Review Article

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# Fetal Therapy: A Review of Literature

**Liza Bulsara*, Sunil Mhaske****

**Author's Affiliation:**
*Resident **Professor & Head, Dept. of Paediatrics, DVVPF's Medical College, Ahmednagar-414111. Maharashtra.

**Reprint Request:**
**Liza Bulsara,** Resident, Dept. of Paediatrics, DVVPF's Medical College, Ahmednagar-414111. Maharashtra.
Email: liza.bulsara@gmail.com

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**Abstract**

Fetal Therapy is defines as a therapeutic intervention for the purpose of correcting or treating a fetal anomaly or condition. Medical fetal therapy describes any therapy in which a pharmacological agent is administered to a woman or her fetus in order to avoid or alleviate fetal disease. Treatment of the fetus with blood products or injection of other agents can also be considered to be medical fetal therapy. In almost every case, the fetus is at risk of intrauterine death from the abnormality [1]. It is the "operative branch" of fetal medicine. It includes a series of interventions performed on the "sick" fetus with the aim of achieving fetal well being. These interventions include medical (i.e. non-invasive) and surgical procedures [2]. The field of medical fetal therapy has been extremely exciting and continues to evolve at a rapid pace. No doubt, future advances involving genetic manipulation or the use of molecular genetic techniques for diagnosis will continue to keep this field at the forefront of treatment and prevention of fetal disorders.

**Keywords:** Fetal Therapy; Fetal disorders; Intrauterine death.

## Introduction

Several types of fetal therapy has been utilised and pioneered. These interventions are limited to a few specific conditions, where therapy has either proven beneficial or is under investigation [3,4]. Largely as a result of the Fetal Treatment Program, the perinatal patient population (maternal and neonatal) is unique with regard to the number of fetuses and newborns with unusual or rare conditions [5].

These patients are discussed at the weekly multidisciplinary Fetal Treatment Meeting

## Discussion

In general a medical intervention is performed by administering medication to the mother. The drug crosses through the placenta and reaches the blood circulation of the fetus.



*Fetal Therapy*

Atherapeutic interventionfor the purpose of correcting or treating a fetal anomaly or condition is called fetal therapy.

*Personals required for it are –*

- Obstetrician
- Pediatrician
- Anesthetists
- Ultrasonologist
- Neurosurgeon
- Social worker etc.

*Tools required for it are –*

- Ultrasound machine
- MRI
- Fetoscope
- laser machine

*The different types of fetal therapy are:*

*1. Pharmacologicalfetal therapy –(noninvasive)*

- Preventive pharmacotherapy
- Therapeutic pharmacotherapy

*2. Surgical fetal therapy- (Invasive)*

Prenatal testing

Prenatal screening tests

Screening tests screen for various fetal metabolic, chromosomal, and anatomic defects.

First-trimester screening tests may include the following:

- Beta human chorionic gonadotropin (β-hCG): To detect and diagnose pregnancy; in quantitative analysis, β-hCG levels lower than expected for presumed gestation can alert the clinician to an ectopic pregnancy or threatened abortion
- Pregnancy-associated plasma protein-A (PAPP-A): To detect trisomy 18 and 21 cases (in conjunction with β-hCG and ultrasonography for nuchal translucency)

*Second-trimester screening tests may include the following:*

- Maternal serum alpha-fetoprotein (MSAFP)
- Serum β-hCG
- Unconjugated estriol (uE3)
- Inhibin A
- Maternal hexosaminidase test
- Fetal cells in maternal circulation

The "triple screen" includes MSAFP, serum β-hCG, and uE3; the addition of inhibin A results in the "quadruple screen." The panel findings, along with gestational age, can suggest a number of fetal abnormalities, depending on the results pattern [6].

*Prenatal Diagnostic Tests*

Diagnostic tests are indicated when conditions that increase the risk of chromosomal anomaly are present or suspected (eg, advanced maternal age, suggestive fetal ultrasonographic findings). Genetic counseling by trained professionals in a timely and sensitive fashion is an essential adjunct to prenatal diagnosis.

*First-trimester diagnostic tests may include the following:*

- Fetal ultrasonography
- Chorionic villus sampling
- Early amniocentesis
- *Preimplantation biopsy:* Controversial; performed for preimplantation diagnosis in a fetus of parents with substantial risk of a known genetic disorder and in women with repeated miscarriages due to chromosomal translocation
- *Coelocentesis:* Considered investigational due to reportedly high rates of pregnancy loss Second-trimester diagnostic tests may include the following:
- Midtrimester amniocentesis
- Percutaneous umbilical blood sampling or cordocentesis
- Late chorionic villus sampling
- Fetal muscle and liver biopsy

For timely and appropriate intervention, assessment of fetal well-being in the third trimester, when preterm birth appears imminent, and in labor may include the following diagnostic tests:

- Amniocentesis
- Nonstress test (NST)
- *Biophysical Profile Test:* Combines the NST with an assessment of amniotic fluid volume (AFV), fetal breathing movements, fetal activity, and fetal muscle tone
- Contraction stress test
- *Doppler Study:* Assesses fetal umbilical arterial blood flow velocity or resistance to flow

*Radiologic Studies*

Diagnostic imaging modalities include the following:

- *Ultrasonography:* Single most valuable modality for identifying fetal and/or placental structural anomalies
- Magnetic resonance imaging (MRI): Important adjunct to ultrasonography
- Computed tomography (CT) scanning: Limited applications in prenatal diagnosis
- *Fetal Magnetocardiography:* Prenatal detection of a prolonged QT interval or Wolff-Parkinson-White syndrome.

*Fetal Management*

The following are options for medical and surgical fetal therapy to manage various fetal malformations:

- Termination of the pregnancy
- Elective cesarean delivery
- Preterm delivery
- Prenatal medical treatment
- Prenatal invasive fetal surgery

*Ethical and Legal Considerations*

Ethically, the fetus as a patient is thought of in different, often competing ways; the lack of legal clarity further confounds decision-making. Key considerations include the following:

- Maternal beneficence and autonomy versus fetal beneficence and autonomy
- Vagaries of the legal status of the fetus as a person
- Identifying viable and previable fetuses as candidates for treatment

The physician's legal duties to the previable fetus depend on the mother assigning the fetus "patient status" by continuing the pregnancy. The ethical concept is that beneficence-based obligations to the fetal patient should be negotiated in the context of the beneficence and autonomy of the mother [7,8].

The pregnant woman has an ethical obligation to accept fetal therapy for a viable fetus if treatment to prevent a serious disease or handicap would benefit or save the life of the fetus, if mortality or injury to the fetus is unlikely, and if mortality or morbidity in the mother is unlikely.

*Patient Selection*

For all interventions, mothers are counseled extensively by appropriate specialists (e.g., Pediatric Surgeons, Perinatologists, Neonatologists, Anesthesiologists, Ultrasonographers, Neurosurgeons, Social Workers) with regard to the nature of the condition, possible risks and benefits, alternative treatments, and potential outcomes [10]. The most common conditions for which fetal interventions are considered are:

*Fetal Therapy: Medical*

*Neural Tube Defects*

All women are advised to take folic acid prior to conception (0.4 mg/day PO for 3 months), and 4 mg/day is recommended for women with a previously affected child, beginning at least 1 month prior to conception through 3 months of pregnancy.

*Congenital Adrenal Hyperplasia*

Because the differentiation of external genitalia begins at 7 weeks' gestation, the mothers of all fetuses at risk (those with a previously affected child) are given dexamethasone (0.25 mg PO qid) at 7-9 weeks.Direct studies using probes or linkage DNA studies are performed with CVS. Affected female fetuses are identified at a rate of 1 case per 8 carrier parents.Treatment is continued until term only in affected fetuses. Stress-dose glucocorticoids are administered at delivery and gradually tapered in the mother after delivery. The long-term outcome of patients treated in utero is still being assessed. The treatment has proven effective in preventing masculinization.

*Thyrotoxicosis*

Fetal thyrotoxicosis is usually seen in infants of mothers with Grave disease or autoimmune thyroiditis. The diagnosis is made with cordocentesis. Maternal treatment with propylthiouracil (300 mg/day PO initially, subsequently titrated according to effect) or methimazole is associated with a good fetal outcome.

*Hypothyroidism*

Fetal hypothyroidism is linked to maternal hyperthyroidism, use of radioactive iodine, drugs, and excessive maternal iodine intake. Fetal status is evaluated at ultrasonography and by direct cordocentesis. Intra-amniotic L-thyroxine (500 ¼g every 2 weeks, initiated at 34 weeks' gestation) has been shown to cause regression of fetal goiters and normalization of hormone levels.

*Methylmalonic Acidemia*

This is caused be a deficiency of methylmalonyl CoA mutase or its coenzyme, adenosylcobalamin, which results in an accumulation of methylmalonic acid and its precursors in body fluids. Clinically, patients present in the first few weeks of life with poor feeding, vomiting, hypotonia, lethargy, dehydration, ketosis and acidosis.Prenatal cyanocobalamin has been empirically administered orally to the mother at a dose titrated to achieve high maternal plasma B12 levels and normal maternal urinary methylmalonic acid excretion. The long-term effects on fetal development have not been studied extensively.

*Multiple Carboxylase Deficiency*

This disorder is caused by a deficiency of

holocarboxylase synthetase or biotinidase, two enzymes essential to rendering the carboxylases functional. The carboxylase enzymes are involved in the metabolic pathways of isoleucine, leucine, and valine. Clinically, patients present in the first few weeks of life or later in childhood with hypotonia, seizures, vomiting, failure to thrive, dermatitis, developmental delay, hearing loss, and acidosis. Maternal biotin supplementation may prevent neonatal complications.

*Lung Maturity Induction*

Betamethasone (12 mg IM q24hr for two doses) or dexamethasone (6 mg IM q12hr for four doses) is recommended for fetuses at less than 34 weeks' gestation who are at risk of preterm delivery. The onset of action in the fetus occurs 48 hours after administration of the first dose.

Repeated courses of antenatal steroids have been linked to neurologic disability in the infant, independent of degree of prematurity. The previous practice of weekly courses has been replaced with a single course given whenever preterm delivery before 34 weeks appears possible.

*Maternal HIV Infection*

Maternal administration of zidovudine (AZT), started by 14 weeks' gestation, continued throughout pregnancy, and given IV during labor, followed by treatment of the neonate for the first 6 weeks, has been documented to decrease the rate of vertical transmission from 25% to 8%.

*Immune Hydrops*

The fetuses at risk are then monitored with serial ultrasonography (for evidence of hydrops) and Doppler assessment of the velocity of blood flow in the middle cerebral artery (higher in anemic fetuses), starting at 16-18 weeks' gestation and repeated every 1-2 weeks until 35 weeks' gestation.Alternatively, one can perform amniocentesis serially (10-day to 2-week intervals) with measurement of bilirubin, beginning at 18 weeks. Serial cordocentesis is indicated for severely affected fetuses for direct measurement of hematocrit, reticulocyte count, and bilirubin. Intrauterine transfusions can be performed as indicated by the results of the diagnostic tests. Direct intravascular transfusions through umbilical vein puncture or a combination of intraperitoneal and intravascular transfusions can be used [11]. The combination achieves a more stable hematocrit and delays the time to the next transfusion.

The volume of intraperitoneal transfusion can be calculated as follows:

- Intraperitoneal transfusion volume (mL) = gestational age (wk) – 20 ×10

This is repeated at 2-week intervals until fetal erythropoiesis decreases.

Monitor this with Kleihauer Betke stains and size of fetal liver and spleen on ultrasonography as indicators of extramedullary hematopoiesis. Repeat at 3- to 4-week intervals, with monitoring of the fetal hematocrit.The intravascular transfusion alone aims to achieve a fetal hematocrit of 35-40%. The intraperitoneal transfusion provides a reservoir of blood and achieves a final hematocrit of 50-60%. A fetus with hydrops requires careful transfusion until the hematocrit reaches 25%. Transfusion is repeated in 2 days and then weekly to achieve the final hematocrit.

O-negative, CMV-negative allogenic or maternal blood is tested for infection, washed, packed (hematocrit, 75-85%), filtered, irradiated with 25 Gy, and then transfused. Repeat transfusions are indicated until pulmonary maturity or a gestational age of 35 weeks is reached.

*Fetal Thrombocytopenia*

Maternal thrombocytopenia has many causes, many of which do not place the fetus at risk of bleeding. In idiopathic thrombocytopenic purpura, the fetus has a low risk for intracranial hemorrhage. Scalp electrodes, forceps, and vacuum are not used at the time of delivery. In early labor, a fetal platelet count may be obtained via cordocentesis or a scalp blood smear. If the count is lower than 20,000/¼L, a cesarean delivery may be preferred.

Alloimmune thrombocytopenia is the most common type of platelet isoimmunization that occurs in a PLA1 Ag–negative mother, with an incidence of 1 per 5000. If a history of an affected sibling exists, the direct fetal platelet count is measured with blood sampling, and maternal platelets can be transfused with cordocentesis. Disadvantages are the short life span of the platelets, which makes frequent transfusions necessary, and the possibility of further sensitization. Maternal intravenous immunoglobulin G (IVIG; 1 g/kg/wk) coadministered with corticosteroids has been tried with some good results.

*Fetal Hematopoietic Stem Cell Transplantation*

Hematopoietic stem cell (HSC) transplantation in utero is an attractive theoretical option for the

treatment of congenital disease that can be diagnosed antenatally and improved by engraftment of HSCs. Before 14 weeks' gestation, the fetal bone marrow has not yet developed sites for hematopoiesis and is receptive to the engraftment of circulating hematopoietic stem cells. Thymic processing of self-antigens has not yet started, and differentiated T cells have not yet been released into the circulation. At this stage, theoretically, foreign HSCs should engraft without inducing an immune rejection or graft-versus-host disease and without needing myeloablation. Human leukocyte antigen (HLA) matching is not required. Additionally, specific tolerance for donor antigen is induced, allowing additional cells or bone marrow to be transplanted postnatally from the same donor. In-utero treatment may also preempt many clinical manifestations of the condition, such as recurrent infections, failure to thrive, and neurologic damage. The disadvantages of the modality are the maternal and fetal risk from the procedures used to diagnose the disease and to perform the actual HSC transplantation, the technical expertise needed for the procedure, and the expense. Diseases theoretically amenable to HSC transplantation are hemoglobinopathies such as sickle cell disease and thalassemias, immune deficiency diseases, and inborn errors of metabolism.

*Congenital Heart Disease*

The precise diagnosis of congenital heart lesions with the aid of newer echocardiographic techniques has created the potential for prenatal surgery or interventional catheterization. In the treatment of hypoplastic left heart syndrome, umbilical vessel catheterization and balloon valvuloplasty in utero for aortic stenosis are being attempted, with equivocal results. In critical pulmonary stenosis, experimental valvotomy in utero may prevent right ventricular hypoplasia. At present, the major goal of prenatal diagnosis of congenital heart lesions is genetic counseling and delivery at a tertiary center, where early and optimal management is possible in the neonatal period.

*Fetal Arrhythmias*

Most fetal arrhythmias are benign, and 90% are atrial extrasystoles. These should be observed twice weekly to exclude sustained supraventricular extrasystoles or atrial flutter. In ventricular extrasystoles, myocardial ischemia and tumors (eg, rhabdomyomas) must be excluded.

Prerequisites prior to starting antiarrhythmic therapy include the following:

- An understanding of the electrophysiologic basis of the abnormal rhythm and its natural history
- Good understanding of the pharmacokinetics of the agent in the mother, fetus, and placenta
- Maternal consent for treatment
- Presence of hydrops fetalis with a sustained supraventricular arrhythmia
- Early gestation with a sustained arrhythmia in which the risk for development of hydrops is perceived to be high

The disadvantages include early and late mortality in the mother and fetus.

*Supraventricular Tachycardias*

These must be treated if they are sustained and associated with hydrops or upon evidence of left atrial preexcitation and a small foramen ovale.

Inpatient maternal treatment is started after 12-24 hours of fetal cardiac monitoring. Maternal workup includes electrocardiography (ECG) to exclude a maternal Wolff-Parkinson-White syndrome and a determination of electrolyte, blood urea nitrogen (BUN), and creatinine levels prior to digoxin loading.

Digoxin is the first-line drug. Propranolol, procainamide, and quinidine have also been used. All fetal antiarrhythmic medications are associated with risks of proarrhythmia and mortality in both mother and fetus. Carefully select patients for treatment and monitor drug levels and toxicity. Structural defects, such as Ebstein anomaly and mitral insufficiency, must be excluded [12].

*Congenital Complete Heart Block*

This is associated with major congenital heart disease in approximately 50% of cases. Diagnoses have included left atrial isomerism, physiologically corrected transposition, atrioventricular canal defects, and ventricular septal defects.

This group has a high incidence of congestive heart failure or cyanosis and requires postnatal permanent pacemakers. The remaining cases (50%) are associated with maternal autoimmune diseases (eg, systemic lupus erythematosus, Sjögren disease). Experimental protocols have used immunosuppressives, β-mimetics, and inotropes, with variable results Erythroblastosis Fetalis:In very severe cases, fetal intrauterine transfusion is performed to treat the hemolytic anemia.

**Anesthesia**

As new intrauterine surgical techniques have been developed, anesthesia for the procedures has also evolved. The major objectives are to ensure maternal and fetal safety. Specific goals are

- The prevention of maternal hypoxia and hypotension, together with the maintenance of optimal uterine blood flow. Lower doses of epidural and spinal anesthetic agents are needed in pregnant women because of increased epidural pressure and a lower volume of cerebrospinal fluid in the vertebral space.
- To promote fetal safety, procedures are generally performed in the second trimester, if possible, to avoid potential teratogenicity from the anesthetic agents.
- To prevent fetal asphyxia. normal maternal PaO2 should be maintained, and blood pressure should be maintained (with intravenous fluids and, if necessary, ephedrine, a vasopressor with central adrenergic stimulant action).
- The uterine incision stimulates uterine contractions, which must be stopped before preterm labor sets in. The agents used for this purpose include indomethacin, magnesium sulphate, and terbutaline. Indomethacin is administered preoperatively and continued postoperatively for 3-5 days. Fetal adverse effects include premature closure of the ductus arteriosus.

Anesthetic agents commonly used are isoflurane inhalation with 100% oxygen along with muscle relaxants. For surgical procedures involving direct fetal manipulation, direct intramuscular fentanyl and pancuronium (a muscle relaxant and vagolytic) administered to the fetus have been tried prior to hysterotomy under ultrasonographic guidance.

*Intraoperative and Postoperative Monitoring*

The parameters monitored during and after surgery include the following:

- Myometrial contractions and intrauterine pressures
- Maternal blood pressure, ECG, and pulse oximetric and blood gas levels
- Fetal pulse oximetric measurement (50-60% saturation), heart rate, blood gases, and ECG
- Ultrasonographic findings in cases of fetoscopic surgery
- Fetal temperature - Maintain temperature with continuous warm sodium chloride irrigation, minimized exposure, and increased ambient temperature

*Approaches to Fetal Surgery*

Three approaches are currently used for invasive fetal therapy, as follows

- Ultrasound-guided shunt placement
- Fetoscopy
- Open surgery

*Fetal Therapy: Surgical*

*Congenital Diaphragmatic Hernia (CDH)*

The major causes of morbidity and mortality with CDH are pulmonary hypoplasia and persistent pulmonary hypertension. In experimental animals, fetal tracheal occlusion stimulates lung growth by lung distension with fetal lung fluid. Although fetal tracheal occlusion is no longer used for most cases of CDH, it is occasionally considered for the most severe cases of CDH for whom survival is < 10%. Fetuses with tracheal occlusion must be delivered by EXIT procedure (partial delivery of the fetus, removal of the tracheal occlusion, administration of surfactant and institution of assisted ventilation while the infant is still on placental support).

*Urinary Tract Obstruction*

Complete obstruction of the fetal urinary tract results in severe renal damage as well as pulmonary hypoplasia from severe oligohydramnios. Despite early enthusiasmfor fetal decompression of the urinary tract, fetal intervention has seldom been beneficial and is now rarely performed.

*Fetal Tumors Causing Hydrops Fetalis*

When the relatively rare fetal tumors, congenital cystic adenomatoid malformation of the lung (CCAM) and sacrococcygeal tumor (SCT), are associated with hydrops fetalis, fetal mortality approaches 100%. These tumors cause hydropsby either venous obstruction due to mediastinal shift (CCAM) or high output heart failure (SCT). Operative removal of these tumors has resulted in survival of ~50% of the affected fetuses.

*Twin-Twin Transfusion Syndrome (TTTS)*

Monochorionic twins have a high frequency of placental vascular shunts that may lead to one twin

(donor) over-perfusing the other (recipient). Complications include oligohydramnios and growth retardation (donor), polyhydramnios and hydropsfetalis (recipient), and fetal death.

Other Conditions:It is likely that other conditions will become subjects of attempted fetal correction or treatment. Currently, consideration is being given to fetal intervention for certain cases of hypoplastic left heart syndrome.

An example of medical intervention is a fetus who is diagnosed with arrhythmia, such as atrial flutter. This condition may result in hydrops, and if no intervention is performed the fetus may die. In this case, medication may be administered to the mother to treat the fetal arrhythmia.

Surgical intervention on the fetus may involve either a direct operation of the fetus.

*Ex-utero Intrapartum Treatment (EXIT)*

Ex-utero intrapartum treatment (EXIT) refers to a special technique used to deliver a baby through an incision in the uterus. In an EXIT procedure a functioning airway is established before separation from the placenta. EXIT can be a lifesaving procedure for many babies with airway obstruction.

*Fetal Shunt Placement*

This procedure is performed when there is a severe renal/urinary abnormality in the fetus in order to drain the fetal bladder and obtain a fetal urine sample for testing. Stents can also be used to drain extra fluid from the fetal chest.

*Fetoscopic Laser Surgery*

Fetoscopy refers to the insertion of a small laparoscope into the uterus in order to visualize the fetus and placenta. Through the fetoscope a number of devices can be inserted to treat a number of conditions. This procedure is most frequently performed to carry out laser ablation of placental anastomoses for the treatment of twin-to-twin transfusion syndrome and the tracheal balloon placement for congenital diaphragmatic hernia [13].

*Fetoscopic Tracheal Occlusion (FETO)*

Fetoscopic tracheal occlusion (FETO) is an experimental procedure used for fetuses diagnosed with congenital diaphragmatic hernia (CDH) and impaired lung development. FETO reversibly blocks the trachea of the fetus with a latex balloon. Research has shown that this temporary tracheal occlusion can improve development of the fetal lung, which may lead to improved survival in babies with CDH.

*First-Trimester Fetal Echocardiography Program*

The First-Trimester Fetal Echocardiography Program allows for the diagnosis of major congenital heart defects early in pregnancy.

*Intrauterine Transfusion*

This procedure is done using ultrasound guidance to place a small needle through the mother's abdomen into a small fetal blood vessel. Blood, platelets or medications can be administered to the fetus through this technique.

*Neonatal Care*

A still unsolved complication of most fetal interventions is premature birth. The degree of prematurity varies with the condition, the type of fetal intervention, and the gestation at which it was performed. In some cases (e.g., TTTS), no specific neonatal care is needed other than care of the premature infant. In other cases (e.g., CDH), the infant will require intensive and complex resuscitation necessitating a large neonatal team [14].

Fetal treatment, and advanced fetal therapy in particular, is a relatively new field in medicine. Because of its complex nature and the significant risks involved with a surgical or medical intervention on a pregnant woman and her fetus, these procedures are usually performed in specialized centers and involve a multidisciplinary team of specialists. In addition, most of these fetal conditions are relatively rare, and the methods used to diagnose them are becoming increasingly sophisticated. Finally, there remain a lot to learn about the natural history of some of these disorders and the safest way to treat them.

It is for all these reasons that the North American Fetal Therapy Network (NAFTNet) was established. NAFTNet's goals are sharing of knowledge regarding complex fetal disorders, promoting research into these conditions and facilitating access to diagnosis and treatment, both for pregnant couples and their physicians [15].

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