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REVIEW ARTICLE

Overview of Fetal Therapy

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ABSTRACT

An improving ability to diagnose fetal conditions with higher accuracy prompts an attempt for a salvage treatment *in utero*. Fetal conditions amendable for prenatal intervention are limited to only diseases that can either kill the baby *in utero* or leave the baby with significant handicap. Therapeutic intervention has to be highly selective. Factors that need to be considered before offering *in utero* treatment include the highly investigative nature of certain procedures. For instance, at the time of writing this paper, fetal endoluminal tracheal occlusion for severe congenital diaphragmatic hernia is still under a randomized controlled investigational trial to validate its potential benefits and risks to the fetus with severe congenital diaphragmatic hernia with suboptimal growth of the residual lung tissue. There are chances of procedure-related miscarriages, preterm premature rupture of the membranes, and maternal morbidity that need to be discussed in an unbiased counseling session. The right balance between potential benefits and harms requires validation with rigid scientific methodology before the practice has become a "standard of care." For example, laser photocoagulation of anastomosing chorionic vessels has become a standard of care in many places due to its superior perinatal survival and composite outcomes, particularly for the childhood neurodevelopmental status. With an ongoing technological development, it is foreseeable that there will be more proposals of implementing novel medical technologies to the use of fetal therapy. Currently, there are only a handful of fetal care centers, and most of the experienced ones are clustered in developed part of Europe and the USA. Dissemination of this type of service which requires years of experiences to develop surgical skill and the support by the most technological advanced instrument and setting is a real challenge that need to be addressed, discussed, and solved as a global agenda.

Keywords: Congenital diaphragmatic hernia, Fetal therapy, Fetoscopy, Fetal tracheal occlusion, Lower urinary tract obstruction, Myelomeningocele, Open surgery, Shunting, Twin-twin transfusion syndrome.

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HISTORY OF FETAL THERAPY

Certain diseases can develop before the baby is born. Serious diseases are not compatible with fetal life. The fetus may survive with significant neurodevelopmental challenges or physical handicaps. Prenatal detection of fetal anomalies or diseases was fostered by an introduction of ultrasound for diagnosis in 1958 by Donald et al.[1] The advent of real-time ultrasound aided in both fetal diagnosis and intervention. The first published report of fetal therapeutic intervention was intraperitoneal blood transfusion for severely anemic fetus from Rhesus disease by Sir Liley in 1963.[2]

High-quality fetal ultrasound has become broadly available since 1980s. Fetal anomaly scan has become a standard in many places, particularly in developed nations. This practice increases the chance to pick up a fetus with conditions amendable for prenatal intervention. Our center (Faculty of Medicine, Siriraj Hospital, Bangkok, Thailand) has adopted ultrasound-guided fetal blood sampling and transfusion, and published our first case report and case series in 1987 and 1989 respectively.[3,4] In those years, ultrasound-guided intravascular (umbilical vein) fetal blood transfusion was performed in the main operating theater, as shown in Figure 1. Adding Doppler studies in prenatal well-being evaluation protocol allows for better assessment of fetal anemia and oxygenation.[5]

Since then, there has been significant development of various kinds of techniques for prenatal interventions. The interventions can be categorized into (1) medical treatment, (2) minimally invasive intervention (including ultrasound-guided needle intervention and shunting), (3) fetoscopic surgery, and (4) open fetal surgery. Fetal therapy is driven by progressively sophisticated fetal

Fig. 1: Historical picture of first *in utero* fetal blood transfusion using ultrasound guidance. Note the linear transducer probe being used in the procedure back then

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imaging, i.e., magnetic resonance imaging (MRI) and molecular genetics technology.[6]

Intrauterine intervention is aiming to improve the outcome of fetal conditions before the baby is born. Prenatal surgery may reduce irreversible damages inflicting on certain developing organs. With this goal in mind, a number of prenatal interventions have been proposed over the past four decades. The benefits from most proposed prenatal interventions were not reproducible, and hence they were abandoned. Until recently, only short-term perinatal outcomes have been the benchmarks for the benefits of prenatal interventions. The current evaluation has become more critical. All the new treatments have to undergo a rigorous validation for its true benefits and risks, as well as short-term and long-term health impacts, compared to the conservative or traditional treatments. Most of them are conducted as randomized controlled trial (RCT).

In 1980s, Harrison and his colleagues from University of California at San Francisco (UCSF) have pioneered the use of sheep as an experimental animal model for experimenting fetal intervention. Knowledge from this animal studies has led to the first invasive treatment in human fetus in 1981, which is the placement of a double pigtail shunt in a case of urinary tract obstruction.[7] This intervention is considered the very first minimally invasive intervention performed directly on human fetus. This first fetal patient was born alive, and lived well for at least 25 years later.[8]

Using an ultrasound to guide the shunt placement, this type of procedure was originally called "image-guided percutaneous fetal access." "Open hysterotomy" was subsequently developed for a broader access to the fetus. It is also known as "open fetal surgery." Initially, UCSF offered open fetal surgery performed using vesicostomy, a surgical procedure to create continuous *in utero* bladder drainage for fetuses with lower urinary tract obstruction (LUTO).[9] *In utero* intervention could significantly improve perinatal outcomes and reduce long-term morbidity. However, open hysterotomy was related to higher maternal morbidity and increased risks of premature birth due to its invasiveness.

Videoendoscopic surgery started to gain popularity in the 1990s. Many fetal care centers shifted their practice toward videoendoscopic-assisted access for its minimally invasive nature. Initially, hysteroscope was used to visualize and perform simple intrauterine procedures. Dedicated fetoscope was subsequently commercially developed, and has become the most common access for fetal intervention until today. Fetoscopic approach has overcome the following limitations of open fetal surgery: (1) Because of smaller incision, the chance of preterm premature rupture of the membranes (pPROM) and unstoppable preterm delivery is less. (2) Because of its less invasiveness, maternal morbidity is reduced.

Fetoscopic approach allows safer operation for both mother and fetus. Figure 2 shows our first fetoscopic surgical unit used in our Faculty of Medicine, Siriraj Hospital over 30 years ago. The fetoscope was used to sample blood from chorionic vessel for prenatal diagnosis of severe thalassemia diseases. It was subsequently replaced by ultrasound-guided fetal blood sampling.

Fetoscopy has recently regained its clinical usefulness. There are quite a few fetal interventions that enjoyed the benefits of direct visualization, small access, and advancement in the technology of laser surgery, such as laser ablation of anastomosing vessels on chorionic plate in severe twin–twin transfusion syndrome (TTTS) and laser ablation of fetal posterior urethral valve (PUV). However, the best example of this paradigm shift may lie in the treatment of fetuses with severe congenital diaphragmatic hernia (CDH).

Data on long-term health impact of fetuses with CDH is still lacking. There have been a number of proposed *in utero* interventions to improve perinatal outcomes of fetuses with prenatally diagnosed severe CDH. Real benefits of these interventions can only be proven and compared through well-designed RCTs. Interventions for other fetal diseases have also been undergoing rigorous scientific validation, such as laser photocoagulation of chorionic anastomoses in severe mid-trimester TTTS, fetal tracheal occlusion (FETO) for severe CDH, and open repair of meningomyelocele (MMC).[10-12]

These examples of landmark trials were designed to validate both short-term and long-term benefits of

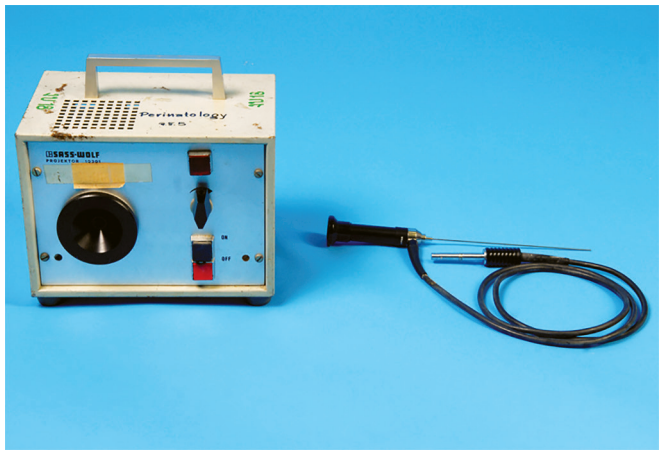

Fig. 2: The first fetoscopy unit used in Department of Obstetrics and Gynecology, Faculty of Medicine, Siriraj Hospital. Note the traditional light source, rod lens, and eyepiece. Back then, videoendoscopic unit was not available, and the operator needed to directly look through the eyepiece. This fetoscopy unit was used to sampling blood from chorionic vessel under direct visualization to diagnose severe thalassemia disease of the fetus. It was then replaced by high-resolution ultrasound-guided fetal blood sampling from the umbilical cord vein

the procedure. Neurocognitive performance is a major indicator of long-term outcome. For instance, FETO can improve neonatal survival in severe left-sided CDH from 24.1% (historical noninterventional controls) to 49.1% (FETO cases) ($p < 0.001$).[13] Many fetal care centers start offering FETO to their patients. The real benefits of FETO should be available after the Tracheal Occlusion To Accelerate Lung Growth Trial (TOTAL trial) led by Eurofoetus group is completed.

Some fetal intervention procedures are considered a standard of care, i.e., fetal blood transfusion. Some procedures, on the other hand, were abandoned due to its failure to show genuine benefits to the fetus after rigorous scientific validation. *In utero* interventions for fetal LUTO can be used as a good example here; LUTO is a serious disease. The obstruction results in secondary pulmonary and renal malfunction, which can be reversed only if obstruction is released *in utero*. Traditionally, vesicoamniotic shunting (VAS) was a standard of care for fetuses with LUTO. The benefits of VAS are based on small case series without control groups. A meta-analysis by Clark et al[14] showed perinatal outcomes of 342 fetuses with severe LUTO diagnosed by ultrasound in the second trimester. Of these, 195 fetuses were from 7 controlled studies and another 147 fetuses were from 9 case series without controls. Fetal bladder drainage procedures, including serial vesicocentesis, VAS, and open fetal vesicostomy, improve overall neonatal survival, particularly in poor prognosis group. The odds ratio (OR) was 26.19 [95% confidence interval (CI): 4.39, 156.2] for poor prognosis (2 controlled studies, 46 fetuses) and 2.25 (95% CI: 0.65, 7.81) for good prognosis (2 controlled studies, 49 fetuses).

The real benefit of VAS was questioned after percutaneous VAS in LUTO trial (PLUTO trial) that was published in 2013.[15] This RCT involving 31 fetuses with LUTO showed a borderline increased survival rate in VAS group, compared to expectant management group [intention-to-treat relative risk (RR) 1.88, 95% CI 0.71–4.96; $p = 0.27$]. Most babies had impaired renal function irrespective of VAS. Fetoscopic cystoscopy with laser ablation of PUV has gained an interest in recent years. Data showed that laser ablation of PUV can improve the 6-month survival rate and renal function [absolute RR, 4.10 (95% CI, 1.75–9.62; $p < 0.01$) and 2.66 (95% CI, 1.25–5.70; $p = 0.01$) respectively].[16] To study the real benefit of fetal cystoscopy in management of severe LUTO RCT is underway.

Fetal conditions amendable for *in utero* treatment are relatively rare. In order to get adequate power, multicenter or international collaboration is frequently needed. There is one significant drawback for this approach. It takes time and experiences for any center to achieve the same outcomes as those previous reported by more established fetal care center. There is a tendency that the complete treatments are concentrated only in a handful of centers, mostly in the USA and Europe.[17]

Newer treatments have been subjected to scientific validation, as to how these new approaches can change the perinatal prognosis. Animal studies and RCTs are generally required prior to clinical implementation of any new technology. Neonatal survival (more than 28 days after birth) used to be the main outcomes to evaluate the benefit of *in utero* intervention. Improvement of neonatal outcomes can be observed after newer interventions. However, there are some factors that may as well be contributing to the improved outcomes compared to traditional expectant management. These factors include:

- Liberal administration of glucocorticoid to enhance fetal lung maturation
- Advancement of fetal imaging modality, including ultrasound and MRI
- Increased number of experienced pediatric surgeon with formal training
- Upgrade of neonatal intensive care unit (NICU) and availability of more advanced respiratory support, such as high frequency neonatal ventilator.

PRINCIPLES OF FAMILY COUNSELING FOR FETAL THERAPY

Once fetal disease is suspected from ultrasound examination, it should be confirmed by experienced hands or team approach. Controversial ultrasound findings need to be interpreted for its clinical relevance, as being advised by the recently published recommendation from our Working Group on Ultrasound in Obstetrics of the World Association of Perinatal Medicine (WAPM).[18] Doppler studies and three-dimensional sonography are frequently used for more details. When more advanced sonographic modalities are used, potential thermal effect that may lead to neuronal apoptosis has to be cautioned. This concerned was outlined in another separate publication from our WAPM working group.[19] Occasionally, MRI, or molecular genetics investigations may be required to reach definitive diagnosis and prognosis.

The patient and her family should be offered a counseling session by multidisciplinary team. Besides emotional stresses that the family needs to deal with, they have to mentally process large and complicated information provided by the medical team. It is important to know that, first, people in general can only process a limited piece of information in a single counseling session. Second, there are both intuitive and emotional factors involved, when a decision for an unborn child is being made. Lastly, the information on maternal risks is not usually "weighed" adequately after the first counseling session.

It is important that cultural, religious, legal, and technological aspects need to be considered in each counseling session. The ability for people to comprehend and rationalize this piece of information is affected by their intelligence and education level. Even in a country with good educational system like the UK, only half of the adults can adequately understand medical information after a counseling session.[20]

It has been estimated that over 40 million people in the USA have limited literacy, particularly in ethnic minority group.[20] In addition to this, stress and anxiety created from the distressful information can further add to how people can retain the information when the counseling is over. With all these factors, counseling for fetal disease and its corresponding treatment modality is a real challenge to everyone to reach an informed decision.

PRINCIPLES AND TYPES OF FETAL THERAPY

Only serious diseases are amendable for prenatal treatment. The objectives of initiating the treatment before the fetus is born are to save life and to prevent permanent disabilities. There are many ways to categorize fetal therapeutic interventions. For the purpose of practicality, categorization based on fetal approaches is used. The categorization of fetal therapy is as follows:

- Medical treatment
  - Transplacental
  - Transamniotic
  - Intramuscular
  - Intravenous
- *In utero* stem cell transplantation and gene therapy
- Minimally invasive fetal intervention
  - Needle-guided intervention
  - Shunting procedure
  - Fetoscopic intervention
- Open fetal surgery.

More details and examples for this categorization are shown in Table 1. Fetal therapy is, in fact, a heterogeneous cluster of interventions. It is ranging from simple transplacental medical treatment to invasive surgical intervention. Administration of therapeutic agents to the mother, so that it crosses the placenta to the fetus, carries very small risks to the mother. An example of transplacental medical treatment is maternal administration of antiarrhythmic agent to reverse decompensated fetal arrhythmia. Invasive surgical intervention carries potential maternal morbidity. An example of invasive fetal treatment is open repair of fetal MMC. More invasive procedures are related to a higher chance of membranes rupture and iatrogenic preterm birth.[21]

Fetal therapy used to be offered arbitrarily, based on institutional expert opinion. In 1982, there was the very first congregation of international experts in fetal therapy in Santa Ynez, California.[22] This panel of expert has suggested five main rules to guide an optimal clinical application of invasive fetal interventions. This guideline, as shown in Table 2, is frequently quoted, and remains the principles of fetal surgical intervention until these days.[23]

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 immune deficiency syndrome (SCID)
Minimally invasive fetal intervention	Laser ablation of chorionic anastomoses	Twin–twin transfusion syndrome
Open fetal surgery	Closure of high-risk MMC	Improvement of neurological outcomes

ETHICS OF FETAL THERAPY

"The fetus as a patient" is the central ethical concept for fetal medicine.[24] However, this quote should not be taken in an absence of the maternal context. It is imperative during the counseling session that cultural, religious, legal, and technological aspects of fetal disease and the corresponding interventions have to be discussed in an honest way. It is true that *in utero* intervention can potentially benefit the fetus, but occasionally it comes with an increasing maternal risk.

In terms of research for new fetal therapeutic interventions, investigators should address the initiation and assessment of clinical trials to determine the following issues:

- A standard of care has been established.
- An appropriate informed consent process has been used to recruit and enroll subjects.
- The selection criteria should include the abortion preferences of the pregnant woman.

Table 2: Criteria for invasive fetal intervention

Criteria for invasive fetal intervention
1 Accurate diagnosis and staging possible, with exclusion of associated anomalies
2 Natural history of the disease is documented, and prognosis is established
3 Currently no effective postnatal therapy
4 *In utero* surgery proven feasible in animal models, reversing deleterious effects of the condition
5 Interventions performed in specialized multidisciplinary fetal treatment centers within strict protocols and approval of the local Ethics Committee with informed consent of the mother or parents

(Adapted from Deprest et al[23])

- The doctors have an obligation to offer referral to such investigation. It means that the doctors have obligations to both the fetal patient and the pregnant woman.

In terms of clinical judgments whether to or not to offer fetal therapy, it is important to know that the definitive goal of fetal interventions is improve the health of children by intervening before birth. Once feasibility and potential benefit of particular procedure are identified, it should be subjected to rigorous scientific validation. "Innovative therapy" is therefore a part of careful care and ongoing research.

Pregnant women receiving fetal treatments entitle for the same legal and health protection as participants in interventional research study. They need to be adequately counseled for the potential risks and benefits of the procedure they are embarking on. These health impacts should be specific from maternal and fetal aspects, or as short- and long-term effects. Written informed consent must be obtained prior to any intervention. The language in this consent must be explicit. 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 published in 2011.[25]

Termination of pregnancy, even for medical indications, is not acceptable in many parts of the world. This is important to respect the community's legal and spiritual restrictions. The choice of pregnant women and their family can be limited. In some other communities, termination of pregnancy for fetal indications is possible. Most of fetal indications involve lethal malformations or malformations that result in significant handicap after birth.

In utero therapy can "cure" some diseases, such as laser surgery for severe mid-trimester TTTS, but can only palliate in the others, such as FETO in severe CDH. There is a possibility that *in utero* therapy may turn deadly disease into lifelong debilitating condition. Experienced doctors know when to offer "intervention" and "termination" to avoid that tragic possibility. 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.

Unbiased counseling is crucial. The counselor has to make sure that the pregnant woman will not undergo fetal treatment without a full awareness of alternative options. Multidisciplinary approach is therefore mandatory in many centers.[26]

CONCLUSION AND FUTURE DIRECTIONS OF FETAL THERAPY

The world is now globalized. Fetal therapeutic technique created at one place can quickly be communicated and adopted in other places. Effective communication has made the greatest impact in quality health care. Ability to intervene certain fetal diseases prenatally has significantly reduced neonatal and maternal morbidity. Traumatic delivery of an anomalous baby can sometimes be avoided with *in utero* intervention.

Quality medical care is a basic service in most developed nations. But in developing nations, even basic 2nd trimester fetal ultrasound is still lacking. Unequal distribution of resources in medicine may obstruct the access of fetal diagnosis and therapy. A good example of how to maximize a limited resource to the benefits of maternal and fetal care can be seen in Africa. This concern has been addressed in our recent publication from Working Group on Ultrasound in Obstetrics of the WAPM.[27] Dissemination of technology and funding is crucial to bring down the boundary of fetal care throughout the world.

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