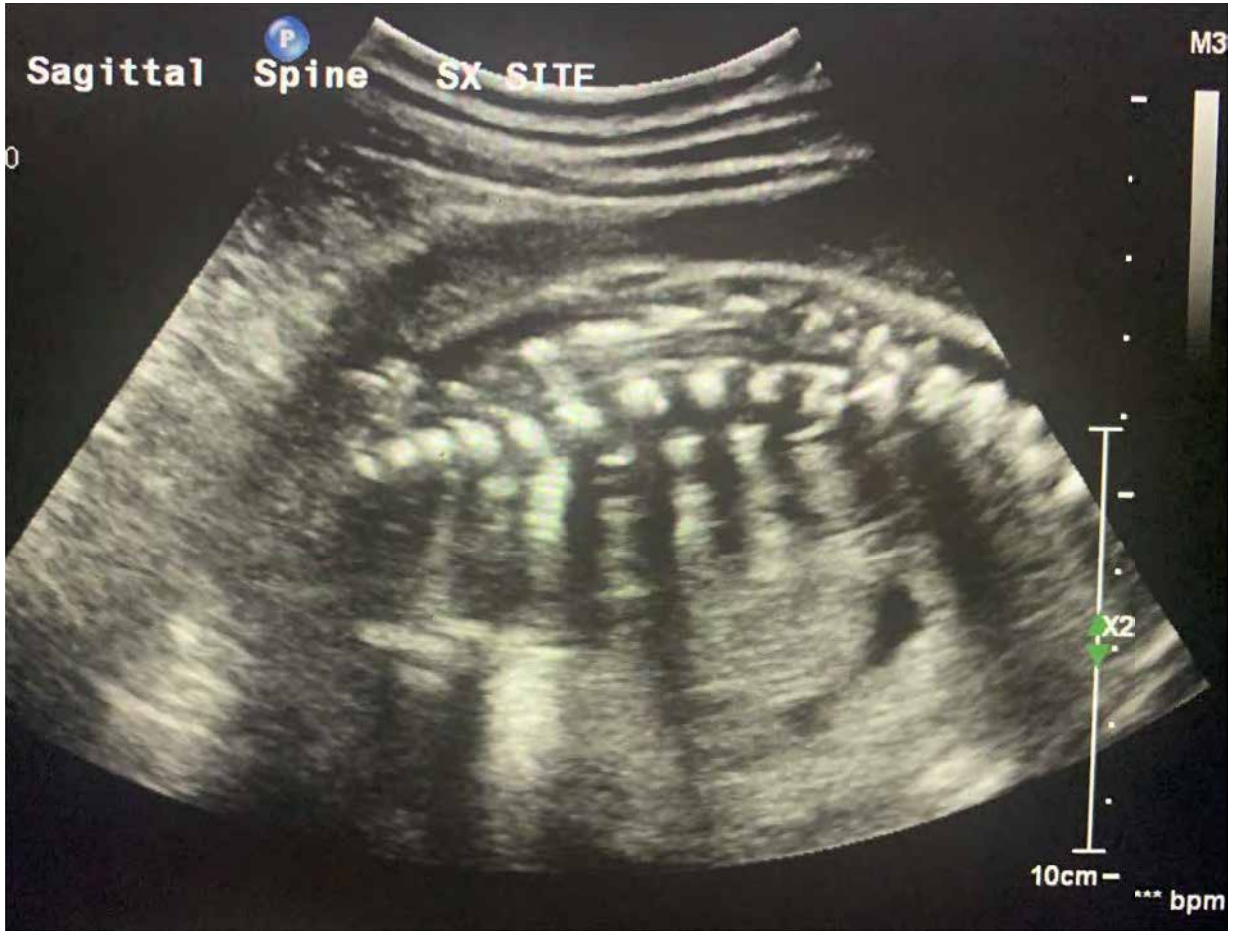
Discharge Instructions

- Continue oral pain medication as needed
  - Patient may need short (3-day supply) of narcotic
- Blood pressure cuff needed – Instruct on use and ensure operational
  - Check blood pressures before and 1 hour after Nifedipine use
  - Parameters 90-140/50-90. Hold Med. and call/text if outside of range.
- Continue Nifedipine at dose of 10 mg Q 6 hours
- Continued use of Incentive Spirometer (give to take home)
- Regular Diet
- Modified activity with bed rest when possible
- Complete Pelvic Rest!
- Patient will go to Ronald McDonald House and follow-up at The Fetal Care Center within 5 days
- At least weekly follow-up thereafter
- Discharge from Ronald McDonald House after approximately 2 week stay
- Precautions given!!!

Weekly Outpatient Follow-up

- Clinical, Laboratory and Sonographic Evaluation
- Nifedipine, Prenatal Vitamins and Iron Supplementation

Evaluation of the Spine



Reversal of Hindbrain Herniation

- By Ultrasound

Reversal of Hindbrain Herniation

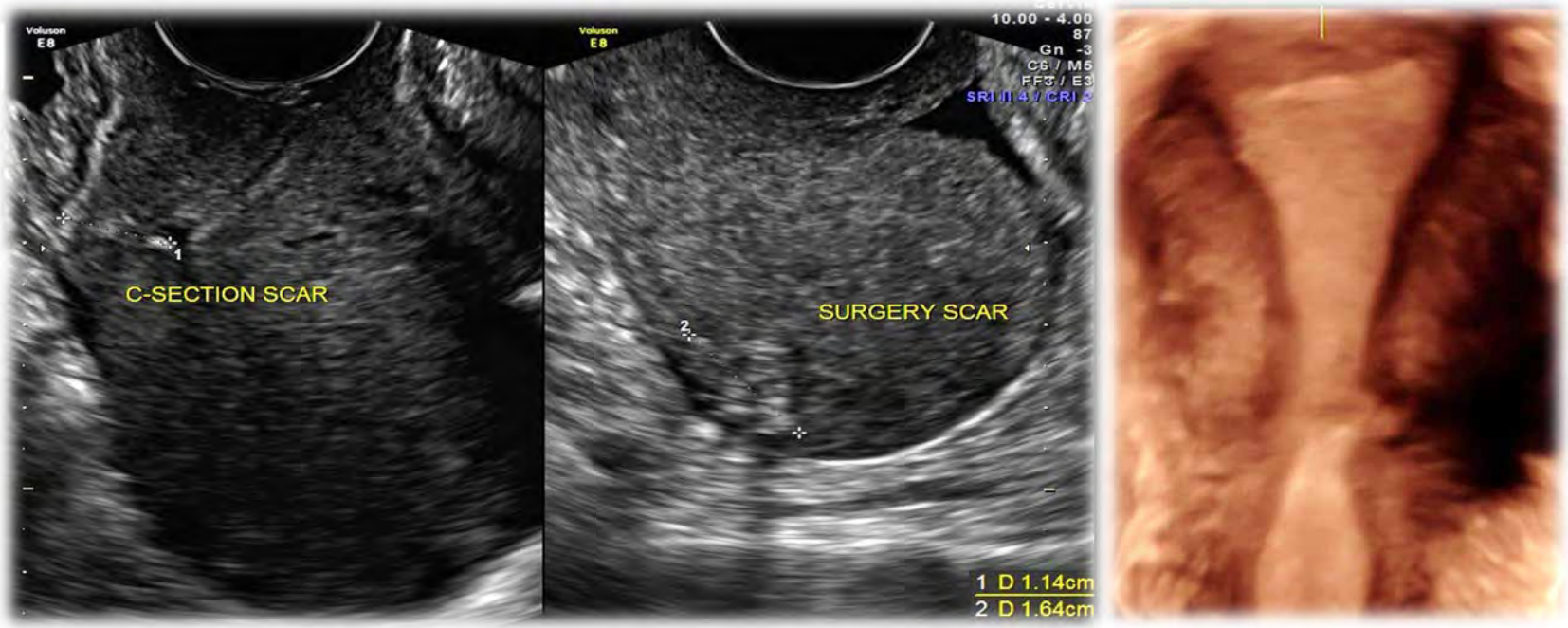
- By MRI

Postpartum Uterine Scar Evaluation

- Should always occur at delivery
  - Many are very thin or may have cleft
  - Can be reinforced or excised and re-stitched

Reproductive Counseling Regarding Future Pregnancies

- Uterine ultrasound evaluation as a part of reproductive counseling
- Increased risk for hysterotomy related complications
  - Placental implantation abnormalities
  - Dehiscence, uterine rupture - 20% < 24 months ; 10% > 24 months



Johnson MP – FMF Congress 2015

Long Term Follow-up: Motor Function and Anatomical Level

Two or more levels better – 29%

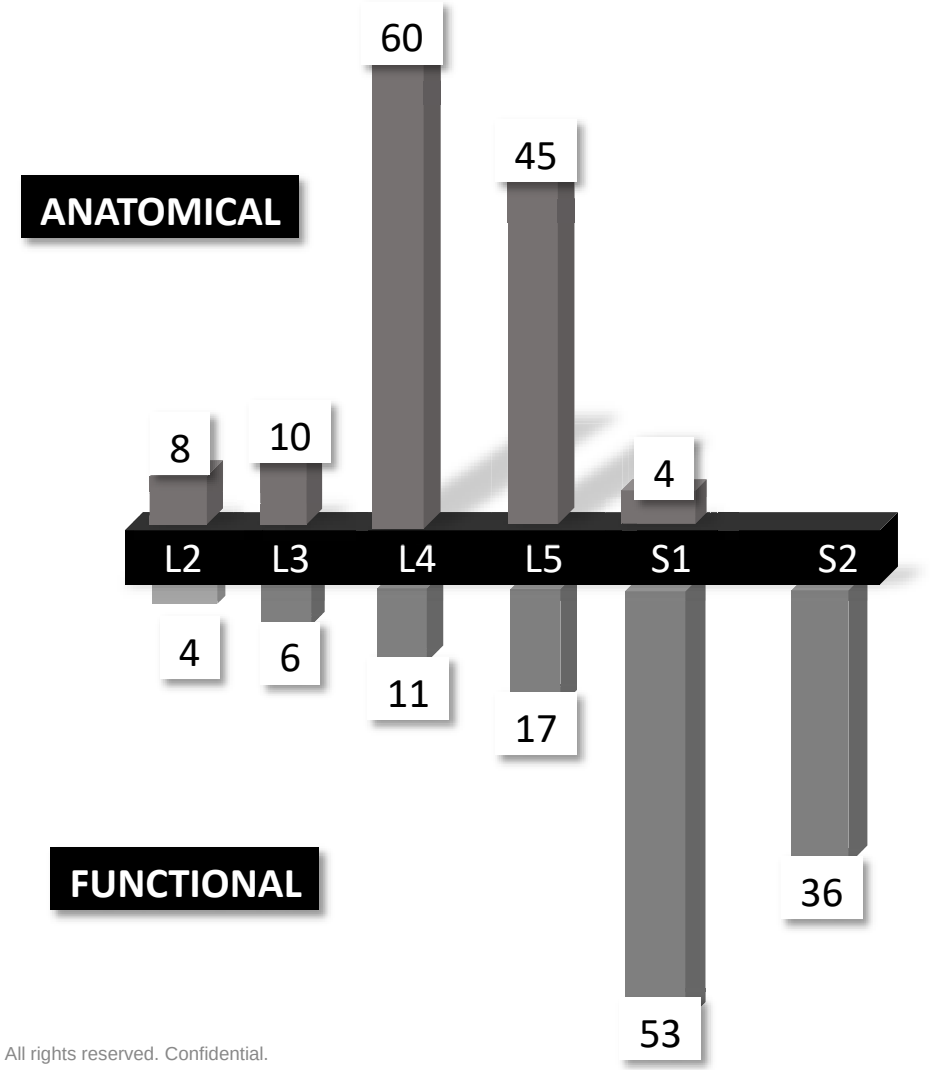
One level better – 39.2%

No difference – 18.2%

One level worse – 11.8%

Two or more levels worse – 1.8%

** Children should be cared for at multidisciplinary clinics for follow-up



Fetal Therapy Center Requirements

- Institutional commitment
- Experienced fetal care team
- Multidisciplinary spina bifida program
- Level III Neonatal Intensive Care Unit
- Labor and Delivery unit capable of caring for perioperative complications and obstetric emergencies
- Availability of Maternal-Fetal Medicine (MFM) specialists skilled in managing delivery of patients with a recent hysterotomy
- Institutional Review Board
- Ethics committee
- Institutional commitment to track long-term pediatric neurodevelopmental outcomes

Cohen AR et al Position Statement on Fetal Myelomeningocele Repair.Am J Obstet Gynecol. 2014 Feb;210(2):107-11.

Outcomes Data – Winnie Palmer Hospital

- Surgeries completed – 39
- Delivered patients – 36
  - (2 at 34 6/7 weeks and 1 at 32 0/7 weeks)
- Mean Gestational Age at Delivery – 34 0/7
- Median Gestational Age at Delivery – 35 1/7 weeks
- Mode – 37 0/7 (8)
- < 30 weeks gestation – 10.3% (4/39)
- Delivery at 30-33 6/7 weeks – 29.7
- Delivery at 34+ weeks – 60%
  - Delivery at 37+ weeks – 28.6%

- Preterm PROM – 38.5%
- 1 intrauterine fetal demise
- 1 perinatal death
- No maternal deaths
- Impact of COVID – 14 cases performed 5/21/20 – 10/18/21

Additional Considerations

- Fetoscopic repair
  - Differing techniques
  - Lack of data from rigorous randomized controlled trial similar to MOMS
  - Surgical time, technical proficiency for adequate closure
  - Insufflation
  - Placental implantation site may limit access
    - Need for open incision
  - Maternal and Fetal outcomes
  - Cesarean section rate may be as high as 50%
- Use of tissue engineering
- Use of stem cells to aid healing/promote scarless healing

Open Fetal Surgery to Improve Outcome…

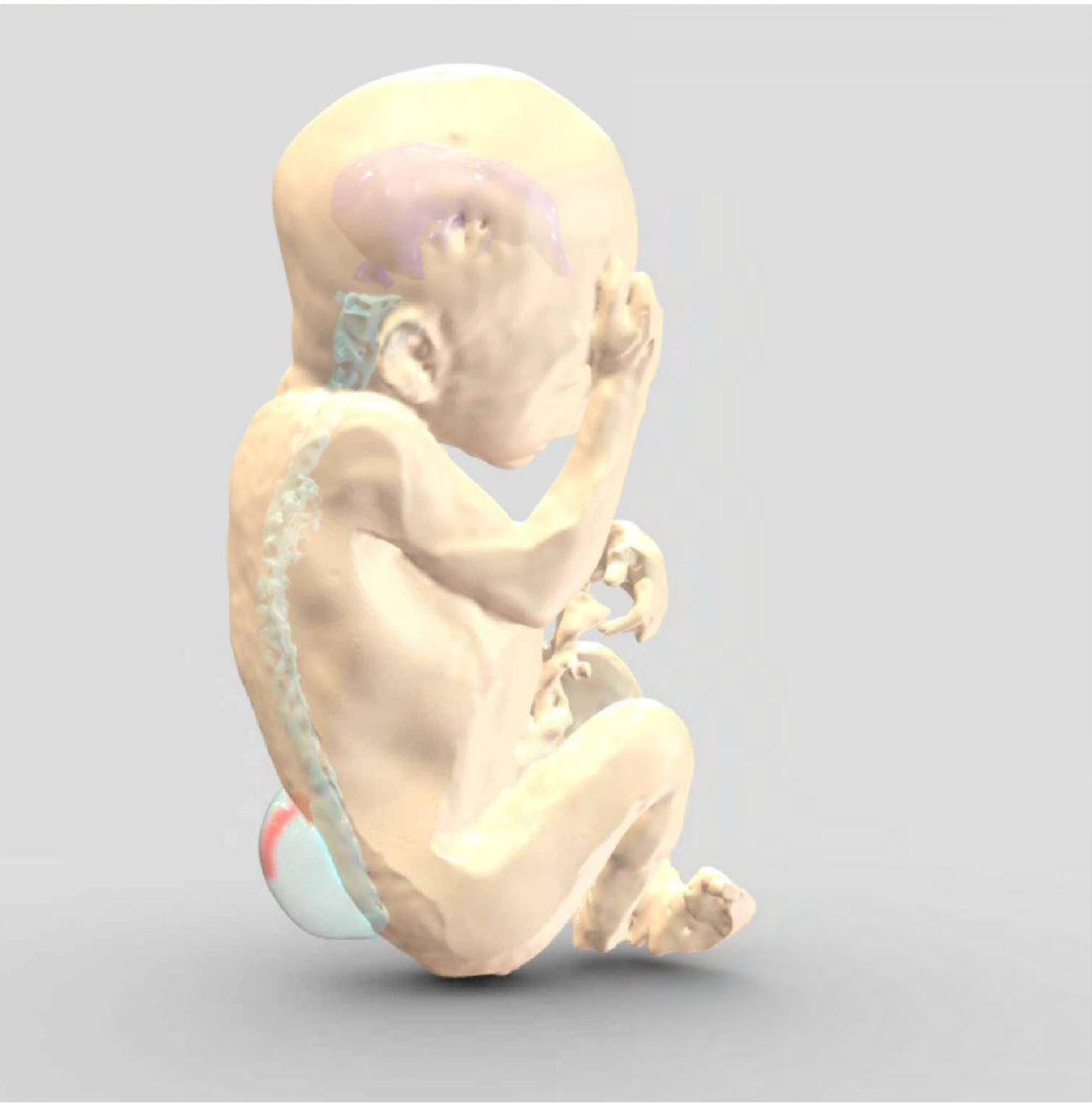
…Everywhere

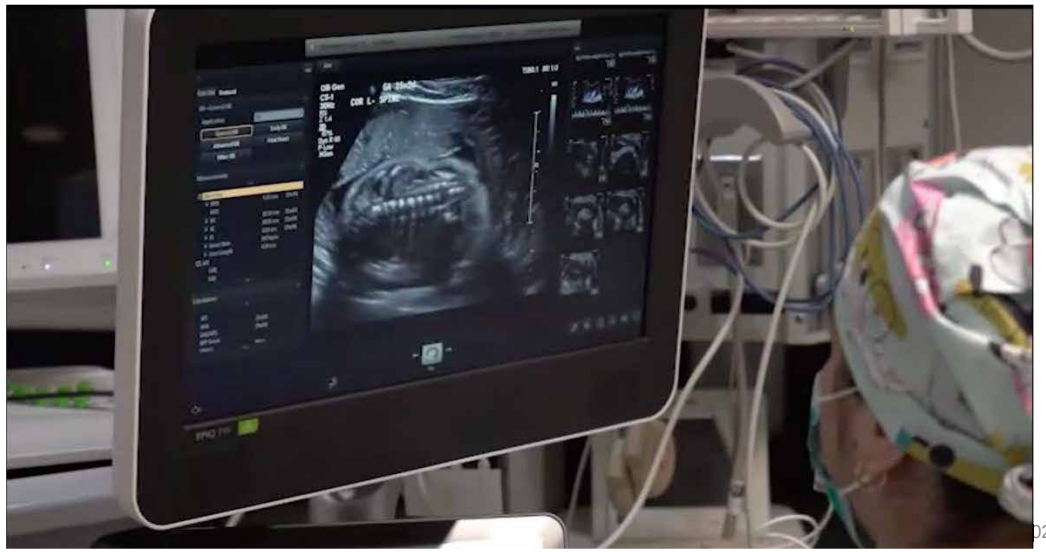
NERDS!!

3D Printing for Spina Bifida Repair – Fetal Surgery

DASH – Orlando Health's 3D Printing Partner

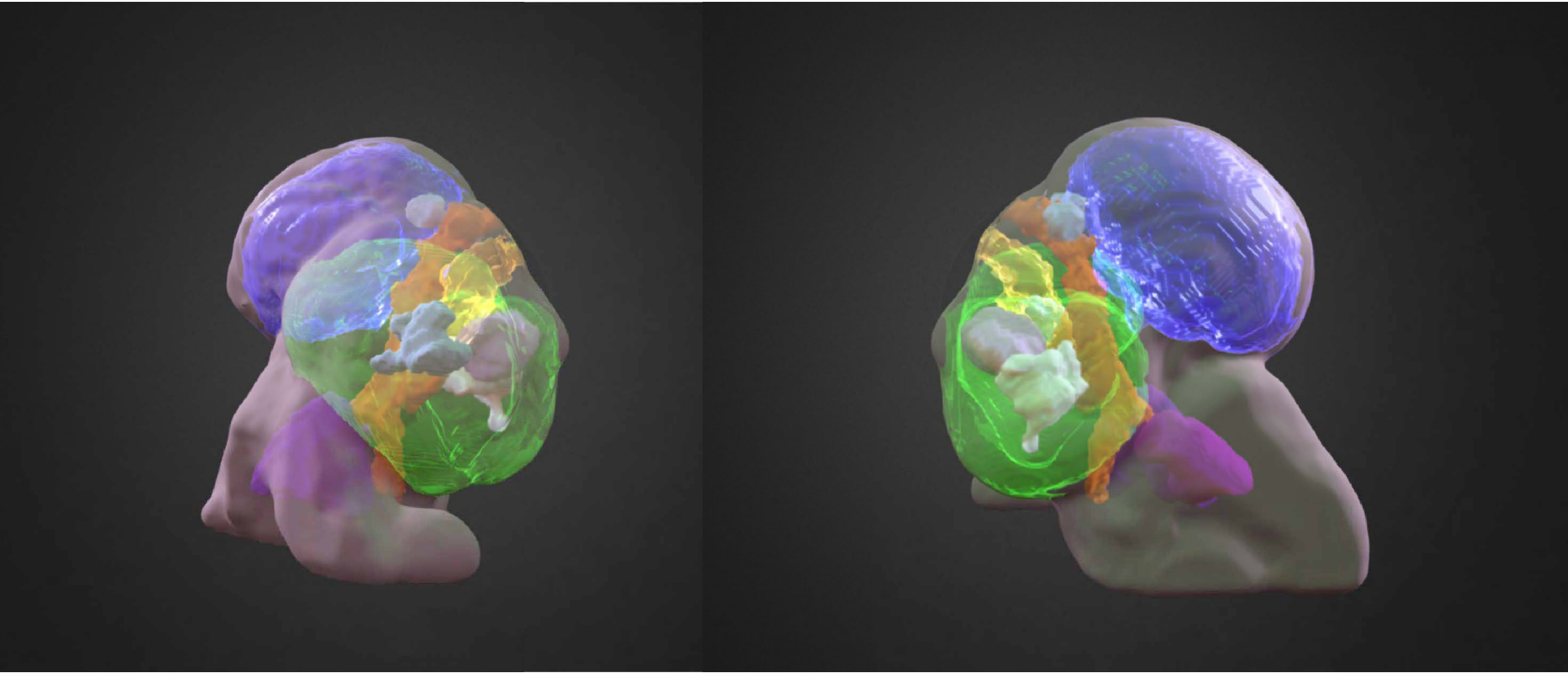
DASH





3D Visualization – Fetal Airway

3D Renderings for Airway Evaluation Before Delivery



Thank You!