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Intrauterine Fetal Therapy: Past, Current, and Future

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Abstract

Background: As many novel intrauterine diagnostic techniques for life-threatening conditions advance, the efforts of maternal-fetal medicine (MFM) physicians to expand therapeutic boundaries should never be underestimated. This fact can be noticed in the rapid growth and revolutionary achievements in intrauterine fetal therapy (IUFT). **Objectives:** This study aims to gather the current available data about the intrauterine fetal therapy (IUFT), as a new rapidly advancing field of medicine, from a general perspective rather than diving deep into its complex information. **Methods:** It is a comprehensive literature review article done at the Batterjee Medical College, Jeddah, Saudi Arabia. By using the keywords (*mentioned below*), a cross-search of seven different medical databases (AMED-Allied and Complementary Medicine Database, BIOSIS Previews on Web of Knowledge, Cochrane Library, Embase, and the Medline on Web of Knowledge, OvidSP, and PubMed) was conducted to examine the progresses in the field of intrauterine fetal therapy. **Results:** The IUFT includes intrauterine pharmacological treatment, minimally invasive fetal interventions, and open fetal surgeries. Each of these interventions is subsequently subdivided into different categories. The future aspects of IUFT focus on intrauterine stem cell transplantation and intrauterine gene therapy, among others. **Conclusion:** Prenatal diagnosis of congenital fetal anomalies necessitates early intrauterine intervention to manage the current problem and avoid further complications. Ethical standards and family counseling should always be considered, and a risk-benefit scale should be applied. Further exploration of this rapidly advancing field is crucial, and extensive clinical trials and studies are recommended.

Keywords

Intrauterine Fetal Therapy, Intrauterine Pharmacological Treatment, Minimally Invasive Fetal Interventions, Open Fetal Surgery, *In-Utero* Stem-Cells Transplantation, Intrauterine Gene Therapy

1. General Overview

In the rapidly developing field of MFM, intrauterine fetal therapy (IUFT) aims to treat a range of fetal abnormalities and disorders while the fetus is still inside the mother's uterus [1]. By identifying and treating fetal anomalies at an early stage of gestation, this method may improve perinatal outcomes and lower long-term morbidities and mortalities [2]. IUFT includes a variety of therapeutic interventions that are carried out directly on the fetus himself or to the intrauterine environment surrounding him [3]. Conditions, such as congenital diaphragmatic hernia, twin-to-twin transfusion syndrome (TTTS), neural tube malformations (NTDs), congenital heart disease (CHDs), and other anatomical anomalies frequently require such interventions [4]. The range and validity of IUFT have been greatly increased by advances in perinatal care, imaging technology, and surgical instruments, making it a more attractive alternative in some situations [5]. However, many hazards and difficulties are still associated with IUFT, such as maternal and fetal risks, ethical issues, and resources allocation [6]. Consequently, healthcare practitioners who are involved in the treatment of pregnant women and their unborn fetuses must have a thorough awareness of the indications, procedures, risks, and ethical considerations close to it [7].

For previous studies, the literature searched mainly for the keywords; "intrauterine fetal therapy, intrauterine pharmacological treatment, minimally invasive fetal interventions, open fetal surgery, *in-utero* stem-cells transplantation", as well as, "intrauterine gene therapy" at the Saudi Digital Library (SDL) online, in addition to the pertinent online medical journals and magazines. Additionally, we looked for articles that are indexed in CINAHL Plus, MEDLINE, PubMed, EMBASE, the Cochrane Methodology Register, and MEDLINE. Since proximity searches are not possible in PubMed, Ovid was used to search for MEDLINE.

2. History of Fetal Therapy

The early invasive fetal therapy was an intrauterine blood transfusion in 1963. The Fetal Treatment Center (FTC) was founded by Michael Harrison in the early of 1980s at the University of California at San Francisco (UCSF), in the United States of America. It was credited as the birthplace of fetal surgery. The first recorded successful open surgery for fetal lower urinary tract obstruction was in 1981, with the first recorded open repair of a fetal diaphragmatic hernia was in 1989 [1] [8].

In Europe, the introduction of minimally invasive fetal surgical techniques led to the establishment of fetal treatment centers. Open fetal surgery to correct con-

genital anomalies was, at early dates, associated with unacceptable high rate of maternal morbidities. However, with the start of minimally invasive LASER intervention for severe cases with TTTS, the King's College in London, in the United Kingdom, becomes the focus for fetal therapy.

Intrauterine blood transfusion to treat hemolytic diseases of the fetuses was the first successful fetal intervention. Interventions for other fetal diseases such as repair of fetal myelomeningocele were fully investigated, followed by conducting many randomized clinical trials (RCTs) before adoption of these interventions widely [5].

3. Benefits and Risks

Benefits of IUFT include refining long-term outcomes by improving fetal growth and development through interventions targeting fetal growth abnormalities along with reducing the morbidity and mortality rates in certain conditions like genetic disorders and congenital anomalies through timely interventions [9]. Moreover, intrauterine fetal therapies can restore or preserve organ functions like lungs, heart, and kidneys. By preserving the organs' functions this will improve the quality of life postnatally and reduce the healthcare burden on concerned families and healthcare authorities. Early intrauterine therapeutic interventions can also stop disease progression and give better planning for postnatal management [10].

Table 1. Benefits and risks of IUFT.

Category	Benefits	Risks
Fetal Outcome:	Enhances fetal growth and reduces neonatal morbidity and mortality rate among fetuses with congenital anomalies and genetic disorders [1].	Potential fetal harm and/or unsuccessful procedure [1].
Organ Functions:	Restores organ function, improves postnatal quality of life, and/or stops disease progression [2].	Risk of organ failure or damage, and increased maternal financial burden and psychological stress.
Procedure steps:	Correct the underlying pathology and improve fetal survival [5].	Risk-related complications: as intra-uterine bleeding [8], fetal injury, intra-uterine infection (Chorioamnionitis), intra-uterine growth restriction (IUGR), intra-uterine fetal demise (IUFD), premature amniotic fluid leakage [41], placental abruption, fetal bradycardia, and/or anesthesia complications [42].
Timing of Labor:	Elective delivery, either vaginal or cesarean section.	Increased risk of premature labor and its associated complications [61].

Risks of IUFT may involve procedure-linked risks. These risks include bleeding, infection and possible injury to vital organs or blood vessels of the fetus or the mother. In addition, many reported complications related to the anesthesia type

and mode of its administration [11]. Premature labor sometimes happened and resulted in high neonatal morbidities such as mental and physical developmental abnormalities, pulmonary hypoplasia and respiratory distress syndrome, as well as long-term disabilities. Other procedures such as open fetal surgery may carry the risk of injury to the fetus, placenta, or to the maternal surrounding structures. Other probable worries may include amniotic fluid leakage and placental abruption [12] (**Table 1**).

The ability to interfere with normal fetal development, carry a higher chance of genetic mutation being passed down through the germline, and cause genotoxicity and/or oncogenesis are the main hazards associated with intra-uterine gene therapy. These are the main known or suspected specific risks of prenatal gene therapy that raise moral questions.

Finding a balance between the ethical standards of beneficence (behaving in the patient's best interests) and nonmaleficence (avoid hurting the patient) is the main concern because of the novelty and high level of ambiguity in the findings.

4. Family Counseling

The parents, and sometimes their family members, should have counsel from a multidisciplinary healthcare team. Beyond the emotional strain they experience, they must understand complex medical information. It is crucial to realize the fact that some individuals typically can absorb a limited amount of information during one counseling session. Furthermore, decisions about an unborn fetus involve both feelings and lucidity. In-addition, some maternal risks are often not fully considered after the initial counseling session. Cultural, social, economic, religious, legal, and technical factors should be considered in every counseling session. The capacity of counselled individuals to understand and process this information is influenced by their level of intelligence and education. Even in developed countries with strong educational systems, only around half of adults can fully grasp medical information following one session. Anxiety and stress resulting from bad news can affect information remembering. Therefore, family counseling for IUFT presents a challenge, thus, a structured training is required [13].

5. Ethical Consent

It is very curious in the MFM to deal with the fetus as a human being. This means that medical teams have to pact with uncertainties about the fetal condition and treatment outcomes. As new interventions are developing, it is crucial to establish standards of care, to ensure appropriate informed consent, respect the pregnant woman's preferences, and uphold the responsibilities of doctors referring patients to trials. As advised by the American Academy of Pediatrics (AAP) and the American College of Obstetricians and Gynecologists (ACOG), a written agreement is essential for fetal therapy. Experienced doctors understand when to offer intervention or termination to prevent the tragic outcome of a severe condition resulting in a livebirth with anomalies incompatible with life. The legal gestational age

limit for termination varies among different countries, and once the pre-viable age is decided, the woman's choices after may become restricted [14] [15].

6. Intrauterine Pharmacological Treatment (IUPT)

Intrauterine pharmacological interventions (IUPT) are typically reserved for cases where there is a significant medical necessity to address specific medical conditions or developmental issues affecting the fetus. These involve administering drugs indirectly into the amniotic fluid and placenta through maternal circulation or directly to the fetus through intramuscular or intravenous routes [16]. Trans-placental administration is convenient for medications with small molecules like glucocorticoids to enhance fetal lung maturity, immunoglobulin to prevent neonatal alloimmune thrombocytopenia, anti-retroviral drugs to reduce perinatal transmission of human immunodeficiency virus (AIDS), digoxin to convert cardiac arrhythmia, and dexamethasone to prevent virilization in congenital adrenal hyperplasia [17].

Table 2. Intrauterine pharmacological treatment (IUPT).

Intrauterine Pharmacological Treatment	Indications
Trans-placental administration [1]	
Glucocorticoids	Enhance fetal lung maturity.
Immunoglobulins	Neonatal allo-immune thrombocytopenia.
Anti-retroviral drugs	Reduce perinatal transmission of HIV.
Digoxin, Flecainide, Sotatol	Convert cardiac arrhythmia.
Dexamethasone	Prevent virilization in CAH.
Intra-amniotic installation [14]	
Thyroxine (Levothyroxine)	Fetal goiter hypothyroidism.
Growth factors	Improve fetal growth in the case of IUGR.
Intravenous administration [17]	
Amiodarone	In refractory fetal SVT with hydrops.
Fetal intramuscular injection [18]	
Thyroxine (Levothyroxine)	Fetal hypothyroidism if there is esophageal obstruction.
Methimazole	Fetal hyperthyroidism (2ry to maternal auto-immune hyperthyroidism).
Fetal anesthetic drugs	For fetal Surgical Interventions [26].

The end-fetal dosage could be affected by maternal volume of distribution, hepatic first-pass effect, and renal clearance. Intra-amniotic installation is convenient for thyroxine for the fetus to swallow in case of fetal hypothyroidism caused by trans-placental passage of maternal anti-thyroid medication or antibodies. Growth factors may be administered into the amniotic fluid to improve fetal growth and development in the case of Intrauterine Growth Restriction (IUGR). Intravenous administration is convenient for Amiodarone in refractory fetal su-

praventricular tachycardia with hydrops. Direct fetal intramuscular injection is convenient for the administration of thyroxine in case of fetal goitrous hypothyroidism if there is an esophageal obstruction. In addition, fetal anesthetic management for surgical interventions, can be achieved by the use of Fentanyl (10 μg/kg) intramuscular to induce fetal anaesthesia with muscle relaxants as Pancuronium (0.3 mg/kg) [18] (**Table 2**).

7. Minimally Invasive Fetal Intervention (MIFI)

Minimally invasive fetal interventions (MIFI) include procedures performed with a minimal disruption to the uterus and the developing fetus. These precise interventions aim to address specific fetal conditions or abnormalities while minimizing maternal and fetal risks. Minimally invasive fetal surgery is broadly divided into 3 categories: Fetoscopic interventions, Needle-guided interventions, and shunting procedures. Ultrasound guidance is critical to the all interventions as it is identify a safe entry to the uterus [19].

Fetoscopy involves inserting an endoscope into the uterine cavity to visualize the fetus and perform the surgical procedure. This technique allows precise interventions such as a fetoscopic LASER to coagulate the connecting blood vessels that cross the fetal membranes in cases of twin-to-twin transfusion syndrome (TTTS), and in cases with twin-reversed-arterial-perfusion (TRAP) sequence. It is advised to perform elective fetal reduction by umbilical cord ligation, fetoscopic LASER coagulation, ultrasound-guided bipolar cord coagulation, or by radiofrequency ablation in certain complex monochorionic pregnancies where there is a high risk of hemodynamic compromise or intrauterine fetal death [20].

Fetal cystoscopy is another example of fetoscopic intervention used for lower urinary tract obstruction, in which a fetoscope is placed through a trocar within the fetal bladder, to diagnose the source of obstruction or to ablate the posterior urethral valve. Fetal cystoscopy is more intrusive than vesico-amniotic shunting, but it has the advantage of properly identifying fetuses who will benefit from valve ablation [21]. Fetal endoscopic balloon tracheal occlusion used for congenital diaphragmatic hernia (CDH) is another example, in which a fetoscope is introduced into the fetal trachea. A balloon is inflated just proximal to the carina. Fetuses with CDH benefit from tracheal occlusion because it enhances postnatal lung functions, reduces abdominal visceral herniation, and increases lung capacity [22] [23].

In situations like amniotic band syndrome, involving fetal extremities, fetoscopic band release may allow the fetus to retain limb function. *In-utero* repair of the meningo-myelocele before later damage occurs to the exposed structures improves distal neurologic function and reverses the Arnold-Chiari malformation. The malformation is dissected with a needle electrode, and the placode (embryonic ectoderm) is manually dissected free from surrounding tissues with micro scissors and micro grasper [24].

Needle-guided interventions can be used for fetal blood sampling and transfu-

sion, which involves cordocentesis for sampling fetal blood from the umbilical cord to diagnose certain fetal blood disorders or infections. In some cases, intrauterine transfusions may also be performed to treat fetal anemias due to Rh-incompatibility or fetal-maternal hemorrhage. This involves injecting blood products directly into the fetal circulation via ultrasound-guided needle insertion into the umbilical vein. A sequential non-invasive testing with middle cerebral artery Doppler is required for monitoring to ensure timely intervention with intrauterine blood transfusion in high-risk fetuses [20].

Ultrasound guidance to insert a needle or a probe to ablate or shrink the tumor is successful in the case of sacrococcygeal teratoma and certain cardiac tumors [22]. Shunting procedures include vesico-amniotic shunting in case of lower urinary tract obstruction, a double pigtail stent is placed percutaneously under ultrasound guidance, usually in conjunction with amnioinfusion [21].

Table 3. Minimally Invasive Fetal Interventions (MIFI).

Minimally invasive interventions	Indications
Fetoscopic interventions	
Fetoscopic LASER ablation:	Posterior urethral valve obstruction [1].
	Placental chorioangioma [3].
	Twin-Twin Transfusion Syndrome (TTTS) [4].
	Twin Reversed Arterial Perfusion (TRAP) [5].
Fetal cystoscopy:	Lower urinary tract obstruction (LUTO) [6].
Fetoscopic Endoluminal Tracheal Occlusion (FETO):	Congenital diaphragmatic hernia (CDH) [8].
Fetoscopic band release:	Amniotic band syndrome [11].
Fetoscopic repair of myelomeningocele:	*In-utero* repair of the myelomeningocele [12].
Needle-guided interventions	
Fetal blood sampling and transfusion:	Management of fetal blood disorders [16].
	Hemolytic anemia, Sickle-cell disease [19].
	In-utero stem cell and gene therapy [20].
Ultrasound-guided probe:	Tumors like sacro-coccygeal teratoma (SCT).
	Percutaneous fetal valvuloplasty [21].
	Amnio-reduction in severe polyhydramnios [23].
	Amnio-infusion in severe oligohydramnios.
	Thoracocentesis in severe pleural effusion.
Shunting procedures	
Vesico-amniotic shunting:	Lower urinary tract obstruction (LUTO) [6].
Surgical shunt operation:	In ventriculomegaly (Hydrocephalus) [25].
	Congenital lung masses [32].
Thoraco-amniotic shunting:	Congenital Adenomatoid Malformations [40].
	Pleural effusion [53].

Thoracoamniotic shunt placement is used for congenital lung masses, congenital cystic adenomatous malformations, or for pleural effusion to relieve the mass effect of excess fluid and to allow for normal pulmonary development [25] [26] (**Table 3**).

8. Open Fetal Surgeries (OFS)

Open fetal surgeries (OFS) are sometimes called mid-gestation open procedures. Early detection of fetal abnormalities enables mid-gestation interventions to prevent irreversible harm or secondary complications. The fetus is accessed via a hysterotomy after localization of the placenta by using an ultrasound guidance. Following surgery, the fetus is returned back to the uterus until the end of gestation. Fetal surgery is done through a low transverse abdominal incision, and a specially designed absorbable stapler is used to close the uterine incision. For example, repairing meningo-myelocoele at 22 weeks of gestation aims to stop the damage to central nervous system tissues caused by prolonged exposure to amniotic fluid [27] [28].

The Ex-utero intrapartum treatment (EXIT) procedures are also known as operation on placental support "OOPS" which is done during cesarean section or vaginal delivery. The EXIT procedure allows for the safe management of the fetal airway and the application of critical fetal interventions under controlled conditions, all while the fetus continues to receive placental circulatory support. These procedures are typically conducted at or close to full-term gestation since the fetus is delivered at the end of the procedure. The aim of the procedure is to secure the airway of fetuses with oropharyngeal masses, neck masses, or severe micrognathia that lead to airway blockage [29]-[32] (**Table 4**).

Table 4. Open Fetal Surgeries (OFS).

Aspect	Mid-Gestation Open Procedures	EXIT Procedures
Timing:	Typically performed mid-gestation (± 22 weeks).	Conducted at, *or close to*, full-term gestations [1].
Objective:	Address fetal abnormalities detected early in pregnancy [5].	Manage fetal airway and apply critical interventions during birth.
Method of Access:	Fetus accessed via Hysterotomy after placental localization.	Done during C-section or vaginal delivery [22].
Surgical Approach:	Low transverse abdominal incision (Bloodless Hysterotomy).	Ensure controlled conditions for fetal interventions [26].
Benefits:	Prevent irreversible harm or secondary complications.	Secure airway of fetuses with oropharyngeal masses or micrognathia [27].
Examples of Procedures:	Repairing myelomeningocele, Repair of opened spina bifida, Sacrococcygeal teratoma resection Artificial graft for gastroschisis [29].	Managing oropharyngeal masses or neck masses [30], Congenital pulmonary airway malformation (CPAM), Severe micrognathia [31].

Tackling genetic conditions and impeding *in-utero* organ failure might be what

the future holds for fetal therapy [33]. This is especially complemented by the fact that precise diagnosis of life-threatening genetic disorders during pregnancy through advanced techniques such as whole exome sequencing and gene panels are now more of a reality than ever [34]. Among the novel intrauterine therapies undergoing extensive research are hematopoietic stem cell transplantation and intrauterine gene therapy.

9. *In-Utero* Stem-Cell transplantation (IUSCT)

Fetal tissue, rich in stem and progenitor cells, is valuable for various treatments due to its ease of culture and rapid proliferation compared to adult tissue cells. With its expression of human leukocyte antigen (HLA) G and lower antigenicity, the risk of rejection and the need for exact tissue matches is reduced. Sourced from cadaveric fetuses after abortion, stillbirth, or ectopic pregnancy surgeries, the tissue is processed into a cell suspension for grafting, typically injected intravenously or intraperitoneally, or transplanted into specific sites during surgery. Modern safety measures like cytogenetic testing (including comparative genomic hyperdization array and karyotyping) ensure the success of stem cell transplants [35].

Recently, with the widespread use of advanced diagnostic techniques including high-resolution ultrasound scanning and maternal serum free fetal DNA, many congenital disorders are diagnosed early in gestation. Some of these disorders can be tackled and treated early. *In-utero* stem cell transplantation (IUSCT) provides a promising cure for some of genetic disorders. Furthermore, if prenatal stem cell therapy is started early enough, it can get the advantage of the naive fetal immune system and accept the grafts without myeloablation or immunosuppressive medications, which are usually required for postnatal transplantation [36].

The first successful IUSCT was performed in 1989 for Bare Lymphocyte Syndrome (BLS), which is an immune deficiency disorder [35]. Subsequent consistent success has been shown in fetuses with severe combined immune deficiency (SCID), where it was able to restore defective cell lines and improve genetic defects [37]-[39]. Hematopoietic stem cell (HSC) transplants have been previously attempted for transfusion-dependent beta-thalassemia, but mesenchymal stem cells (MSC) have shown broader potential, with successful cases reporting improvements in conditions like osteogenesis imperfecta [40] [41]. However, other studies have been less successful, such as sickle cell disease (SCD), where a female fetus received donor liver fetal cells at 13 weeks of gestation with no evidence of improvement at birth or 8 months of age. The future clinical use of IUSCT may involve either a single transplant achieving adequate engraftment levels for treatment or an initial transplant inducing tolerance for a subsequent postnatal transplant to enhance engraftment without myeloablative or immunosuppression techniques [42].

Given the limited current evidence on safety and efficacy, the IUSCT should be conducted only in clinical trials with a safety as the primary outcome. If both safety and efficacy are demonstrated, IUSCT could become a standard of care fol-

lowing best practice protocols developed throughout these trials [43].

10. Intrauterine Gene Therapy (IUGT)

Prenatal or intrauterine gene therapy (IUGT) is a prospective treatment modality that is on its way to becoming a clinical reality. The IUGT involves the delivery of genetic material to fetal cells to cure life-threatening genetic disorders [44]. Since the efficacy and hazards of IUGT are not yet completely established, it must be reserved for conditions that have poor outcomes, have a well-established genotype or phenotype link that can be accurately identified during pregnancy, and have an *in-utero* gene therapy in animal model simulating the human disease to produce preclinical data [45]. The above-mentioned genetic material is typically transported through a vector, whether viral or else [46]. The vector can be delivered intravenously through the umbilical vein for systemic distribution, intra-amniotic to allow for increased distribution of the genetic material by fetal movements such as swallowing and breathing, as well as through other routes such as intramuscular and intraperitoneal [47]. Viral vectors such as *Lentiviruses* and *Adeno-associated Viruses* (AAV) are utilized in most gene therapy trials to transfer functioning copies of genes in cases of haploinsufficiency, with the aim of establishing a long-term physiological expression [48].

Shangaris *et al.* [49] demonstrated that the injection of lentiviral vectors containing the β-globin gene achieves normal postnatal hemoglobin levels in mice with β-thalassemia. On the other hand, non-viral modalities involve conjugating genetic material with polymer-based or lipid nanoparticles, which, like viral vectors, allow cell entry and prevent degradation by endonucleases [46] [50]. In RCTs, these non-viral technologies have been used to deliver gene-editing machinery, such as the CRISPR-Cas9 complex, which was utilized for in-vivo editing of transthyretin amyloidosis [51]. Although viral vectors shine over the non-viral methods in terms of more efficient DNA delivery and prolonged gene expression, this comes at the cost of decreased packaging capacity and potential tumorigenicity [48].

The IUGT has shown noteworthy results for several well-defined monogenic disorders that cause severe morbidities. One such condition is Crigler-Najjar type-1, caused by a mutation in the UGT1A1 gene, which is characterized by the body's inability to convert unconjugated bilirubin into a water-soluble form. This leads to an accumulation of bilirubin in the serum, causing kernicterus or bilirubin-induced encephalopathy. Seppen *et al.* [52] demonstrated that injecting lentiviral vectors containing the human UGT1A1 gene into rat models *in-utero* brought about partial improvement in elevated bilirubin levels. Another example is Gaucher disease, caused by a deficiency in the lysosomal enzyme glucocerebrosidase. In its most severe forms, this condition presents with seizures, developmental delays, and even fetal hydrops [53]. A study by Massaro *et al.* in 2018 [54] showed that injecting fetal mouse models with functioning copies of the affected gene prevented neurodegeneration and considerably extends survival.

11. Ethical Concerns

Although IUGT appears promising, it is crucial to mention that it is subject to ethical concerns due to the dangers it might pose to the fetus and the mother. Prenatal gene therapy could harm the fetus through infection, fetal bradycardia, preterm labor, fetal loss, disruption of normal development, and oncogenesis. However, it is important to note that tumorigenicity is a possibility with gene therapy as a whole and not exclusively with fetal therapy [55] [56]. A valid concern regarding the IUGT is the potential for germline transmission, which is an absolute prohibition in gene therapy, as the goal has always been the treatment of the person and not their future offspring. Appreciatively, multiple investigations in animal models illustrated the absence of vector DNA in germ cells following fetal gene therapy [57] [58]. Nevertheless, further unbiased studies are required to assess the risk of germline cell involvement [54].

The impact of prenatal gene therapy on the mother may include risk of emergency cesarean section following fetal compromise or infection, an immunological response to the vector, and maternal gene editing [56] [59]. However, it is worth noting that the dose administered might be too small to affect maternal genes or cause a harmful immune reaction [60] [61]. A study done by Rossidis *et al.* [62] described the absence of maternal gene editing following the administration of CRISPR machinery into mice. On the other hand, a study on macaques by Mattar *et al.* [63] demonstrated transplacental transfer of vector genes into maternal tissues following prenatal therapy. Anyway, additional research is needed to elucidate the impact of IUGT on the mother.

Upon considering the above-mentioned problems, one must ask as to why perform IUGT while postnatal gene therapy is already a clinical reality and appears to be safer, particularly when the mother is considered [64]. Prenatal gene therapy is believed to be advantageous over postnatal therapy for several reasons. IUGT could prevent *in-utero* organ failure present at birth; this is demonstrated by Massaro *et al.* [54] who compared fetal and neonatal gene therapy for neuropathic Gaucher disease (nGD) in mice, showing that only IUGT completely avoided neuronal loss. Moreover, the smaller fetal size necessitates a smaller effective vector dose compared to postnatal therapy, which is especially important when considering the manufacturing costs associated with gene therapy [65]. In addition, tolerogenic fetal immunity reduces the likelihood of an immune response interfering with the function of the vector or eliminating the gene-edited cells. Besides, the increased accessibility of fetal bodily compartments due to immature blood-tissue barriers allows the therapy to reach a broader range of cells, such as those targeting the central nervous system [54].

Prenatal gene therapy could lead to a promising future for the early management of genetic disorders and the aversion of crippling fetuses which manifest at birth. With further research, IUGT could revolutionize prenatal medicine, offering hope for families affected by genetic diseases.

12. Conclusions

Intrauterine fetal therapy (IUFT) stands as a revolutionary advancement in maternal-fetal medicine (MFM) tackling different fetal conditions during pregnancy, aiming to improve fetal survival and outcome. Despite the recent remarkable evolution in the IUFT, its conceptualization dates back to the early 1980s, and since then, IUFT has undergone significant progress in its indications, coverage, techniques, as well as ethical and moral guidelines. Nevertheless, some drawbacks and side effects are still present and should be consistently considered on a risk-benefit scale.

Currently, the IUFT includes a diverse spectrum of interventions that can be broadly categorized into intrauterine pharmacological treatments (IUPT), minimally invasive fetal interventions (MIFI), and open fetal surgeries (OFS). As with most branches of medicine, IUFT has yet to mature, and many groundbreaking inventions in fetal therapy are currently under development. Fetal therapy's future progressions highlight the commitment of physicians to push far away the frontiers of medicine while adhering to moral and ethical standards and enhancing the health and wellbeing of newborns.

13. Limitations and Future Work

Our knowledge of the short-term and, more importantly, long-term prognoses of many fetal diseases, both treated and untreated, has advanced more slowly than our capacity to diagnose and treat them. Significant congenital anomalies for which natural history predicts a death outcome or the development of severe disability despite the best postnatal treatment can result from advancements in prenatal diagnosis. In certain specific situations, intrauterine treatment may be recommended. The only area of medicine where abortion is a viable option for treating lethal illnesses is prenatal diagnosis. Therefore, fetal therapy has emerged as a substitute for both termination of pregnancy (TOP) and fatal expectant prenatal care.

Physicians' opinions regarding prenatal abnormalities are typically influenced by a mix of their expertise, personal convictions, scientific curiosity, and ethical standards. All of these add to the effectiveness of the counselling given to expectant mothers whose fetus has been found to have a serious defect that can be treated with fetal therapy. A woman's choice is mostly influenced by her cultural, religious, social, familial, and personal background. Their comprehension of the illness and its prognosis is mostly based on medical advice, the most recent treatment options, and the prognosis.

It is recommended that countries, health organizations, and scientific scholars encourage broader collaboration, and form a multicentre research collaboration in the field of foetal therapeutic research for advances in early recognition of fetal abnormalities, and prompt *in-utero* therapy for more healthy outcomes.

Authors' Contributions

Remah M. Kamel, the main author of the study, participated in the idea and design of this study, proofreading of the manuscript, critical review, and submis-

sion for publication.

Mohamed M Soliman, Mohammed Bagunaid, Mohammed A Radwan, Adnan A Moallem, Mohammed Borah, and Bader M Almurad, all contributed by sharing in collecting the references for the study and in writing the draft form of the manuscript.

Conflicts of Interest

The authors have no conflict of interest.

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