Fetal Surgery for Congenital Neurological Abnormalities

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Abstract:

Since the last century, multiple imaging and surgical techniques have been developed to detect and treat congenital abnormalities of the central nervous system. Even though multiple technologies and approaches have been developed there is still a risk of complications or fatal outcomes. It is possible to perform neurological surgery on a patient before their birth (fetal surgery) with the correct diagnosis. Our literature review aims to gather the most current information available about fetal neurosurgery and its outcomes.

KEYWORDS: Fetus, Neurosurgical Procedure, In-utero surgery, Fetal Surgery, Congenital Abnormalities

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Introduction

Congenital Central Nervous System (CNS) abnormalities are among the prenatally diagnosed congenital abnormalities; the most common congenital abnormalities compatible with life are neural tube defects[1]. Hydrocephalus and myelomeningocele (MM) were some of the first proposed targets for fetal surgery [2,3]. due to the reliability in prenatal diagnosis of neural tube defects, they have greater scope in the field[4]. Before 1980, hydrocephalus cases were diagnosed only during delivery on an emergency basis due to arrested delivery or uterine rupture[5], prenatal diagnosis was not possible because of the non-availability of imaging techniques. The present review aims to provide the currently available information regarding fetal surgery for congenital neurological abnormalities considering its prognosis.

Need for Prenatal Repair

Conventionally, an open neural defect is closed in the postnatal period. It has an excellent cosmetic result and mitigates meningitis risk by establishing a skin-covered layer above the defect. Nevertheless, with the advancement of prenatal ultrasonography, progressive neurological deterioration in the fetus with MM was found[6]; this is attributed to the "two-hit hypothesis" that states that the first neurological injury occurred during primary neurulation failure; then, the additional damage is caused by the neural tissue contact with neurotoxic intrauterine contents[7]. In addition, the caudal suction effect of the CSF pocket within the spinal defect is believed to result in a Chiari Malformation type II (CM-II)[8]. Hence, it was hypothesized that Intrauterine Repair (IUR) might prevent the subsequent neurological damage and thence improve child neurological function and morbidity avoidance[8]. This theory became the rationale for prenatal repair.

Historical perspective

The first reported successful fetal procedure was performed in an animal in 1925 by Bors[9]. Animal studies gave three insights suggesting the role of fetal surgery to alter pathophysiological processes that may be irreversible in the neonate, rapid healing of fetal skin and other tissues, and minimal scar formation, even compared with neonatal tissues[10,11]. The first fetal therapeutic procedure was performed by Liley (1963)[12], by the injection of blood into the peritoneal cavity in a 32-week fetus affected by Rhesus (Rh) isoimmunization; three years later, fetal neurosurgery was introduced when Barke et al (1966)[13] confirmed the diagnosis of fetal hydrocephalus through gas ventriculography, this diagnostic procedure marked the beginning of fetal neurosurgical procedures. Birnholz and Frigoletto were the first neurosurgeons to attempt treatment of fetal hydrocephalus[14]; serial cephalocentesis were done (to decompress the ventricles in a fetus with ventriculomegaly) under ultrasonographic guidance every two weeks since the diagnosis at 25 weeks of gestational age, until 34 weeks of gestation when an elective cesarean section was done to deliver the baby. In 1981, Clewell et al. first described a ventriculo-amniotic shunt to treat a human fetus[15]; a Silastic shunt with a one-way valve was inserted percutaneously under ultrasonographic guidance with a needle through the posterior cranium into

the ventricle of a male fetus[15]. Moreover, Frigoletto et al[16] placed a ventriculoamniotic shunt in a fetus with a facial cleft at 23 weeks of gestational age in 1981. In 1982, Depp et al[17] performed a third ventriculo-amniotic shunt on a fetus with Dandy-Walker malformation. The Kroc Foundation Symposium (later renamed the International Fetal Medicine and Surgery Society [IFMSS]) was formed in 1982; here, fetal surgeons established patient selection guidelines for the fetal treatment of hydrocephalus with the help of Harrison et al[18] at the University of California, San Francisco (UCSF). Manning et al[19] consolidated the results of 41 fetal interventions for progressive hydrocephalus, recorded in the *"International Fetal Surgery Registry"*. Bruner et al[20] published the first report of in utero coverage of myelomeningocele in 1997 by the endoscopic placement of a maternal split-thickness skin graft over the fetal neural placode. In 1999, Tulipan et al[21] demonstrated a reversal of CM-II after the prenatal repair of fetal myelomeningocele using open fetal surgery when performed before the 26th week of gestation. In 2003, Cavalheiro et al[22] performed the first fetal endoscopic third ventriculostomy to treat hydrocephalus by aqueduct stenosis in a fetus at 26 weeks of gestation.

Clinical Studies

The endoscopic approach of Fetal MM Repair (FMMR) in humans began in the early 1990s in the US and Europe at Vanderbilt University and Children's Hospital of Philadelphia[20,23,24]. During this time, it was found that patients treated via open FMMR displayed less hindbrain herniation and normalization of CSF dynamics, which resulted in a reduction of postnatal shunting procedures[25-28]. Vanderbilt, in 2014 compared 43 patients who underwent fMMR at Vanderbilt to the MOMS prenatal cohort to evaluate a modification to the uterine opening in an effort to reduce amniotic membrane separation and other related maternal complications. Improved maternal outcomes were observed relative to the original trial cohort[29,30]. In 2015, the Children's Hospital of Philadelphia (CHOP) reported the largest cohort of patients post-MOMS describing 100 consecutive fMMRs and their postoperative course[31].

Two-hit hypothesis and animal model research

In myelomeningocele, the neural injury happens for two reasons, termed the two-hit hypothesis. The first injury is due to the primary neural tube defect during neurulation. The secondary injury is caused by environmental factors during intrauterine life (like amniotic fluid alterations), causing neuronal damage[32]. In murine and porcine models, the cohort undergoing intrauterine surgical repair showed improved neurological function and minor physical deformity than those undergoing postnatal repair[8,33]. In a primate model, Michejda demonstrated that fetal repair could improve neurological results relative to untreated monkeys[34]. The ovine model by Meuli et al[35] and its modification was perhaps, the most accurate model reflective of human MM pathophysiology[35-37]. However, animal model research suggested that prenatal coverage of myelomeningocele can preserve neurologic function and minimize hindbrain herniation risk[29]. The animal model research included both large and small animal models like rabbits and primates[3,32]. Michejda reported that fetal myelomeningocele repair yielded the best results in monkeys, as there was no

paraplegia, incontinence, or sensory disturbances[34]. In another animal model, lambs were used as an animal model since preterm labor prevalence is much less in sheep. This model produced better intrauterine damage to the neural tissue by supporting the two-hit theory[4]. Myelomeningocele was surgically done in this model at 10-11 weeks of gestation, corresponding to 20 weeks in humans. The surgical repair of the myelomeningocele was performed at 14-15 weeks of gestation. However, this model did not address the first hit (the induction of neural tube defect). A good animal model should induce both neural tube defect and intrauterine injury, but this was practically not[4]. The newer methods using bio-adhesives, stem cells, and biodegradable scaffolds are being studied in animal models[38-40]. It was reported that these methods were not flawed and were comparable to the postnatal methods. The ovine model studied by Meuli et al[35] was considered the best for studying myelomeningocele.

Emerging Surgical Techniques and Future Perspectives

At CHOP, Moldenhauer and Adzick created two membrane-lined myofascial flaps using needlepoint electrocautery beyond the dura. They sutured them together in the midline for a thicker, tension-free spinal canal covering[41,42]. Vanderbilt pioneered at first the endoscopy for fetal dysraphism in animal models in 1993[43]. Employing a maternal graft only, the first fMMR surgery in a human was performed endoscopically in 1994[43]. Kohl and colleagues[44] had described a percutaneous fetal procedure first in sheep and then in humans. He placed a synthetic patch over the spinal defect, thus protecting the neural elements from intraamniotic fluids; however, this technique mandated formal skin closure in the postnatal setting[24]. By 2012, the technique was improved to include suturing of an absorbable patch over the defect followed by skin approximation with synthetic graft supplementation[45]. In 2016, Pedreira et al[46] published their series of 10 patients treated with endoscopic placement of a biocellulose patch followed by single-layer skin closure. Though lay patches were technically simpler than primary dural closure, they resulted in less favorable wound results and persistent maternal morbidity; hence, the so-called “patch-and-glue” technique lost traction. At Texas Children’s Hospital, Whitehead et al pioneered an endoscopic multilayer closure after exteriorization of the uterus through a laparotomy, which has the advantage of minimal uterine manipulation by minimizing CSF and wound complications associated with non-sutured graft closures. This approach seems to be a promising alternative to open fetal surgery[47,48].

Fetal neurosurgical techniques

Frigoletto et al[16] observed the development of seizures, sepsis, and diabetes insipidus, and the child died five weeks after birth. Depp et al[17] observed hemiparesis, spastic diplegia, and developmental delay. These children had VA shunts inserted prenatally for hydrocephalus. However, these complications provided essential lessons which improved the future applications of fetal neurosurgery. It is important to consider if the surgery can be planned prenatally or postnatally depending upon the associated comorbidities of the mother and fetus.

In the earlier days, fetal neurosurgery was done by using the open method. However, due to recent advances, fetal neurosurgery

has become “easier” on the patient by applying percutaneous and minimally invasive methods[49]. The back-biting uterine clamps and absorbable staplers were invented mainly for use in fetal neurosurgery; these devices will decrease blood loss and will not impair subsequent chances of conceiving, which is very common with the use of metallic staplers[50,51]. Advanced anesthesiologic techniques and tocolytics have decreased the chances of premature delivery and rupture of membranes[4]; it was reported that fetal neurosurgery for hydrocephalus had decreased the prevalence of postnatal shunt placement[23,52]. Still, fetoscopic techniques, which aimed to decrease fetal and maternal morbidity, were unsuccessful due to the inaccurate closure of the back defect[23]. Compared to postnatal surgery, fetal surgery for myelomeningocele, if performed before the 26th week of gestation, gave the best results by decreasing mortality and morbidity, such as the need for shunting[29]. Motor and mental function scores were also increased, and the children were able to walk independently. The children who underwent fetal meningocele repair had higher psychosocial health and total quality of life assessment scores[29].

Management of Myelomeningocele Study (MOMS)

MOMS was a prospective, randomized clinical trial that compared prenatal and postnatal closure; it was performed at three distinct institutions: the University of California, San Francisco (UCSF), Vanderbilt University Medical Center, and the Children’s Hospital of Philadelphia (CHOP)[29]. The method was standardized across these centers. Initially, the fetal surgery team created an adequately sized hysterotomy after maternal laparotomy; this was followed by an intramuscular injection of fentanyl and vecuronium administration to the fetus[29]. The study observed that the prenatal surgery group showed shunt requirement in only 40% of cases compared to 82% of the postnatal surgery group ($p < 0.001$). It was also reported that the ventriculoperitoneal shunt was more durable in the prenatal repair group than in the postnatal surgery group and required stent revision at less than half the rate[43]. However, oligohydramnios, spontaneous preterm labor, chorionic membrane separation, premature rupture of membranes, and spontaneous membrane rupture were considered complications of fetal neurosurgery. The mothers required blood transfusion during the delivery in the majority of cases[43].

Fetal neurosurgery and the role of ultrasound

Myelomeningocele was endoscopically repaired in humans during the early 1990s[25,29]. Recent advances such as real-time high-resolution ultrasound have made it possible to study the fetus in detail, including neurulation[29]. Before completion of the first trimester, the fetal skull and lateral ventricles can be identified[29]. Hydrocephalus in the developing fetus can be identified as early as in the second trimester, but it is challenging to manage. Glick et al[53] observed additional CNS anomalies in fetuses, which were diagnosed with ventriculomegaly, and they suggested that fetal ultrasonography is of limited scope. Prenatal myelomeningocele repair in humans was performed by hysterotomy in 1997[29]. Nevertheless, nowadays fetal ultrasonography is very much improved and helping in prenatal diagnosis. Well-trained

radiologists can assess the anatomy of the ventricles, posterior cranial fossa, and vertebral column. The anomaly scan can also detect anomalies other than the nervous system, suggesting genetic syndrome[54]. The ultrasound scanning also indicates the prognosis of the fetus, which may help counsel the parents. Mapping the placenta before uterine incision and checking fetal heart rate can be done under ultrasound guidance. In addition to ultrasonography, fetal MRI can also be done and will show detailed information about the structural anomalies of brain-like heterotopia[4].

Neonatological care

Fetal neurosurgery requires support by neonatologists[4]. Neuroprotective supporting measures are essential to managing premature babies and neonatal cerebral injury. Neuroimaging at regular intervals, electroencephalogram monitoring, and therapeutic hypothermia are very much essential[22]. Physiotherapy is also an essential requirement for the neonate[4].

Disadvantages of the fetal neurosurgery

The significant benefits of fetal surgery must be compared with the risks of premature delivery and fetal and maternal morbidity[43]. Fetal surgery carries the risk of a higher rate of maternal transfusion, intraoperative complications, uterine-scar defects, and preterm labor[43]. Preterm labor can lead to placental abruption and pulmonary edema in the fetus[55]. Chorioamniotic separation can happen in 25% of cases of prenatal surgery, which increases the chances of premature rupture of membranes[51]. It was observed that the hysterotomy site incision made during fetal surgery had to thin, and an area of dehiscence was present in 33.3% of cases; this increases the risk of uterine rupture during subsequent pregnancies[50]. Mothers undergoing fetal neurosurgery should be informed about the need for cesarean section for future deliveries. Cesarean section should be planned before the onset of labor[29]. Fetal neurosurgery is contraindicated in obese females with a body mass index above 35. However, it was observed that mothers of myelomeningocele fetuses are usually obese. The inclusion of cysts like dermoid and epidermoid, and spinal cord tethering syndrome, are significant complications that can occur following fetal neurosurgery[56]. It was described that unresected epithelial tissue from the surrounding zone of the placode might be the source of these dermoid and epidermoid cysts. The prevalence of inclusion cysts is less in the hands of experienced fetal neurosurgeons[43].

Quality of Child Life and Long-Term Development

Among 42 children treated at CHOP preMOMS, Danzer and colleagues[57] found at a median follow-up of 10 years: nearly 80% - community ambulators, 14% - wheelchair-bound. 25% - Normal bladder function. MOMS II study: funded by the Eunice Kennedy Shriver National Institute of Child Health and Human Development, Assessment of children from the original MOMS cohort, now aged 5 to 8 years old, for adaptive behavior, cognitive functioning, motor level, and function, urological health brain morphology and connectivity using high-resolution imaging. Other things measured in this study were the quality of life, maternal health, and family impact[57].

Future implications

Houtrow et al[58] reported that children who had undergone fetal neurosurgery had the best competency in the skill of their self-care ambulatory with a better quality of gait and higher-level mobility skills as they performed a 10-meter walk test one second quicker. Danzer et al[57] reported that about 80% of the children who underwent fetal meningocele repair were community ambulators examined after ten years old. Only 14% of the children were wheelchair users, and they also observed that 25% of the children had normal urinary bladder function[57]. The continuous ultrasound studies from fetuses with myelomeningocele revealed that there would be progressive insults to the central and peripheral nervous systems[29]. Neural tube defects can lead to CM- II due to the caudal suction effect of the CSF pocket[43]. The child may suffer from motor abnormalities in the lower limbs, herniation of the hindbrain, and hydrocephalus[59,60]. One emerging indirect application of fetal neurosurgery is gene therapy for congenital neurodegenerative disorders[61,62]. Along with the hydrocephalus and myelomeningocele, the other CNS anomalies like vascular malformations and encephaloceles can also be repaired with fetal surgery[5]. The steal and brain resorption in the intrauterine life can be decreased by the endovascular technique like in the repair of great cerebral vein of Galen malformations[4]. Gene therapy can be tried for congenital neuronal degeneration. Stem cell therapy has been tried for the Pelizaeus–Merzbacher disease (PMD clinical trial) and Batten disease[63]. In the future fetal neurosurgery can help in treating diseases like Parkinson's disease and Huntington's chorea with the application of gene therapy[61]. Immunological tolerance performed prenatally can prevent long-term immunosuppression in adults[4]. The open micro neurosurgical technique has a lower prevalence of hydrocephalus, preterm delivery, and increased gestational age than classical open fetal surgery[55].

Conclusions

According to the available literature, the recent advantages in fetal surgery allow for correction of CNS abnormalities such as repair of myelomeningocele or shunt placement for hydrocephalus, vascular malformations repairment, and some other neurosurgical fetal procedures. However, regardless of these, multiple risks have been associated. More studies are required to establish a gold standard for this type of treatment while minimizing the risk for mothers and fetuses. Also, we consider it essential to establish the importance of multidisciplinary management to improve and give high-quality medical care.

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