Fetal Therapy in 2011: A Review

Tuangsit Wataganara, M.D.*, Namtip Triyasunant, M.D., Sommai Viboonchart, B.N.***

**Department of Obstetrics and Gynecology, **Department of Anesthesiology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.*

Siriraj Med J 2011;63:97-101
E-journal: http://www.sirirajmedj.com

Fetal medicine is founded by diagnostic and therapeutic aspects. Intrauterine interventions could be divided into four categories: medical treatments, gene therapy and stem cell transplant, minimally invasive procedures, and fetal surgeries. Local anesthetics can be applied in most procedures. Loco-regional or general anesthesia may be required in more invasive interventions. Invasive treatment should be offered only when there is a realistic chance to save the life of the fetus or to prevent serious or irreversible disability. A team of professionals is gathered for an optimal care before, during, and after delivery. Fetal medicine specialists, neonatologists, anesthesiologists, pediatric surgeons, as well as perinatal nursing staffs have to communicate, and come up with unanimous strategies for a seamless flow of care for both fetus and the mother. This invited review lays out the principles of commonly performed fetal therapeutic interventions. Special ethical considerations are also discussed.

MATERIALS AND METHODS

Medical treatments of the fetus are generally performed by administration of therapeutic agents through the mother. The drug crosses the placenta and reaches the fetal circulation. Perhaps the most commonly performed fetal medical intervention is an administration of steroids to the mother to alleviate the severity of respiratory distress syndrome associated with prematurity. An administration of anti-retroviral agents to prevent vertical transmission of human immunodeficiency virus (HIV) also falls into this category.

Although most fetal arrhythmias are benign, certain kinds of arrhythmias can lead to fetal hydrops and demise. Common causes of fetal tachyarrhythmia (ventricular rate over 180 beats per minute) are paroxysmal supraventricular tachycardia, such as sustained supraventricular tachycardia with 1:1 atriventricular relation, and atrial flutter with 2:1 atrioventricular relation. Fetal tachyarrhythmia may increase the fetal arterial and venous pressure, leading to congestive heart failure. Non-randomized experiences in the treatment of fetal supraventricular tachycardia with transplacental drug transfer are available with a number of anti-arrhythmic agents. Digoxin is widely accepted as the first-line treatment. Sotalol, flecainide, and amiodarone can be used when digoxin fails to achieve conversion to sinus rhythm. There are sporadic reports of administering these agents directly to the fetus to control the heart rate pattern.

Fetal bradyarrhythmia can be diagnosed when the ventricular rate is persistently slower than 100 beats per minute. Approximately half of the fetuses affected with bradyarrhythmia have structural cardiac defects. The most common cause of fetal bradyarrhythmia in a structurally intact heart is atrioventricular block. It is associated with transplacental crossing of maternal autoantibodies directed to fetal Ro/SSA ribonucleoproteins. Their interactions may lead to inflammation at the atrioventricular node and the myocardium in susceptible fetuses. Fibrotic changes of the inflamed tissue may then result in heart block, endocardial fibroelastosis, and cardiomyopathy. Dexamethasone administration to the mother has been shown to improve incomplete atrioventricular block, myocardial dysfunction, and cavity effusions in the affected fetus. In complete atrioventricular block, steroids may alleviate myocardial inflammation and enhance cardiac output.[1] In the presence of fetal hydrops from a severely compromised cardiac output, beta-adrenomimetic agents may increase the fetal heart rate, and immediately rescue the fetus. Owing to associated cardiac malformations and fibrotic atrioventricular node and myocardium, the efficacy of prenatal treatment for fetal atrioventricular block is limited, compared to the treatment outcome in fetal tachycardia.[2,3]

Fetal goiter can be the result of antithyroid drugs used for the treatment of maternal hyperthyroidism. Esophageal obstruction from the goitrous mass can result in polyhydramnios. A persistently hyperextended position of the fetal neck may make vaginal birth complicated or improbable. Neonatal airway management could also be problematic. Fetal hypothyroidism can be confirmed by cordocentesis. It can be treated with levothyroxine. Levothyroxine has a poor placental transfer, therefore direct intraamniotic administration has been advocated. Prenatal treatment of fetal goiter has dual benefits: reduction of goiter size and to prevent neonatal cretinism.[4,5]

In order to prevent virilization, dexamethasone has been given to the mother carrying a female fetus affected with classic congenital adrenal hyperplasia from

Correspondence to: Tuangsit Wataganara
E-mail: sitwg@mahidol.ac.th
Received 3 June 2011
Revised 13 June 2011

21-hydroxylase deficiency.[6] This is to avoid unnecessary genitoplasty in female neonates. Several human and animal studies have evaluated cognitive functions, behavioral traits, and metabolic alterations in treated children and animals. The data are conflicting, but no firm conclusions regarding the potential risks of prolonged exposure to the oral therapeutic dexamethasone have been reached.[7]

Gene therapy and stem cell transplant

Gene therapy means the delivery of genetic material into the cells to treat diseases. In adults, a wide range of diseases, mostly degenerative, including cancer, vascular, neurodegenerative, and inherited genetic disorders, are amendable for this treatment. Application of this treatment modality to the fetus may yield a better outcome than in the adult. It may treat, or prevent permanent disabilities from certain genetic disorders, such as cystic fibrosis and Duchene muscular dystrophy.[8] Gene transfer to the developing fetus targets stem cells, which are rapidly expanding. These cell clusters are inaccessible after birth. It is indicated that the use of integrating vector systems may result in permanent gene transfer. In animal models of congenital disease such as haemophilia, studies show that the functionally immature fetal immune system does not respond to the product of the introduced gene. Therefore, long-term immune tolerance can be induced.[9] Treatment could be repeated after birth.

Fetal gene therapy would broaden the options for the clinician and affected parents. Traditionally, termination of pregnancy or acceptance of an affected child are the only options following prenatal diagnosis of genetically inherited disease. Application of this therapy in the fetus must be safe, reliable and cost-effective. Recent developments in the understanding of genetic disease, vector design, and minimally invasive delivery techniques have brought fetal gene therapy closer to clinical practice. However more research needs to be done before it can be introduced routinely.

Stem cell transplantation is an attractive approach to the treatment of a variety of fetal immunological, metabolic, and hematological diseases. A large number of cells can be transferred at an early stage of life. There is also an advantage of physiologic fetal stem cell migration and development. During fetal life, the capacity to mount an immune response to allogeneic cells is impaired compared with adult life. This provides an opportunity to induce tolerance to alloantigens without a prior myeloablation. Fetal hematopoietic stem cell transplantation is of a particular interest in Thailand, where thalassemia is prevalent. Sporadic reports suggest that *in utero* stem cell transplantation can significantly reduce the morbidity from thalassemia diseases during the childhood period.[10]

Minimally invasive procedure

Minimally invasive intervention involves an introduction of small-caliber instruments into the amniotic cavity under ultrasound guidance. Maternal morbidity is limited. It can be categorized into: needle interventions, shunting procedures, and fetoscopic interventions.

Intrauterine fetal transfusion is the most widely known example of fetal needle intervention.[11] Life threatening fetal anemia as a result of red blood cell isoimmunization is the most common indication for this procedure. Serial transfusions are often required. Fetal infection with Parvovirus B19 can cause aplastic crisis, and a single blood transfusion can be life-saving, as shown in Fig 1.

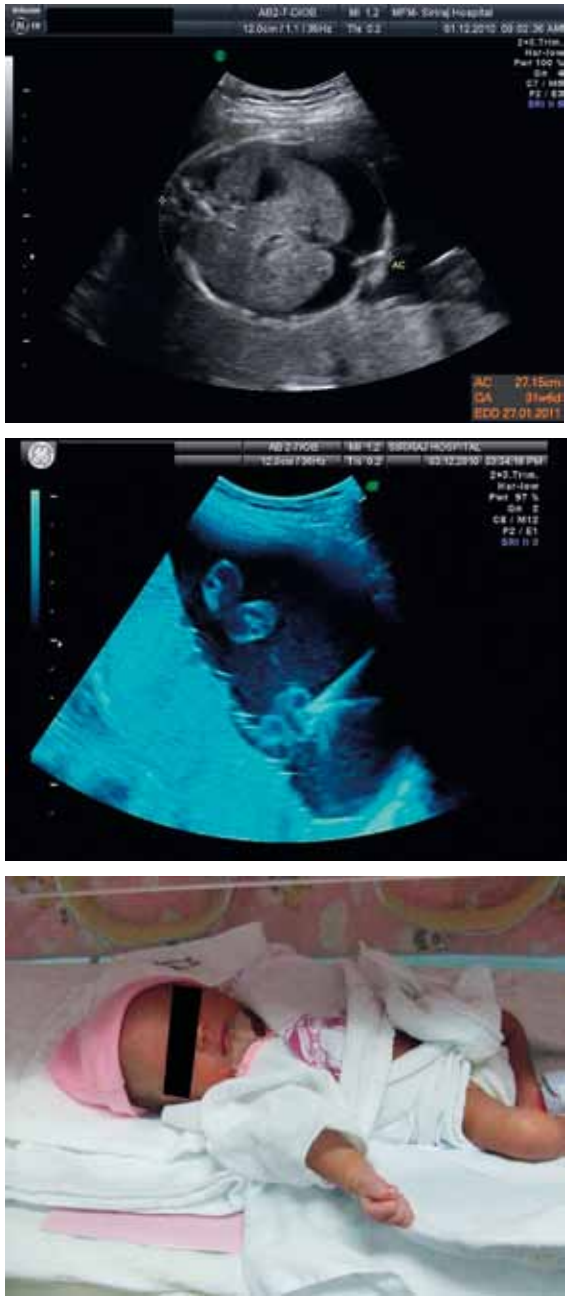

Fig 1. Intrauterine blood transfusion performed to salvage the hydropic fetus affected with intrauterine Parvovirus B19 infection. It was accomplished with single donor packed red blood cells. The baby was born at term with a normal hematocrit.

Fetal platelets transfusion is indicated in alloimmune thrombocytopenia. It is one of the major causes of severe thrombocytopenia and intracranial hemorrhage in fetuses and neonates.[12] Transplacental passage of maternal immunoglobulin G alloantibodies are directed against human platelet antigen (HPA) on fetal platelets. The mechanism is equivalent to Rhesus disease, but it can occur in a severe form in the first pregnancy. It will get worse in subsequent pregnancies. Testing for maternal-fetal HPA incompatibility should be confirmed in cases with unexplained fetal intracranial hemorrhage (detected from ultrasound examination) or neonatal intracranial hemorrhage associated with severe thrombocytopenia. Fetal blood sampling and serial intra-

uterine platelet transfusion, followed by Cesarean delivery, has become a standard treatment since 1984.[13] Maternal administration with intravenous immunoglobulin, but not steroids, has been shown to increase the fetal platelet count.[14]

Other examples of fetal needle interventions include stem cell transplantation (to transfer stem cells into the fetal abdominal cavity or placenta), amnioreduction, and septostomy in twin-twin transfusion syndrome.

Collection of high-pressure fluid in fetal cavities can cause damage to the surrounding organs.Chronic drainage through shunting procedures is then indicated. The most common indication lies in the massive collection in the pleural cavity that can lead to fetal hydrops and demise. Once structural and chromosomal anomalies have been excluded, optimal management depends on gestational age, rate of progression, the development of hydrops, and associated maternal symptoms. Neonatal survival can be maximized by pleuroamniotic shunting, which can reverse hydrops and polyhydramnios, and prevent pulmonary hypoplasia. Pleuroamniotic shunting can also be used for the treatment of other large cystic lung lesions, such as macrocystic congenital cystic adenomatoid malformation (CCAM).

Fetoscopic intervention has regained its application since the landmark publication of a randomized controlled trial in 2004, showing a better survival of fetuses affected with severe midtrimester twin-twin transfusion syndrome (TTTS) after treatment with laser ablation of anastomosing chorionic plate vessels, compared to serial amniodrainage.[15] TTTS occurs in approximately 15% of all monochorionic twins, and is defined sonographically by using an oligo-polyhydramniotic sequence. Intertwin anastomoses on the chorionic plate are responsible for the development of the disease.[16] Fetoscopic mapping of the vascular equator, followed by selective laser coagulation of the pathologic anastomoses, is considered the best modality of treatment up to 26 weeks of pregnancy. On rare occasions, selective feticide may be considered when one fetus is severely distressed or an anomaly of one twin has compromised the other. This procedure can be performed with locoregional anesthesia. If fetal immobilization is needed, maternal sedation can be applied.

A fetus affected with congenital diaphragmatic hernia (CDH) will have surgical correction of the defect after birth. The correction of this anatomical defect lies in its impairment of lung development. Currently, up to 30% of babies with isolated CDH die from the consequence of lung hypoplasia and/or pulmonary hypertension. When the lung area to head circumference ratio (LHR) is less than 25% of the normal value at that gestational age, postnatal death is very likely. Percutaneous fetal endoscopic tracheal occlusion (FETO) is currently offered in selected high-risk cases to improve lung development.

Cardiac interventions in the fetus are currently in a clinical experimental phase. Three most commonly performed are aortic balloon valvuloplasty, atrial septostomy, and pulmonary valvuloplasty. Fetuses with critical aortic stenosis with a small or poorly functioning left ventricle may benefit from aortic balloon valvuloplasty. Atrial septostomy can be a salvage therapy in fetuses with a highly restrictive or intact atrial septum in hypoplastic left heart syndrome. Pulmonary atresia, leading to hypoplastic right ventricle, may benefit from pulmonary valvuloplasty. These procedures can be performed percutaneously under local anesthesia.[17]

Surgical interventions

In utero correction of spina bifida is an example of direct operation onto the fetus. It is done through a hysterotomy incision to expose the fetal parts that require an operation. Maternal morbidity is significant and these interventions are often complex. Therefore, they are only performed when the prognosis suggests the fetus may either not survive or be severely handicapped without prenatal intervention. Certain procedures may be performed at the time of delivery, so called *ex utero*-Intrapartum (EXIT) procedure.

Myelomeningocele can cause significant disabilities. Babies affected with this condition may have impairments in their lower extremity function and sphincter continence. Standard postnatal closure may not be able to fully restore these functions.[18] A randomized trial recently published in the New England Journal of Medicine suggests the benefit of *in utero* repair of the defect in fetuses with an isolated meningomyelocoele between the menstrual age of 19 and 26 weeks with hind brain herniation (Chiari II malformation), but intact movement of the lower extremities.[19] Preliminary data suggests that prenatal surgery results in reversal of hindbrain herniation and a decrease in shunt-dependent hydrocephalus. It may also slightly improve the function of lower extremities. In this kind of surgery, direct administration of medications to achieve fetal analgesia and immobilization are required. Continuous dual monitoring of both mother and fetus, has to be performed throughout the surgery. Maintenance of uterine relaxation and hemodynamics are also the keys to maximize the success of this complex kind of surgery.

A fetus affected with congenital high airway obstructions (CHAOS), either primary or secondary, may have difficulty to breathing soon after birth. Neck mass, such as goiter, may directly compress the trachea. Difficult intubation which may require an immediate neonatal tracheostomy can be facilitated by having an intact placental circulation to ensure fetal oxygenation during the procedure.[20] Bronchoscopy may be required soon after the fetal head and chest are delivered. On rare occasions, if complete obstruction is encountered, placement of an extracorporeal membrane oxygenation can proceed, while fetal oxygen exchange remains intact.[21] In short, EXIT is a strategy to establish the fetal airway in a controlled manner. Monitoring of fetal oxygenation may be required until its airway is secured.

Some authorities have advocated *in utero* resection of certain fetal tumors that cause fetal hydrops.[22] Congenital cystic adenomatoid malformations that are predominant in solid or multicystic form are amendable for surgical resection to save the life of the fetus. Fetal sacrococcygeal teratoma complicated with progressive high-output cardiac failure may also benefit from *in utero* resection of the tumor. The scientific data for the genuine benefit of open fetal surgery for these conditions are accumulating. Significant maternal morbidities have to be discussed with the family of these candidate fetal patients. Dual (maternal and fetal) perioperative management by a multidisciplinary team is tremendously important.

Anesthetic considerations and managements

Seamless coordination between the surgical and anesthetic teams is vital. It is important to understand the physiologies of the mother, the fetus, and the placenta to arrange for an optimal anesthetic management. Maternal physiologic changes during pregnancy have significant

anesthetic implications. Potential risks for the fetus during the procedures can be prevented with good communication. These include the prevention of fetal asphyxia from uterine hypoperfusion, cardiovascular compression from anesthetics and aortocaval compression. Certain anesthetic agents which are categorized as teratogens, and should be avoided. Timely administration of tocolytic agents is also important to optimize perinatal outcomes.[23]

The choices of anesthesia rely on the procedural specification which mandates various degrees of maternal and fetal anesthesia. For extrafetal needle intervention (such as amnioreduction, umbilical cord sampling or intrauterine infusion), fetal analgesia is not required. Local anesthesia at the procedural site is usually adequate. Intravenous conscious sedation with opioids and benzodiazepines can be supplemented at the surgeons discretion.[24]

Fetoscopic interventions, such as umbilical cord coagulation or laser treatment for TTTS, may require both maternal and fetal anesthesia. The additional benefit is to minimize fetal movement that might get in the way. Either general or regional anesthesia are applicable. Regional anesthesia includes spinal, epidural, and combined spinal-epidural blocks. Choices of anesthetic approaches can be made accordingly to the location of the placenta (anterior or posterior), fetal position, and potential window for trocar insertion.[23,25] The requirement for uterine relaxation and fetal immobilization also determine the anesthetic choice. Regional anesthesia is optimal in the majority of the procedures. Distracting fetal movement can be obviated by direct fetal administration, either intramuscular or intravascular, with certain anesthetic agents. Opioids such as fentanyl, and neuromuscular blocking agents, such as pancuronium or vecuronium, are warranted. It also has an additional benefit of decreasing fetal autonomic, metabolic and stress responses to noxious stimuli.[24]

Exceptional uterine relaxation may be required in certain procedures. Various kinds of tocolytic agents can be applied for this purpose. Intravenous nitroglycerin, either bolus injection (50 to 100 μg) or continuous infusions, is applicable during the surgery. Continuous prevention of premature uterine contraction can be achieved with magnesium sulfate, terbutaline, or calcium channel blocking agents.

A placenta located anteriorly poses a special challenge. General anesthesia may be required in these selected cases. General anesthesia additionally provides fetal anesthesia and uterine relaxation.[25] Deep inhalation anesthesia or volatile anesthetics at concentrations of 2 minimum alveolar concentrations (MAC) can relax the uterus. Higher concentrations of volatile anesthetics should be avoided, as it can cause maternal hypotension and impair uteroplacental perfusion. Airway patency and aspiration should also be cautioned in the mother receiving general anesthesia.

EXIT procedure can be performed at the time of Cesarean delivery. Profound uterine relaxation has to be achieved to facilitate delivery of the fetal head while preventing placental separation. These have to be concomitant with an adequate fetal anesthesia, maintenance of maternal hemodynamics and uteroplacental circulation.[26] General anesthesia with a potent volatile agent is, therefore, the preferred method.[27] Successful Cesarean EXIT has been reported using only combined spinal-epidural anesthesia.[28] Uterine relaxation can be enhanced with concomitant use of tocolytic agents (such as nitroglycerin). Profound maternal hypotension is a major concern of nitroglycerin usage. Blood pressure and uteroplacental perfusion can be maintained by judicious use of selected vasopressors (such as ephedrine or phenylephrine). Sedatives, such as opioids, ketamine and muscle relaxants, can be administered directly to the fetus through an intramuscular or intravenous route to ensure adequate analgesia. Fetal monitorings are required if the procedure is expected to be protracted. Pulse oximeter probe, scalp electrode for continuous fetal heart rate monitoring, fetal echocardiography and umbilical blood sampling for blood gases, are examples of intensive fetal monitoring during the intervention.

Perioperative massive hemorrhage can be encountered during the EXIT procedure. A number of factors can contribute to intra- and postoperative profuse blood

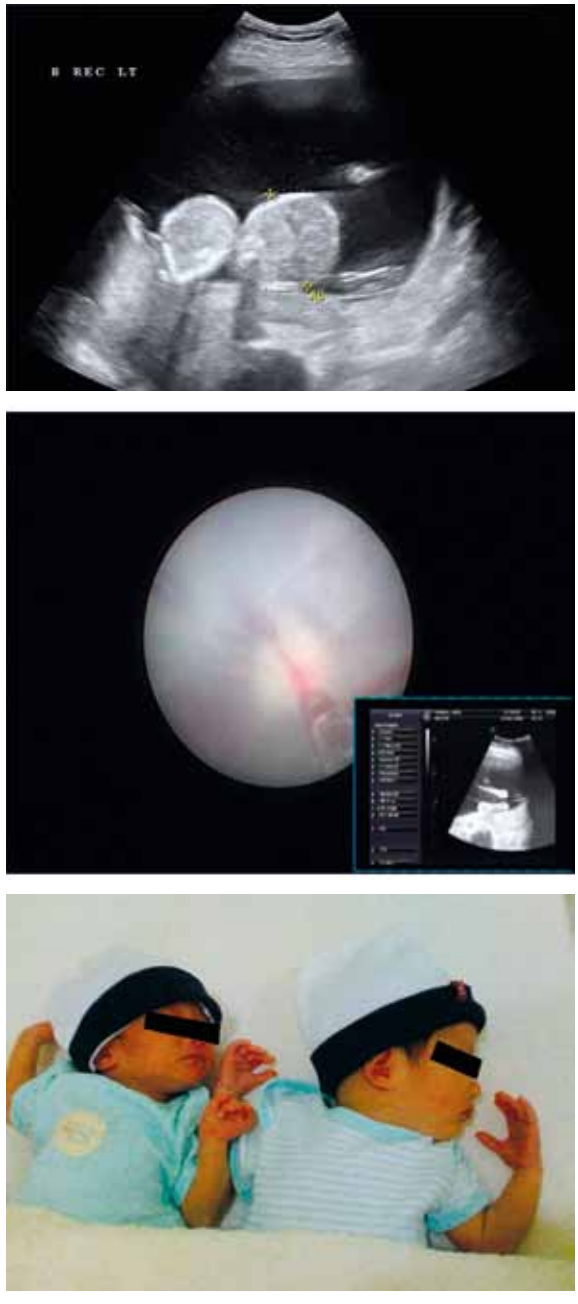

Fig 2. Laser photocoagulation of chorionic arterio-venous anastomosis in severe midtrimester twin-twin transfusion syndrome. The babies born after this treatment might have some residual growth discordance.

loss. Prolonged duration of surgery coupled with uterine relaxation from medications and a volatile anesthetic are major contributors. Delayed postoperative hemorrhage can be a result of uterine atony. Oxytocin infusion and uterine massage are universally required to minimize the bleeding after the placenta is delivered.[29] In the light of the need for a prospective massive blood transfusion, direct arterial and central venous pressure lines may need to be placed prior to the surgery for adequate invasive hemodynamic monitoring.

Ethical considerations in fetal therapy

Respect should be paid to maternal perception or assessment of risk, especially when an unsuccessful therapy can cause profound fetal morbidity. Fetal therapy should not be undertaken without a thorough maternal consent. The family should not be intimidated to perceive the intervention as an option to avoid a termination of pregnancy. Procedures which their efficacy which remain to be proven should be performed accordingly to a clearly defined research protocol that has been approved by institutional review board. Risks from the procedures imposed on the mother should be minimal.

SUMMARY

Fetal treatment, and advanced fetal therapy in particular, is a relatively new field in medicine. The treatments range from medical interventions, which are not invasive, to surgical intervention, which can cause maternal morbidities. 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. Minimally invasive fetal procedures, such as fetoscopic interventions, have been widely embraced, especially in the condition of complicated monochorionic twins. There has been an accumulation of data and development of surgical skills and perioperative care for open fetal surgery. Due to its significant morbidity to the mother, it should be offered only for carefully selected fetuses with life-threatening anomalies.

Refinement of surgical techniques and sharing of knowledge can broaden the indications for minimally invasive and more invasive fetal interventions. Gene therapy may also alleviate, if not cure, the severity of genetically inherited diseases. Most fetal conditions amenable for therapy 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. Promoting research into these conditions, and facilitating access to diagnosis and treatment, both for pregnant couples and their physician, are also the keys to improve the quality of fetal treatment.

REFERENCES

1. Hutter D, Silverman ED, Jaeggi ET. The benefits of transplacental treatment of isolated congenital complete heart block associated with maternal anti-Ro/SSA antibodies: a review. Scand J Immunol. 2010 Sep;72(3):235-41.
2. Maeno Y, Hirose A, Kanbe T, Hori D. Fetal arrhythmia: prenatal diagnosis and perinatal management. J Obstet Gynaecol Res. 2009 Aug;35(4):623-9.
3. Eliasson H, Wahren-Herlenius M, Sonesson SE. Mechanisms in fetal bradyarrhythmia: 65 cases in a single center analyzed by Doppler flow echocardiographic techniques. Ultrasound Obstet Gynecol. 2011 Feb;37(2):172-8.
4. Abuhamad AZ, Fisher DA, Warsof SL, Slotnick RN, Pyle PG, Wu SY, et al. Antenatal diagnosis and treatment of fetal goitrous hypothyroidism: case report and review of the literature. Ultrasound Obstet Gynecol. 1995 Nov;6(5):368-71.
5. Gruner C, Kollert A, Wildt L, Dorr HG, Beinder E, Lang N. Intrauterine treatment of fetal goitrous hypothyroidism controlled by determination of thyroid-stimulating hormone in fetal serum. A case report and review of the literature. Fetal Diagn Ther. 2001 Jan-Feb;16(1):47-51.
6. Mercà Fernéndez-Balsells M, Muthusamy K, Smushkin G, Lampropulos JF, Elamin MB, Abu Elnour NO, et al. Prenatal dexamethasone use for the prevention of virilization in pregnancies at risk for classical congenital adrenal hyperplasia because of 21-hydroxylase (CYP21A2) deficiency: a systematic review and meta-analyses. Clin Endocrinol (Oxf). 2010 Oct;73(4):436-44.
7. Vos AA, Bruinse HW. Congenital adrenal hyperplasia: do the benefits of prenatal treatment defeat the risks? Obstet Gynecol Surv. 2010 Mar;65(3):196-205.
8. Dejneka NS, Surace EM, Aleman TS, Cideciyan AV, Lyubarsky A, Savchenko A, et al. In utero gene therapy rescues vision in a murine model of congenital blindness. Mol Ther. 2004 Feb;9(2):182-8.
9. Manno CS, Pierce GF, Arruda VR, Glader B, Ragni M, Rasko JJ, et al. Successful transduction of liver in hemophilia by AAV-Factor IX and limitations imposed by the host immune response. Nat Med. 2006 Mar;12(3):342-7.
10. Renda MC, Maggio A. In Utero Haematopoietic Stem Cell Transplantation (IUHSCT). Mediterr J Hematol Infect Dis 2009;1:e2009031.
11. Wataganara T, Wiwanichayakul B, Ruengwuttilert P, Sunsaneevithayakul P, Viboonchart S, Wantanasiri C. Noninvasive diagnosis of fetal anemia and fetal intravascular transfusion therapy: experiences at Siriraj Hospital. J Med Assoc Thai. 2006 Jul;89(7):1036-43.
12. Bussel JB, Zacharoulis S, Kramer K, McFarland JG, Pauliny J, Kaplan C. Clinical and diagnostic comparison of neonatal alloimmune thrombocytopenia to non-immune cases of thrombocytopenia. Pediatr Blood Cancer. 2005 Aug;45(2):176-83.
13. Daffos F, Forestier F, Muller JY, Reznikoff-Etievant M, Habibi B, Capella-Pavlovsky M, et al. Prenatal treatment of alloimmune thrombocytopenia. Lancet. 1984 Sep 15;2(8403):632.
14. Bussel JB, Berkowitz RL, McFarland JG, Lynch L, Chitkara U. Antenatal treatment of neonatal alloimmune thrombocytopenia. N Engl J Med. 1988 Nov 24;319(21):1374-8.
15. Senat MV, Deprest J, Boulvain M, Paupe A, Winer N, Ville Y. Endoscopic laser surgery versus serial amnioreduction for severe twin-to-twin transfusion syndrome. N Engl J Med. 2004 Jul 8;351(2):136-44.
16. Wataganara T, Chanprapaph P, Chuangsuwanich T, Kanokpongsakdi S, Chuenwattana P, Titapant V. Reverse twin-twin transfusion syndrome after fetoscopic laser photocoagulation of chorionic anastomoses: a case report. Fetal Diagn Ther. 2009;26(2):111-4.
17. Matsui H, Gardiner H. Fetal intervention for cardiac disease: the cutting edge of perinatal care. Semin Fetal Neonatal Med. 2007 Dec;12(6):482-9.
18. Rintoul NE, Sutton LN, Hubbard AM, Cohen B, Melchionni J, Pasquariello PS, et al. A new look at myelomeningoceles: functional level, vertebral level, shunting, and the implications for fetal intervention. Pediatrics. 2002 Mar;109(3):409-13.
19. Adzick NS, Thom EA, Spong CY, Brock JW 3rd, Burrows PK, Johnson MP, et al. A randomized trial of prenatal versus postnatal repair of myelomeningocele. N Engl J Med. 2011 Mar 17;364(11):993-1004.
20. Wataganara T, Ngerncham S, Kitsommart R, Fuangtharnthip P. Fetal neck myofibroma. J Med Assoc Thai. 2007 Feb;90(2):376-80.
21. Kunisaki SM, Fauza DO, Barnewolt CE, Estroff JA, Myers LB, Bulich LA, et al. Ex utero intrapartum treatment with placement on extracorporeal membrane oxygenation for fetal thoracic masses. J Pediatr Surg. 2007 Feb;42(2):420-5.
22. Adzick NS. Open fetal surgery for life-threatening fetal anomalies. Semin Fetal Neonatal Med. 2010 Feb;15(1):1-8.
23. Galinkin JL, Gaiser RR, Cohen DE, Crombleholme TM, Johnson M, Kurth CD. Anesthesia for fetoscopic fetal surgery: twin reverse arterial perfusion sequence and twin-twin transfusions syndrome. Anesth Analg. 2000 Dec;91(6):1394-7.
24. Rosen MA. Anesthesia for fetal procedures and surgery. Yonsei Med J. 2001 Dec;42(6):669-80.
25. Myers LB, Bulich LA, Hess P, Miller NM. Fetal endoscopic surgery: indications and anaesthetic management. Best Pract Res Clin Anaesthesiol. 2004 Jun;18(2):231-58.
26. Schwartz DA, Moriarty KP, Tashjian DB, Wool RS, Parker RK, Markenson GR, et al. Anesthetic management of the exit (ex utero intrapartum treatment) procedure. J Clin Anesth. 2001 Aug;13(5):387-91.
27. Gaiser RR, Cheek TG, Kurth CD. Anesthetic management of cesarean delivery complicated by ex utero intrapartum treatment of the fetus. Anesth Analg. 1997 May;84(5):1150-3.
28. George RB, Melnick AH, Rose EC, Habib AS. Case series: Combined spinal epidural anesthesia for Cesarean delivery and ex utero intrapartum treatment procedure. Can J Anaesth. 2007 Mar;54(3):218-22.
29. Chang LC, Kuczkowski KM. The ex utero intrapartum treatment procedure: anesthetic considerations. Arch Gynecol Obstet. 2008 Jan;277(1):83-5.