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Advances in Fetal Surgery: Current Challenges and Future Perspectives

Richa Shrivastav[1], Kahkasha Bano[2], Ajay Kumar Singh[*1]

[1]School of pharmaceutical sciences, Chhatrapati Shahu ji Maharaj university Kanpur – 208024, Uttar Pradesh, India

[2]Department of pharmacology Seth Vishambhr Nath Institute of pharmacy college (AKTU).

***Corresponding Author:**

Ajay Kumar Singh

Email ID: Ajayks09451244476@gmail.com

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ABSTRACT

In maternal-fetal medicine, fetal surgery has become a game-changer, providing life-saving treatments for congenital defects that were previously thought to be incurable before to birth. The range of fetal interventions has increased because to developments in prenatal diagnostics, imaging modalities, and surgical procedures, which have improved long-term results and survival rates. Spina bifida, congenital diaphragmatic hernia, twin-to-twin transfusion syndrome, and sacrococcygeal teratoma are among the disorders that have been corrected thanks to open fetal surgery, fetoscopic treatments, and minimally invasive approaches.

The dangers of preterm labor, complications for both the mother and the fetus, and the technical difficulties of in utero procedures are some of the obstacles that still exist in spite of these developments. Further influencing the development of this discipline are ethical issues pertaining to the autonomy of the mother and fetus, the possibility of fetal death, and the financial strain on healthcare systems.

Enhancing minimally invasive procedures to lower maternal risks, developing biomaterials for fetal wound healing, and incorporating gene and stem cell therapy to treat genetic and developmental abnormalities in utero are the main goals of future perspectives in fetal surgery. Developments in regenerative medicine and artificial womb technology also have the potential to completely transform fetal interventions. Fetal surgery has the potential to provide even safer and more effective treatment choices with further study and technology advancement, revolutionizing newborn care and expanding the scope of perinatal medicine.

Keywords: *Fetal Surgery, Prenatal Intervention, Congenital Anomalies, Open Fetal Surgery, Fetoscopic Surgery, Ex Utero Intrapartum Treatment (EXIT)*

1. INTRODUCTION

Fetal surgery, sometimes referred to as prenatal surgery or antenatal surgery, is a rapidly expanding area of maternal-fetal medicine that includes a wide range of surgical procedures intended to correct congenital defects in fetuses still inside the pregnant uterus (Holzman RS et al., 2021).

The three primary types are percutaneous fetal therapy, which involves inserting a catheter under continuous ultrasound guidance; minimally invasive fetal surgery, which involves tiny incisions and is guided by fetoscopy and sonography; and open fetal surgery, which entails opening the uterus completely to operate on the fetus (Yamamoto M et al., 2022).

Common Fetal Surgical Interventions

Congenital Diaphragmatic Hernia (CDH)

Incomplete diaphragm formation during embryogenesis causes congenital diaphragmatic hernia (CDH), which can result in a series of mild to severe and often deadly consequences. About 1 in 2,500 to 1 in 3,500 live births cause CDH, with the posterolateral diaphragm (Bochdalek hernia) being affected in 90% of cases, primarily on the left side (>85%). Abdominal viscera can move into the thoracic cavity due to the diaphragmatic defect, which has a mass effect on the growing lungs. Pulmonary hypoplasia and pulmonary hypertension result from this displacement, and the magnitude of the defect frequently corresponds to the severity of the clinical presentation (Yang MJ et al., 2021).

Myelomeningocele (Spina Bifida)

The publication of the Management of Myelomeningocele Study (MOMS) marked a paradigm shift in the early management of children with myelomeningocele. The MOMS trial demonstrated that open fetal surgery for myelomeningocele significantly reduced the need for shunt placement in hydrocephalus cases while maintaining acceptable risks for both the mother and fetus. Subsequent studies have shown that children who undergo fetal surgery are more likely to ambulate earlier, exhibit similar early cognitive outcomes, and experience a better quality of life compared to those treated with postnatal surgery (Foy AB et al.,021).

Ten to fifteen percent of monochorionic twin pregnancies result in twin-to-twin transfusion syndrome (TTTS), a frequent complication that usually manifests in the second trimester. It is caused by an uneven distribution of hormones and blood volume between twins via vascular anastomoses on the same placenta. With fatality rates in advanced instances approaching 90–100%, TTTS is the primary cause of fetal loss before to viability if it is not identified and treated in a timely manner (Bamberg C et al., 2022).

The monitoring plan for these pregnancies is guided by the most accurate ultrasound diagnosis of monochorionicity, which is made during the first trimester. Ultrasound is used to diagnose TTTS, which is characterized by polyhydramnios from volume overload and polyuria in one twin and oligohydramnios from decreased urine output (oliguria) in the other twin. Bladder filling, arterial and venous Doppler patterns, and fetal cardiac function are used to stage the severity of the disease and identify infants who need postnatal follow-up (Miller JL. et al., 2021).

The typical treatment for TTTS is fetoscopy laser ablation of the vascular anastomoses. By breaking the aberrant vascular link, this treatment efficiently separates the twins' blood supplies. According to recent outcome data, laser surgery can result in dual survival in as many as 65% of instances and single-fetus survival in as many as 88% of cases (D'Antonio F et al., 2024).

Surgical Techniques and Innovations

Open fetal surgery

The placental circulation is preserved when open surgeries are carried out using a hysterotomy. The fetus is usually put back into the uterus, and the pregnancy lasts until it is almost term. Although open surgery offers superior surgical exposure to the fetus, there is a considerable risk of early labor and maternal morbidity (Guilbaud L et al., 2021).

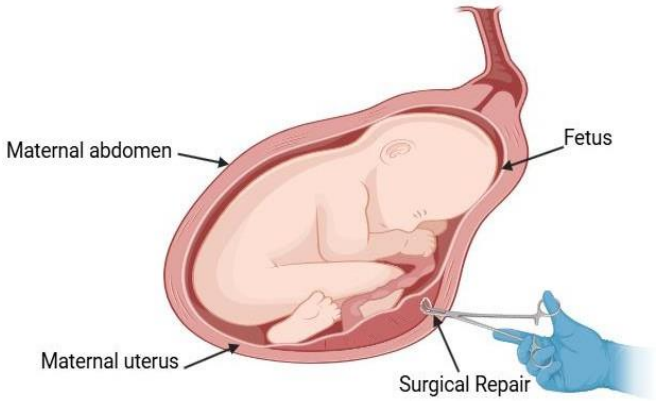


Fig. 1. Open fetal surgery: Surgical intervention on the fetus inside the uterus to correct congenital anomalies before birth.

Fetoscopic Surgery

Fetoscopic surgery has been suggested as a substitute for open fetal surgery, since laparoscopic and video-assisted surgery have grown in popularity (Durmaz LO et al., 2022). In the hopes that avoiding a big hysterotomy will also lower the risk of preterm labor after surgery, fetal surgery circumvents the maternal morbidity linked to a large laparotomy incision. As with other fetal operations, adequate tocolysis must be accomplished and strict intraoperative monitoring of the mother and fetus is crucial. A flexible fetoscope is inserted into the amniotic cavity, and trochars are inserted using the Seldinger technique. To reduce harm to the uterine wall and membranes, balloon-tipped trochars can be employed (Nassr AA et L.,2021).

Ex utero intrapartum treatment (EXIT) procedure

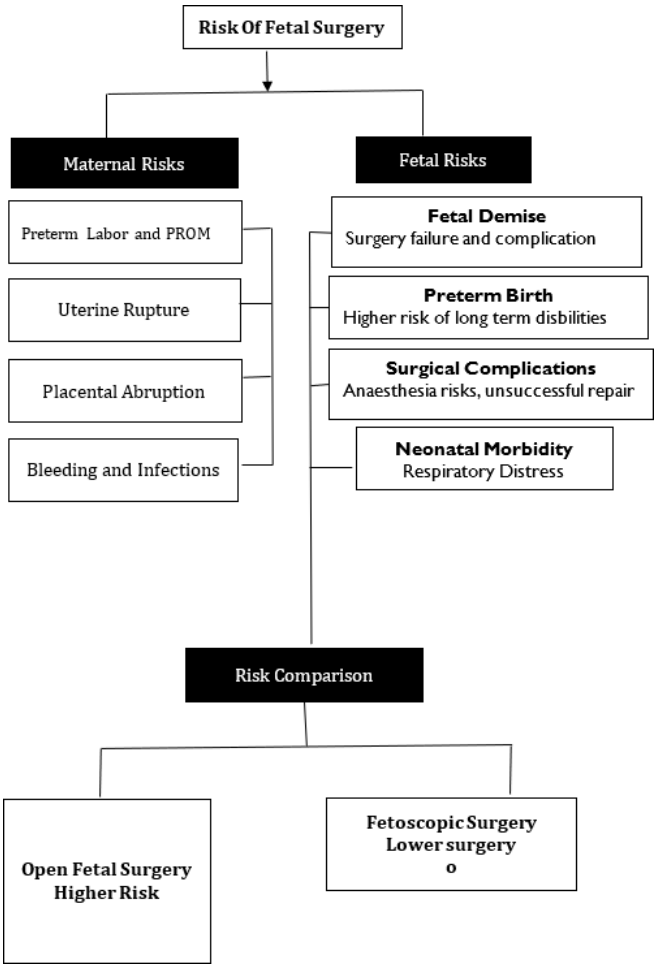
In rare, high-risk situations where stabilizing the fetal airway in utero is crucial prior to delivery, a specific operation known as ex utero intrapartum therapy (EXIT) is carried out. It is mostly utilized for fetuses that would otherwise be deadly due to congenital cardiopulmonary abnormalities or airway blockages. Interventions can be made during the EXIT process while the fetus is still being maintained by placental circulation. Establishing an airway, starting extracorporeal membrane oxygenation (ECMO), clearing obstructive masses, or even separating conjoined twins are some examples of these treatments. (De Jong R et al.,2024).

Risk of fetal Surgery

Fetal surgery carries significant risks for both the mother and the fetus. Maternal hazards include preterm labor and premature rupture of membranes (PROM), which increase the likelihood of early birth and related problems. There is also a danger of uterine rupture, particularly in subsequent pregnancies, as well as placental abruption, which can cause fetal distress and demand emergency delivery. Other potential consequences include bleeding and infection, sometimes requiring blood transfusions or antibiotic therapy. Maternal anaesthesia risks and long-term pregnancy complications, such as abnormal placental attachment, must also be considered (Cass DL.et al.,2021).

Fetal dangers include the possibility of fetal death, especially in extreme situations where surgery is not effective. Because preterm birth is linked to long-term developmental difficulties, such as neurological and pulmonary issues, it is a serious worry. Risks associated with surgery include possible organ damage, side effects from anesthesia, and postnatal neonatal morbidity, such as low birth weight and respiratory distress (Hendriks S et al.,2022).

Open fetal surgery has a greater risk profile than other surgical techniques, with significant complications occurring in 4.5% of cases and maternal problems occurring in about 20.9% of cases. Fetoscopic surgery, on the other hand, carries a reduced risk, with major complications occurring in 1.7% of cases and maternal problems occurring in roughly 6.2% of instances. Because of these concerns, fetal surgery is only carried out when the possible advantages outweigh the risks, and a multidisciplinary team's careful assessment is crucial (Bellieni CV et al.,2021).



Flow chart 1. Maternal and Fetal Risks of Fetal Surgery: A Decision-Making Framework

2. ETHICAL AND LEGAL CONSIDERATIONS

Ethical Consideration -

Fetal surgery involves at least two clinical patients—the mother and the fetus—and is usually invasive. As such, the ethical concerns surrounding this technique are complicated. Because results vary and there is a dearth of consistent data, calculating success rates is still difficult. (Rousseau AC et al.,2022).

Although there is sporadic and contradictory evidence about the benefits of fetal surgery, many institutions perform it to treat fetal abnormalities in both established and experimental settings. Only a few numbers of situations, including twin-to-twin transfusion syndrome and myelomeningocele, have had randomized clinical studies evaluating the efficacy of fetal surgery for both pregnant mothers and fetuses. Fetal procedures are more frequently carried out in clinical settings without comprehensive post-operative outcome reporting in medical literature, which makes evaluating long-term efficacy and safety even more difficult (Chervenak FA et al.,2017).

When a woman and her partner receive a prenatal diagnosis of fetal abnormalities, they have a number of options. The choice between carrying the pregnancy to term and aborting it must be taken, taking into account the advantages and disadvantages of both prenatal and postnatal surgery. Further diagnostic testing, the pregnant lady's health, the couple's medical status, and the availability of medical facilities that might provide a wider variety of possible treatment options could all influence the pregnant woman and her partner's decision. The advantages and disadvantages of surgical intervention are also influenced by the personal values and beliefs of the expectant mother and her partner. (Begović D. et al.,2021).

3. ADVANCES IN MINIMALLY INVASIVE FETAL SURGERY

Fetoscopic laser surgery (FLS) -

Twin-to-twin transfusion syndrome (TTTS) stages II–IV between 16 and 26 weeks of gestational age (GA) are best treated with fetal laser surgery (FLS), which offers superior neurological and survival outcomes over repeated amnioreduction. Given that FLS is thought to be more difficult in early TTTS because of the lack of chorioamniotic fusion, the Eurofetus study group advises this stringent GA cutoff[10]. Nonetheless, certain specialist clinics now execute FLS before 16 weeks because to improvements in technique, materials, and surgical experience.

In light of the ongoing lack of agreement regarding the best way to manage early TTTS, this study intends to present an updated systematic review and meta-analysis that compares FLS outcomes before and after 18 weeks with subgroup analysis for cases <16 weeks vs. 16–18 weeks. A 2020 systematic review noted that early TTTS cases (<16 weeks) carry a high risk of perinatal mortality and morbidity, but the data available were limited to small case series without head-to-head comparisons (Mustafa HJ et al.,2024**).**

Congenital diaphragmatic hernia (CDH)

About 1 in 4,000 babies are born with a congenital diaphragmatic hernia (CDH), with the left side being affected in 85% of instances. A substantial risk of infant death from respiratory failure and pulmonary hypertension results from intrathoracic herniation of abdominal viscera in CDH, which interferes with normal airway and pulmonary vascular development. Orthopedic abnormalities, cognitive delays, and respiratory and gastrointestinal problems are among the long-term consequences that survivors frequently experience. For the early identification and treatment of these issues, multidisciplinary follow-up is necessary throughout one's life. CDH is one of the costliest non-cardiac birth abnormalities in the US, with postnatal care expenses exceeding $250 million each year (Deprest JA et al.,2021).

Fetoscopic myelomeningocele

A minimally invasive prenatal surgical procedure called fetal myelomeningocele (MMC) repair is used to improve the neurological outcomes of fetuses with spina bifida. This strategy aims to maintain the advantages of early intervention while lowering the dangers connected to open fetal surgery.

The study "Fetal Surgery for Myelomeningocele: A Systematic Review and Meta-Analysis" offers a thorough assessment of both open and fetoscopic fetal MMC repairs. According to the study, fetoscopic repair offers a lower risk of uterine dehiscence and is a promising substitute for open fetal MMC repair. It does, however, highlight the necessity of refining fetoscopic methods to overcome issues like leaking and dehiscence at the repair site.

Stem cell and gene therapy integration

One possible paradigm change in neonatal medicine is cell therapy. It is especially a potential treatment to lessen the problems of prenatal hypoxia and preterm. It involves administering biological living cells to prevent or reverse the disease process and normalize the structure and function of organs and tissues by reducing inflammation and promoting endogenous repair of damaged or diseased cells or tissues (Razak A et al.,2023). Cell therapy is commonly used to treat cancers and hematological disorders, but its use in neonates for regenerative and immunomodulatory applications remains a relatively new field with many unanswered questions. Preclinical research has shown that cell therapies may be used to prevent or treat

preterm brain injury, necrotizing enterocolitis (NEC), bronchopulmonary dysplasia (BPD), perinatal asphyxia, perinatal arterial ischemic stroke (PAIS), and congenital heart disease, among other preterm pathology (Gentner B et al., 2021). These preclinical studies show that cell treatment may control tissue harm by anti-inflammatory, anti-apoptotic, paracrine, or angiogenic actions, or, in the case of certain stem cells, may replace damaged cells, depending on the type of cell and when it is administered. These advantages are also demonstrated in clinical research examining the function of cell therapy in a number of neonatal illnesses; while some studies indicate that cell therapy may hold promise, the evidence is not conclusive.

The two main types of cell therapies are allogeneic (using cells from other people) and autologous (using one's own cells). Although it is unknown if these two forms of cell treatment differ from one another, studies are being conducted to look at the safety and effectiveness of both in a range of newborn diseases. The fact that autologous cell therapy is not practical for many infants—preterm or problematic births are rarely expected—and that the target cell dose needed for some babies may not be attainable has led to an increase in research into allogeneic cell therapy (Somekh I et al.,2024).

Artificial womb technology

Artificial womb technology, or more precisely Artificial Amnion and Placenta Technology, or "AAPT," is eagerly waited for its potential to assist expectant mothers in risky pregnancies and as a better substitute for neonatal intensive care for prematurely born children. The goal of the technology is to enable the prolonged gestation of human entities from a pregnant person's uterus following an early birth (De Bie FR et al.,2023). Although the technology was first developed for clinical objectives to help people who have clinical difficulties during pregnancy, it may eventually have broader applications, some of which could promote gender equality in reproduction (Werner KM et al.,2022) Some speculate that many people, such as those who find pregnancy difficult or unpleasant or who view opting out of gestation as a way to reduce physical labor in reproducing, might welcome technology that can "take over" gestation, allowing a person with female reproductive biology to become a biological parent without undergoing the full 9-month period of gestation. Additionally, others have proposed that many people may wish to choose not to get pregnant for social reasons, like lowering the likelihood of discrimination at work or the amount of time they must miss from work **(**Cavolo A et al.,2024**).**

Bioengineering in Fetal Surgery

the use of engineering concepts to create biological remedies for prenatal fetal disorders. It uses regenerative medicine, biomaterials, and tissue engineering to fix birth abnormalities (Wheeler ML et al.,2021)

Tissue Engineering and Regenerative Medicine in Fetal Therapy

A field that creates or regenerates tissues and organs by combining cells, biochemical agents, and scaffolds (biodegradable materials). Defects like spina bifida and congenital diaphragmatic hernia (CDH)are repaired during fetal surgery.

Regenerative medicine stimulates the body's natural healing processes by using biomaterials, growth factors, and stem cells. It helps treat ailments like heart abnormalities and fetal lung hypoplasia (Combs H et al.,2022).

Biomaterial Innovations in Prenatal Surgical Interventions

Synthetic or natural materials that have been engineered to work with biological systems to replace or support injured embryonic tissues. Nanofiber scaffolds for skin or organ regeneration and biodegradable patches for diaphragmatic hernia repair are two examples (Winkler SM et al.,2019).

3D Bioprinting and Scaffold-Based Approaches for Fetal Repair

3D bioprinting is a technique that uses hydrogel and cell-based bio-inks to print biological objects layer by layer. It is being studied for the creation of tissues and fetal organ models for the correction of congenital defects (Sen T et al.,2024).

Using biodegradable scaffolds to create a structure for tissue regeneration and cell proliferation. These are especially helpful in fixing neural tube anomalies, tracheal problems, and embryonic skin malformations (Leonel EC et al.,2023).

Future Prospects of Bioengineering in In-Utero Interventions

The incorporation of cutting-edge technology including customized prenatal therapeutics, sophisticated biomaterials, and CRISPR-based gene editing. These could improve long-term results and decrease the need for postnatal procedures by revolutionizing the treatment of congenital diseases.

Table 1. Emerging Bioengineered Solutions for Fetal Surgery and Their Clinical Applications

Approach	Surgery	Benefits	Limitations	Trials	References
Tissue Engineering	Repair of Congenital hernia (CDH), spina bifida	Reduces need for postnatal interventions, enhances tissue regeneration	Risk of immune rejection, biocompatibility concerns	Research on biodegradable scaffolds and amniotic membrane patches	Shin JC et al,
3D Bioprinting	Creation of fetal organ scaffolds, vascular grafts for congenital heart defects	Personalized precise tissue constructs, potential for organ regeneration	Printing complexity, vascularization issues	Studies on bio-printed fetal heart valves and tracheal grafts	O'Connell AE et al.,2020
Stem Cell Therapy	Treatment of myelomeningocele, bronchopulmonary Dysplasia, perinatal brain injury	Regenerative potential, reduces inflammation and apoptosis	Delivery method optimization, risk of tumorigenesis	Clinical trials on mesenchymal stem cell therapy for neonatal disease	Bose SK et al.,2023
Bio-scaffolds Biomaterials	Wound healing for spina bifida repair, fetal membrane sealing	Provides structural support, enhances cellular integration	Risk of degradation immune response	Clinical use of collagen-based scaffolds and amniotic -derived materials	Fils AJ et al.,2024
Extracellular Vesicle Therapy	Neuroprotect in Perinatal asphyxia and stroke	Non-invasive reduces inflammation, promotes neurodegeneration	Limited clinical data, standardization challenges	Early-phase trials investigating based neuroprotection	Lou P et al.,2023

4. CONCLUSION

By combining gene editing, stem cell therapy, biomaterials, and regenerative medicine, bioengineered solutions in fetal surgery have completely changed the way congenital defects are treated. Technological developments like bio-scaffolds, 3D bioprinting, and tissue engineering have made it possible to treat fetal defects in utero with promising alternatives, lowering the need for postnatal procedures and enhancing long-term results. While gene therapy techniques like CRISPR provide hope for rectifying genetic abnormalities before birth, stem cell therapy has demonstrated promise in treating illnesses including spina bifida, bronchopulmonary dysplasia, and congenital diaphragmatic hernia.

Even with these developments, there are still a number of obstacles to overcome: uncertainties about immune rejection, long-term effectiveness, gene editing accuracy, and biomaterial biocompatibility must be addressed; and the safety of these treatments for the mother and fetus must be guaranteed, necessitating extensive preclinical and clinical testing.

5. THE NEED FOR FURTHER RESEARCH AND ETHICAL CONSIDERATIONS

To provide standardized procedures, enhance the safety profile, and perfect bioengineered techniques in fetal surgery, more research is essential. To assess long-term outcomes in newborns and validate the effectiveness of new treatments, more extensive clinical trials are required. To improve present techniques and guarantee responsible clinical application, a multidisciplinary strategy comprising bioengineers, neonatologists, obstetricians, and ethicists is crucial.

Fetal surgery presents special ethical challenges because it frequently involves two patients—the mother and the fetus—and includes interventions that are risky for both. The main ethical issues include informed permission, mother autonomy, and the possible long-term effects of genetic alterations. Global regulatory frameworks are also required to oversee the responsible use of bioengineered fetal treatments and gene-editing technologies.

In conclusion, even if bioengineered solutions have the potential to revolutionize fetal surgery, their effective incorporation into standard clinical practice will depend on their accessibility, safety, and ethical integrity.

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Conflict of Interest-

The authors declare no conflicts of interest related to this work.

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