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REVIEW ARTICLE

Current Strategy of Fetal Therapy I: Principles of In-utero Treatment, Pharmacologic Intervention, Stem Cell Transplantation and Gene Therapy

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Abstract Fetal conditions with high morbidity are amenable for prenatal intervention. It is important that the selective and investigative nature of most procedures needs to be clarified with the family during counseling session. Fetal therapy is fostered by accurate prenatal diagnosis with advanced fetal imaging, and molecular genetics technology. The treatments can be categorized into medical treatment, stem cell transplantation and gene therapy, minimally invasive intervention, endoscopic surgery, and open hysterotomy approach. Scientific validation of their genuine benefits has been a subject of ongoing researches. Prenatal administrations of pharmaceutical agents, for prophylactic or therapeutic purposes, have been broadly adopted. Transplacental administration of betamethasone to enhance the function of pneumocytes type II in premature fetus has been widely practiced for decades, and it might be the most common 'fetal therapy' being performed. However, the optimal dosage and interval of prenatal steroids administration was validated only recently. More invasive route of fetal administration, such as transamniotic, direct intramuscular, and intravenous injection, may be required for other pharmacologic agents. In this article, the authors selected to review common fetal conditions whose proposed prenatal pharmacologic treatments have undergone scientific validations. In-utero stem cell transplantation and gene therapy remain highly experimental. Informed choice and clinical experiment need to be balanced when prenatal treatment is offered.

Keywords Fetal therapy · In-utero intervention · Family counseling · Fetal anemia · Fetal goiter

Introduction

Significant progress of prenatal diagnosis in the last four decades has prompted attempts of in-utero treatment. Fetal conditions amenable for prenatal intervention have been limited to only potentially lethal diseases. Recently, the diseases that may leave the baby with significant handicap are also a candidate for in-utero treatment. Certain procedures are highly investigative in nature. For *example*, at the time of writing this article (March 2017), the randomized controlled trial (RCT) to validate the potential benefits and risks of fetal endoluminal tracheal occlusion (FETO) for severe congenital diaphragmatic hernia (CDH) is still ongoing, yet many fetal care centers, including that of authors, have started to offer this intervention based on the results from interim analysis [1]. Procedure-related miscarriages, preterm premature rupture of the membranes, and maternal morbidity need to be openly discussed with the family. Potential benefits and risks are scientifically validated before adoption as a 'standard of care'.

The number of experienced fetal care centers is still limited, and most of these are located in Europe or North America. Dissemination of this specialized service is a real challenge that needs to be addressed, discussed, and solved as a regional agenda [2]. The purpose of this review article is to explore the current strategy for implementing fetal therapy. Multiple treatment modalities may be applied for a single fetal disease, and appropriate strategy is crucial to

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optimize perinatal outcomes. Chapter I describes the history, principles, and philosophy of fetal therapy. Fetal pharmacologic treatment, stem cell transplantation, and gene therapy are also included. Chapter II describes invasive fetal therapy modalities that may offer fetal benefits at a cost of maternal risks. Albeit the growing body of evidence from large case series or well-designed studies, many issues, such as laser surgery for all stages of twin-to-twin transfusion syndrome (TTTS), remain unanswered. Practical points from authors' own experiences at Faculty of Medicine, Siriraj Hospital in Bangkok are incorporated for a better understanding of how fetal therapy can be adopted in reality.

History of Fetal Therapy

Certain congenital diseases are not compatible with life, or leave the survivors with significant neurodevelopmental or physical handicaps. The first report of prenatal therapeutic intervention was intraperitoneal blood transfusion for severe fetal anemia from Rhesus isoimmunization published by Sir Albert William Liley in 1963 [3]. The authors' center (Faculty of Medicine Siriraj Hospital, Bangkok, Thailand) has published their initial experiences of intrauterine blood transfusion back in 1987 and 1989 [4, 5]. Diagnosis and treatment protocol for fetal anemia was subsequently improved by incorporating Doppler studies of middle cerebral artery [6]. After the advent of high resolution ultrasound in1980's, fetal anomaly scan has become a standard of care in many places, particularly in developed nations. Fetal magnetic resonance imaging (MRI) and molecular genetics technology, which have been integral parts of modern obstetrics increase the chance to detect a fetus with serious conditions amenable for prenatal intervention.

In the 1980's, Michael Harrison and his colleagues from University of California at San Francisco (UCSF) have pioneered the use of sheep for experimenting fetal intervention. Data from animal studies led to the ultrasound-guided placement of a double pigtail shunt in a fetus with urinary tract obstruction in 1981, which was the first minimally invasive treatment in human fetus [7]. This first fetal patient was born alive, and lived well for at least 25 y later [8]. Ultrasound-guided percutaneous access remains in practice until these days. One year later, fetal access with open hysterotomy was developed for more complex procedures. Initially, UCSF offered open fetal surgery for fetal vesicostomy for fetuses with lower urinary tract obstruction (LUTO) [9].

Open hysterotomy approach is associated with higher maternal morbidity and increased risks of premature birth. Dedicated videoendoscopic surgical systems developed in 1990's shifted the practice to minimally invasive approach. Fetoscopy was first used in authors' unit in 1980's, and the equipment is shown in Fig. 1. A combination of direct visualization, small access, and advancement in the technology of laser surgery has led to an introduction of laser ablation of anastomosing vessels on chorionic plate for the treatment of severe mid-trimester TTTS and laser ablation of fetal posterior urethral valve (PUV) [10, 11]. Since then, a variety of prenatal interventions have been proposed, but most were subsequently abandoned because their benefits were not reproducible. Scientific validation for short-term perinatal outcomes and the long-term health impacts of survivors, especially neurocognitive performance, are important to indicate the true benefit of in-utero interventions.

Scientific Validation for the Benefits and Risks of In-utero Interventions

Well-designed animal studies and RCTs are generally required prior to clinical implementation of new procedures in human. Rigorous scientific validations have been performed for selected interventions such as laser photocoagulation of chorionic anastomoses in severe mid-trimester TTTS [10], FETO for severe CDH [12], and open hysterotomy repair of myelomeningocele (MMC) [13]. Other procedures, such as fetal blood transfusion, have been accepted as a standard of care without scientific validation. Some procedures were abandoned because they failed to show genuine benefits to the fetus. Fetal conditions amenable for in-utero treatment are relatively rare, and multicenter or international collaboration is frequently needed. However, it takes time and experience for any center to achieve the same outcomes as those previous reported by more established fetal care centers [14].

Neonatal survival ($\geq$28 day) used to be the most important determining factor for the benefit of in-utero intervention. However, the favorable outcomes following new procedures may also be contributed by the following factors; (a) liberal administration of glucocorticoids to enhance fetal lung maturation, (b) more accurate prenatal imaging and molecular genetic diagnosis, (c) increasing number of experienced pediatric surgeons with formal training, and (d) broader availability of more advanced respiratory support, such as high frequency neonatal ventilator in neonatal intensive care units (NICU).

Family Counseling for Fetal Therapy

The family should be offered a counseling session by multidisciplinary team. They have to both manage emotional stresses and process complex medical information. The ability for people to comprehend and rationalize is affected by their

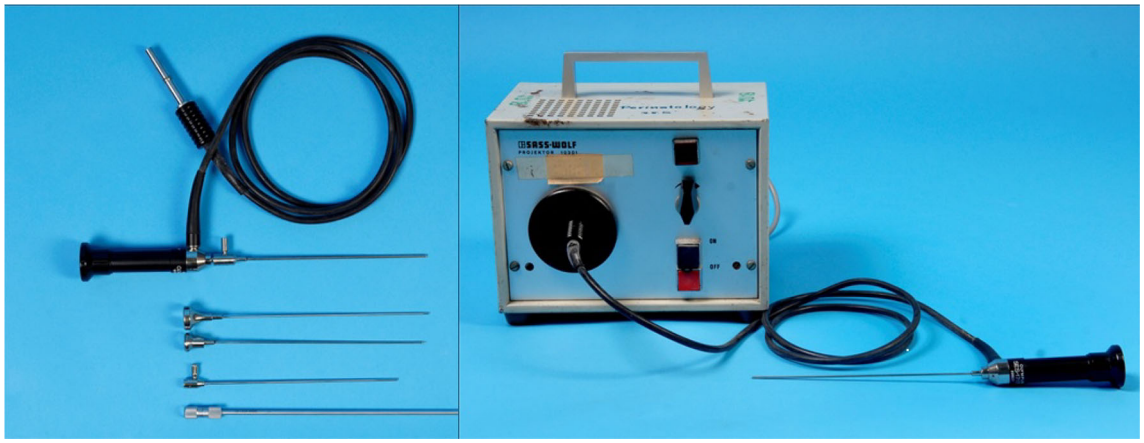

Fig. 1 First fetoscopic set at Department of Obstetrics and Gynecology, Faculty of Medicine Siriraj Hospital. Initially, fetoscopy was used to sample fetal blood from chorionic vessels under direct visualization for diagnosis of severe thalassemia diseases

intelligence and education level. In the United States, over 40 million people have limited literacy, particularly in the ethnic minority group [15]. Even in the United Kingdom, which has good educational system, only half of the adults can adequately understand medical information after one counseling session [15]. Stress and anxiety from the distressful information can impact the retention. Therefore, family counseling for fetal therapy is a real challenge, and preferably, structured training is required. Familial, societal, cultural, and economical factors must be considered for the family to reach an informed choice.

Categorization of Fetal Therapy

Fetal interventions can be categorized according to their invasiveness into (a) pharmacological treatment, (b) stem cell transplantation and gene therapy, (c) minimally invasive interventions (including ultrasound-guided needle intervention, shunting, and endoscopic surgery), and (d) open fetal surgery (Table 1). International Fetal Medicine and Surgery Society (IFMSS) released guidelines [16] to minimize the risk and failure of invasive prenatal procedures (Table 2). Following these guidelines, newer procedure such as FETO (improvement of neonatal survival of severe CDH from approximately 30% to approximately 70%) and in-utero aortic valvuloplasty (improvement of neonatal survival of hypoplastic left heart from 0 to 12%) were developed [17, 18].

Ethics of Fetal Therapy

"Fetus as a patient" is the core ethical concept for fetal medicine [19]. A paradoxical view of "fetus as a person" mandates the medical team to manage uncertainties in the nature of fetal condition and the treatment outcomes [20]. While a novel intervention is developed, investigators must ascertain that; (a) a standard of care is established, (b) informed consent is appropriate, (c) the abortion preferences of the pregnant woman are respected, and (d) the doctors who refer that patient to the trial are obligated to both the fetal patient and the pregnant woman.

The importance of written informed consent for fetal therapy was endorsed in a joint statement from American College of Obstetricians and Gynecologists and American Academy of Pediatrics [21]. Experienced doctors know when to offer 'intervention' and 'termination' to avoid the tragic possibility of turning the disease that would have been deadly into live birth with long-term handicap. Upper limit of gestational age legally permissible for termination is varied from one community to the others. Once this legal gestational age is reached, the woman's choice will become limited.

Fetal Pharmacologic Treatment

In-utero administration of pharmacologic agents can either be indirect (transplacental and transamniotic) or direct (intramuscular, intravenous, and intraperitoneal), as summarized in Table 3. Maternal administration of glucocorticoids to alleviate respiratory distress of prematurity is probably the most commonly performed in-utero pharmacologic intervention. It was first described by Liggins and colleagues in 1972 [22]. The indications of fetal glucocorticoid treatment have now expanded to prenatally diagnosed tumor [23], and congenital heart block (CHB) [24].

Intravenous immunoglobulin (IVIG) to prevent neonatal alloimmune thrombocytopenia, anti-retroviral drugs to reduce perinatal transmission of human immunodeficiency

Table 1 Types of fetal therapy

Type	Examples	Remarks
Medical treatment	Glucocorticoids	Enhance fetal lung maturity
In-utero stem cell transplantation and gene therapy	In-utero hematopoietic stem cell transplantation	Severe combined immunodeficiency syndrome (SCID)
Minimally invasive fetal intervention	Laser ablation of chorionic anastomoses	Twin-twin transfusion syndrome
Open fetal surgery	Closure of high-risk myelomeningocele	Improvement of short and long-term neurological outcomes

Table 2 Suggested guidelines to offer invasive in-utero intervention. (Adapted from Harrison et al. NEJM) [16]

Accurate diagnosis of isolated condition
Natural history of the disease is well documented
Staging of disease's severity and prognosis are available
Associated anomalies are excluded
No effective postnatal therapy
Proofs of feasibility and efficacy in animal models
Availability of multidisciplinary sub-speciality
Strict treatment protocols
Approval of the local ethics committee with informed consent of the mother or parents

Table 3 Routes of pharmacologic administration to the fetus

Route	Examples	Remarks
Transplacental	Digoxin	Fetal supraventricular tachycardia
Transamniotic	Levo-thyroxine	Fetal goitrous hypothyroidism
Intravenous	Amiodarone	Refractory fetal supraventricular tachycardia with hydrops
Intramuscular	Fentanyl	Fetal immobilization

virus (HIV), anti-arrhythmic agents to convert cardiac arrhythmia, and dexamethasone to prevent virilization in congenital adrenal hyperplasia (CAH) are examples of commonly used therapeutic agents. Transplacental administration is convenient; but it is amenable only for a medication with small molecule, and the end-fetal dosage could be affected by maternal volume of distribution, hepatic first pass effect, and renal clearance.

Fetal Anemia

Treatable causes of fetal anemia include red-cell alloimmunization [*i.e.*, rhesus (Rh) isoimmunisation and Kell alloimmunization] and parvovirus infection. Hemolytic disease of the fetus and newborn due to placental transfer of non-rhesus maternal antibodies is increasingly apparent, partly due to greater utilization of blood transfusion in the obstetric population. Unlike RhD, 80% of Caucasian males are positive for Rhc antigen, of whom 60% will be heterozygous. This is in contrast to the situation for Kell, where only about 8% of Caucasian males will be Kell positive, of whom 97% are heterozygous [25]. The current method of choice for determining fetal blood type is examination of maternal plasma for the presence of fetal DNA, which allows for 100, 100, and 98.6% accuracy for fetal RhD, Rhc, and Kell genotyping, respectively [26]. The high-risk fetuses require sequential ultrasound monitoring to ensure timely intervention with intrauterine blood transfusion. Non-invasive testing with middle cerebral artery Doppler is becoming the monitoring modality of choice [6]. Protocol for prenatal assessment and in-utero management of fetal anemia at Department of Obstetrics and Gynecology, Faculty of Medicine Siriraj Hospital, Bangkok, Thailand is shown in Table 4. The outpatient setting of in-utero blood transfusion is displayed in Fig. 2.

Fetal Dysrhythmias

Congenital heart block (CHB) is bradyarrhythmia from an abnormal atrioventricular conduction without any structural defect. The incidence of CHB is 1:15,000 to 1:20,000 of newborns [27]. Most of the CHB detected prenatally are caused by placental transfer of maternal-derived anti-ribonucleoprotein antibodies (anti-SSA or anti-Ro, and anti-SSB or anti-La antibodies). The clinical onset is in late second trimester. These circulating autoantibodies can be found in women with Sjogren's syndrome, systemic lupus erythematosus, and rheumatoid arthritis, regardless of their

Table 4 Protocol for prenatal assessment and in-utero management of fetal anemia at Department of Obstetrics and Gynecology, Faculty of Medicine Siriraj Hospital, Bangkok, Thailand

Investigation	Admit the patient for full investigations
	Investigate maternal blood for:
	• Complete blood count
	• Major and minor blood group typing, Coomb's test
	• Hemoglobin typing
	• IgG and IgM for Toxoplasmosis, Herpes, Rubella, and Cytomegalovirus
	• Acid elution test (for feto-maternal hemorrhage)
	• Contact blood bank for a specially prepared packed red cells
Preparation for in-utero blood transfusion	- Set-up fetal blood sampling and blood transfusion
	- Aseptic technique
	- Pretransfusion heparinized fetal blood 12 ml (gestational age to be considered) for hematocrit (in the operating room) and complete blood count
	- Major and minor blood group typing, indirect Coomb's test
	- Hemoglobin typing
	- IgG and IgM for Toxoplasma, Herpes, Rubella, and Cytomegalovirus
	- PCR for Parvovirus B19 (if available)
	- Fetal karyotype study
Follow-up after in-utero blood transfusion	• Post-transfusion hematocrit
	• Monitor fetal well-being and MCA-PSV
	• Repeat transfusion accordingly to MCA-PSV measurement
	• Terminate pregnancy at or near term, or in the presence of non-reassuring fetal testing

MCA-PSV Middle cerebral artery peak systolic velocity

clinical symptoms. Focal inflammation and scarring of atrioventricular node and myocardium can be found in 2% of fetuses of antibody-positive women. The chance of developing CHB can be up to 17% if there was CHB in a previous child [28].

Heart failure and fetal death may develop in CHB, especially with the following presentations; (1) fetal hydrops, (2) profound bradycardia <55 beats per min, (3) myocardial dysfunction (*i.e.*, high myocardial performance (Tei) index and low ejection fraction), and (4) myocardial fibroelastosis. True benefits of fluorinated glucocorticoid and IVIG for fetal sinus conversion are still elusive [24, 29–34]. Postnatal pacemaker is lifesaving, but the outcome is varied.

Atriovenous re-entry or atrial flutter can cause fetal tachyarrhythmia, such as supraventricular tachycardia (SVT). It is more responsive to medical treatment. Digoxin is the most commonly used agent for prenatal sinus conversion [35, 36]. It can convert SVT to sinus rhythm in approximately 60 and 20% of non-hydropic and hydropic fetuses, respectively [36]. Other medications, such as sotalol, flecainide, and amiodarone, can also be used [35]. If the fetus is hydropic, direct intramuscular, intraperitoneal, or intravenous (umbilical vein) administration may be required, but risks of fetal exanguination, especially with amiodarone, must be considered [37].

Fetal Goiter

Transplacental passage of maternal antithyroid medication is the most common cause of fetal goitrous hypothyroidism [38]. Fetal goiter may cause polyhydramnios, hyperextended neck, and neonatal airway obstruction. It can be alleviated by multiple intra-amniotic instillations of thyroxine for the fetus to swallow. Direct intramuscular injection of thyroxine may be indicated if there is esophageal obstruction [39].

Fetal hyperthyroidism can cause growth restriction, high-output cardiac failure, and hydrops. Transplacental passage of maternal-derived thyroid-stimulating immunoglobulins (TSIs) in Graves' disease is responsible for the condition. It can be controlled by maternal administration of propylthiouracil [40].

In summary, in-utero pharmacologic treatment derives from adaptations of postnatal therapy for similar conditions. There is a broad variety of pharmacological treatments adopted for fetal treatment, and the reported outcomes are based from case series and personal experiences. Only a few of them have been scientifically proven for their benefits and risks through RCTs [32, 33].

In-utero Stem Cell Transplantation and Gene Therapy

Women carrying a fetus affected with genetic conditions causing inevitable death or serious childhood disability used to have only 2 options; termination of pregnancy or expectant management with postnatal supportive treatment. Transplantation during immunologic naïve can avoid myeloablative irradiation or chemotherapeutic immunosuppression, which are major causes of serious transplantation-related morbidity in childhood period [41]. The first successful prenatal transplantation in human was reported in 1989, in which fetal liver cells were transplanted into another fetus with bare lymphocyte syndrome [42]. So far, the consistent clinical success has been limited to only fetuses with severe combined immunodeficiency (SCID), in which defective cell line is reconstituted and genetic defects are ameliorated [43, 44]. In-utero transplantation may overcome histocompatibility barriers without the need for chemotherapeutic induction. Albeit nicely laid 'fetal intolerance' concept, so far it is still considered experimental.

Monocytes, macrophages, and natural killer cells play an important role in graft failure after in-utero transplantation. From 18 wk of gestation, the fetal spleen contains equal numbers of T cells, B cells and monocytes/macrophages, and is therefore considered immunocompetent. In-utero hematopoietic stem cell transplantations (HSC) have been attempted predominantly on the fetuses affected with compound heterozygote, transfusion dependent beta-thalassemia [41]. Mesenchymal stem cell (MSC) has a broader potential then stem cell of hematopoietic origin. Successful in-utero MSC transplantation cases have been reported to improve the phenotype in osteogenesis imperfect (OI) [45]. However, there is a real possibility of publication bias, when most of the failed results are not reported [46]. It is advisable to balance the information when it comes to counseling a couple carrying an affected fetus searching for this in-utero MSC transplantation. So far, there is no report of successful in-utero MSC transplantation to treat a fetus with thanatophoric dysplasia.

In addition to transplantation of HSC and MSC, prenatal gene transfer to the cells with long-term transgenic protein expression is also technically feasible. Preliminary reports from animal models have been promising. In-utero gene therapy approach has a potential to ameliorate certain genetic diseases, particularly those affecting neurological and coagulation system. Gene therapy is the treatment in which desirable genetic material, and not the whole cell, is delivered into the targeted cell to correct its function. Appropriate vector, viral or non-viral, is required to deliver the genes into the targeted cells. Human trials on prenatal gene therapy are not currently available due to unclear answers in the issue of (1) potential effects of vector to the host, (2) post-transfer mutagenesis, and (3) germ line transfer [47].

Fig. 2 The outpatient setting of in-utero blood transfusion

Conclusions

Advanced fetal imaging, coupled with more effective, and ethically conducted, in-utero interventions, the ability to sequence the fetal genome, both directly from fetal tissue and indirectly from maternal blood, allows us to apply personalized medicine approach to the fetus. This will significantly impact fetal therapeutic interventions. Certain medications have been used without adequate evidence from quality clinical trials. For *example*, digoxin has been the first drug of choice for conversion of fetal SVTs. This practice is derived from successful reports from small case series. Challenges for in-utero medical treatment will be faced in fetuses with extremely rare conditions, such as the inborn errors of metabolism. It is unlikely to conduct a trial to prove the efficacy or safety of medical interventions owing to the rarity of these diseases. Appropriate follow-up with ultrasound examination and fetal blood testing are the

only ways to optimize treatment in this difficult situation. The concept of in-utero stem cell transplantation and gene therapy is attractive, but it may complicate ethical principles. To date, they are considered as highly experimental, because the prognosis after the treatment is ambiguous. The possibility of transplantation should be raised only if the parents decide not to terminate the affected fetus. Any couples at risk of giving birth to a baby with serious genetic condition, should seek prenatal care as early as conception is recognized, or preferably even before conception. The couple has to realize that the benefit from this treatment modality is based only on a small number of cases. There are many failed transplantations, and the babies were born with this debilitating disease. Even in cases with successful in-utero MSC transplantation, collecting long-term outcome data of these babies is still a work in progress.

Compliance with Ethical Standards

Conflict of Interest None.

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