SFM Fetal Therapy Practice Guidelines: Fetal Medical Therapy

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J Fetal Med 2023;10:195–199.

Abstract

Fetal medical therapy encompasses a wide range of pharmacological interventions aimed at preventing, treating, or ameliorating specific pathological conditions in the fetus. In contrast to fetal surgery, fetal medical interventions involve administering drugs either through transplacental transfer (maternal oral, intramuscular or intravenous injections) or direct administration to the fetus (intraumbilical, intraamniotic, intramuscular, intraperitoneal and intracardiac). The available interventions can be divided into four categories depending on the impact it has on fetal well-being and physiology, conditions amenable to medical therapy with established benefits, drugs with likely or potential benefits, maternal drug therapy with indirect fetal benefits, and drugs administered for nontherapeutic benefits. Careful selection of the cases, discussion under an institutional review board or a multidisciplinary team, strict adherence to standard guidelines and recommendations, and performance by physicians with adequate expertise are mandatory.

Keywords

- fetal medical therapy
- fetal cardiac arrhythmias
- dexamethasone
- betamethasone
- congenital hypothyroid goiters
- Congenital toxoplasmosis
- fetal analgesia

Introduction

Fetal medical therapy encompasses a wide range of pharmacological interventions aimed at preventing, treating, or ameliorating specific pathological conditions in the fetus as diverse as cardiac, endocrinological, and hematological conditions.[1] In contrast to fetal surgery, fetal medical interventions involve administering drugs either through the mother, thus achieving transplacental transfer (maternal oral, intramuscular or intravenous injections) or direct administration to the fetus (intraumbilical, intraamniotic, intramuscular, intraperitoneal, and intracardiac).

Fetal medical therapy can be broadly categorized into four groups

A. Conditions amenable to medical therapy with established benefits

The fetal conditions that have established benefits from medical therapy with the dosage and mode of administration are described below.

1. Fetal cardiac arrhythmias are a potentially lethal condition of the fetus. Sustained tachycardias and bradycardia

article published online
March 21, 2024

DOI https://doi.org/10.1055/s-0044-1778736.
ISSN 2348-1153.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

can lead to hydrops that is associated with significant mortality. The medical therapy of tachyarrhythmias is now well-established. The drugs used for treating tachyarrhythmias include digoxin, flecainide, sotalol, procainamide, propranolol, amiodarone, and adenosine.[2]

The first-line drugs of choice for fetal supraventricular tachycardia (SVT) are digoxin, flecainide, and sotalol. These may be used as monotherapy or in combination. The initial therapy is transplacental (orally or intravenous to the mother) for stabilization. For refractory cases, direct fetal therapy may be performed. In a study comparing these drugs, flecainide and sotalol were observed to be superior to digoxin for the conversion of fetal tachycardia to sinus rhythm.[3] In fetuses with hydrops, flecainide or amiodarone was observed to be superior to digoxin. Sotalol is recommended in atrial flutter as it establishes sinus rhythm in 50 to 80% of cases. In general, maternal and fetal safety is a concern with these drugs as they are associated with narrow therapeutic margins.

The use of antiarrhythmic drugs is associated with potential side effects in the mother and the fetus in view of their narrow therapeutic margin. Maternal side effects include palpitations, second-degree atrioventricular (AV) block, Wenckebach phenomenon, and hypotension. The fetal side effects include high proarrhythmic activity, negative inotropic effects, and exacerbation of hydrops. Amiodarone has a significant toxicity profile for the expectant mother and the fetus. It is generally used as a third-line drug. Verapamil and procainamide are no longer used.

A suggested regimen adapted from the American Heart Association consensus statement is shown in the box below.[4]

Indication: Sustained tachycardia, atrial flutter, delivery not warranted immediately
First-line drugs: Digoxin, flecainide, sotalol
Second-line drugs: Digoxin, flecainide, sotalol
Third-line drug: Amiodarone
SVT
Hospitalization elicits a history of long QT syndrome in the mother or family digoxin loading dose 1,500 µg/day IV in six divided doses over 24 hours; maintenance dose 375 to 750 µg/day divided 8 to 12 hours orally (depending on maternal serum digoxin levels)
If no response in 24 to 48 hours, second-line therapy with flecainide 100 mg three times a day (TDS) orally. Maintenance dose 100 to 300 mg/day
If hydrops is present, initial intravenous digitization as above followed by direct intramuscular injection of digoxin. Dose 88 µg.kg × 2 doses 12 hours apart
Atrial flutter
Above regimen, instead of flecainide, sotalol 160 mg TDS initially, maintenance dose 160 to 480 mg/day
Maternal monitoring with serum electrolytes, electrocardiogram (specific attention to QT interval)

The benefits of maternal steroids and other agents are less well-established in bradyarrhythmias. For AV block, treatment depends on the etiology, ventricular rate, and cardiac function. Fluorinated steroids (e.g., dexamethasone), β-agonists (terbutaline, salbutamol, and isoprenaline) and intravenous immunoglobulin have been used to increase low ventricular rates. Medical therapy is not recommended for AV blocks due to underlying malformation in the conduction system associated with complex cardiac defects and AV blocks of undetermined etiology. However, β-sympathomimetics have been used in all cases of AV blocks to augment fetal ventricular rates when it falls below 55 beats per minute.[5]

Fetal medical therapy is advised for AV blocks resulting from immune-mediated mechanisms. Fluorinated steroids, intravenous transfusion of gamma globulins or both are used for therapy. Dexamethasone reduces inflammation, reverses, or stabilizes incomplete block and improves or resolves hydrops or endocardial fibroelastosis. Dexamethasone has the advantage of not being metabolized by placenta. Dexamethasone is indicated for second-degree and complete AV blocks at dosage of 4 to 8 mg/day. Intravenous immunoglobulin is indicated in the presence of isolated myocardial endocardial fibroelastosis, administered intravenously at 2 to 3 weekly intervals. It also used in the neonate for the same indication. Dexamethasone is associated with maternal complications such as hypertension, and gestational diabetes and fetal complications, such as oligohydramnios and suboptimal growth and development.[2]

Indication: AV blocks due to immune-mediated mechanisms, positive anti-Rho and anti-La antibodies
First-degree AV block with echogenicity, valve regurgitation, cardiac dysfunction, effusion
Second-degree AV block
Third-degree AV block, to improve survival or reduce the incidence of dilated cardiomyopathy
Dose: 4 to 8 mg/day

2. Congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency results in excess production of androgens that can cause virilization of female fetuses.[6] The differentiation of external genitalia occurs between 7th and 12th weeks of gestation. It is recommended to initiate maternal dexamethasone therapy from 6 to 7 weeks onward. The recommended dose is 20 µg/kg/day in three divided doses with a maximum of 1.5 mg/day. Cell-free DNA can identify fetal gender from 7 weeks onward and may be used where resources and local laws allow its use. A chorion villus sampling performed from 10 weeks onwards can identify the unaffected fetus when the dexamethasone therapy can be stopped. Robust evidence for the routine use of dexamethasone for preventing virilization by early pregnancy administration is

limited. A recent meta-analysis demonstrated a reduction in fetal virilization measured by Prader score and a lack of deleterious effects from increased edema and striae in the mother.[7] However, the need to start early in pregnancy without the knowledge of the fetal gender (7 out of 8 fetuses will eventually not need dexamethasone) with the potential increased risk of somatic and neuropsychological disease later in adult life makes this strategy debatable. Prenatal dexamethasone does not benefit nonclassic and milder forms of CAH.

Indication: Known carriers of classical CAH, previously affected child
Genetic testing is to be done if not done in the index child
Initiate dexamethasone therapy at 6 to 7 weeks of gestation
Recommended dose: 20 µg/kg/day, maximum 1.5 mg/day
Early chorion villus sampling for genetic testing.
Dexamethasone is to be stopped if CAH is ruled out.

3. Congenital hypothyroid goiters if untreated can lead to the development of polyhydramnios, preterm premature rupture of membranes, labor dystocia, tracheal compression, and asphyxia at birth requiring an ex-utero intrapartum procedure.[8] Further, there is a long-term association with impaired language, perceptual motor and visual–spatial development deficits with persistent untreated fetal hypothyroidism. Fetal hypothyroid goiters have to be treated with intraamniotic levothyroxine as its transplacental transfer rate is low. Prior to the procedure, diagnostic confirmation of hypothyroidism is necessary. This is achieved via cordocentesis as amniotic fluid thyroid hormone levels are unreliable. Surveillance of treatment response should be done by serial fetal thyroid volume measurement and estimation of amniotic fluid thyroid-stimulating hormone (TSH) and free T4 levels.[9]

Indication: Fetal hypothyroid goiter, ancillary signs = polyhydramnios, lack of tracheal fluid motion
Fetal blood sampling and assay of fetal thyroid hormone levels (normal fetal blood thyroid hormone levels: TSH-3.9–9.7 IU/L, FT4 = 11.5–14.7 pmol/L)
Dose of Levothyroxine = 100–400 µg, median 250 µg intraamniotic though a 20/22 G spinal needle
Surveillance through amniotic fluid levels (normal TSH-0.04–0.5 IU/L, FT4 = 1.29–9.93 pmol/L) and ultrasound estimation of thyroid volume (normal = 0.24 ± 0.10)

4. Fetal hematological disorders

a. Fetal and neonatal alloimmune thrombocytopenia is seen in 1 in 1,500 pregnancies. They are caused by maternal antibody-mediated response against a fetal platelet-specific antigen. Prenatally, it presents as an intracranial hemorrhage. Women usually have a history of previously affected children. Maternal intravenous gamma globulin increases fetal platelet counts.
b. Rh D alloimmunization can cause hemolytic disease in the newborn and the fetus. Though the standard management is intrauterine transfusion, anti-D immunoglobulin can reduce the need for transfusions.

5. Fetal lung maturation can be promoted by maternal intramuscular administration of synthetic glucocorticoids, betamethasone, and dexamethasone when preterm birth is anticipated.[10] This intervention is associated with a significant reduction in the incidence of respiratory distress syndrome, neonatal mortality, cerebroventricular hemorrhage, necrotizing enterocolitis, intensive care admission, and systemic infections in the first 48 hours of life. Maternal steroid administration is indicated in women at risk of premature delivery between 24^{+0} and 34^{+0} weeks of gestation. The most extensively studied, hence most preferred course consists of two doses of betamethasone 24 hours apart or 4 doses of dexamethasone 12 hours apart. The maximal benefit of this strategy starts from 24 hours of the second dose and lasts for 7 days.

Women who are at risk of preterm birth between 34^{+0} and 36^{+6} can be offered a single course provided they have not received a course earlier. A single repeat dose is advised for women who are at risk of preterm birth before 34 weeks and who have received a course 14 days earlier.[11] A single course of corticosteroids can be considered for women undergoing planned cesarean delivery at 37 to 38^{+6} week's gestation. Antenatal corticosteroid therapy is not contraindicated in women with pre-gestational and gestational diabetes who are at risk of imminent preterm birth. Women who are receiving steroids should have additional insulin according to an agreed protocol and can be closely monitored. There is insufficient evidence to conclude the benefits or harms of antenatal corticosteroid therapy in pregnancies with fetal growth restriction.

Administration of more than two courses is not recommended in view of their deleterious defects on cerebral myelination, lung growth, and function of the hypothalamo-pituitary-adrenal axis.

Dexamethasone (dexamethasone phosphate) is more easily available than the most effective salt preparation of betamethasone (a combination of betamethasone acetate + betamethasone phosphate).[12] It is also cheaper for a standard 24 mg dose. It is also associated with a nonsignificant reduction of intraventricular hemorrhage compared with betamethasone.

6. Magnesium sulfate for fetal neuroprotection—Various studies have demonstrated the neuroprotective benefits of antenatal administration of magnesium sulfate. Three large multicenter studies have shown that antenatal administration of magnesium sulfate reduces the incidence of cerebral palsy. The dose of 4 g given intravenously for 15 minutes continued by 1 g/h until a maximum of 24 h and a minimum of 4 h is the standard regimen proposed in most guidelines. The benefit is directly proportional to the degree of prematurity. Most guidelines strongly recommend magnesium sulfate for the risk of premature births prior to 30 weeks of gestation.[13]

B. Drug therapy with likely or potential benefits

1. Severe polyhydramnios—Maternal oral indomethacin therapy for severe symptomatic polyhydramnios may benefit in terms of prolongation of the pregnancy, avoidance of extreme prematurity especially when the underlying condition is surgically salvageable, and symptomatic relief from cardiorespiratory embarrassment.[14] It provides additional tocolytic benefits also. The recommended dose is 2.2 to 3 mg/kg/day in divided doses to be discontinued at 35 weeks. The most commonly used regimen is 25 mg four times daily. A baseline fetal echocardiography is advised. Weekly or twice-a-week ultrasound to assess liquor volume is recommended. Indomethacin therapy may be stopped when oligohydramnios sets in or there are features of ductal constriction. Increased neonatal complications including oligohydramnios, renal failure, necrotizing enterocolitis, intraventricular hemorrhage, and closure of the patent ductus arteriosus have been reported with the use of indomethacin.
2. Early second trimester, nonhydropic fetal chylothorax can be managed by injection of Picibanil into the pleural cavity to achieve pleurodesis.[15]
3. Idiopathic nonimmune hydrops fetalis have been experimentally treated with intravenous digoxin and furosemide.[16,17] Digoxin at a dose of 0.25 mg orally twice a day has been used for the same.
4. Maternal toxoplasmosis—to prevent fetal transmission, Spiramycin is offered after fetal amniotic fluid polymerase chain reaction (PCR) testing rules out toxoplasmosis in serologically confirmed cases in the mother. If fetal testing shows affection, then sulfadiazine and pyrimethamine are initiated in the mother.[18]

Dosage:
If the infection has been acquired less than 18 weeks, oral Spiramycin is initiated at a dosage of 1 g (3 million units) every 8 hours (for a total of 3 g or 9 million units per day). Spiramycin should be continued till delivery even after amniotic fluid PCR is negative for Toxoplasmosis.
If infection has been acquired more than 18 weeks of gestation and/or those with positive amniotic fluid PCR test and/or those with abnormal ultrasound suggestive of congenital toxoplasmosis, pyrimethamine 50 mg every 12 hours for 2 days followed by 50 mg daily and sulfadiazine 75 mg/kg first dose followed by 50 mg/kg every 12 hours (maximum 4 g/day) with folinic acid 10 to 20 mg daily during and for 1 week after pyrimethamine therapy is recommended.

C. Maternal drug therapy with indirect fetal benefits

1. Tocolysis in preventing preterm birth
2. Penicillin to treat syphilis
3. Antibiotics before delivery to reduce neonatal sepsis
4. Prophylaxis against group B streptococcal infection prior to labor
5. Highly active antiretroviral therapy to prevent/reduce maternal-fetal HIV infection.

D. Drug administration for nontherapeutic benefits

1. For pain relief—Intramuscular fentanyl administration prior to invasive procedures.

Drugs:
Fentanyl (direct fetal intramuscular/intravenous (IM/IV)) 10–15 µg/kg
Remifentanil (direct fetal IV) 0.1–0.2 µg/kg/min

Fetal analgesia should be considered when performing invasive fetal procedures as a neurologic basis for nociception is present from 24 to 28 weeks' gestation and hormonal and circulatory stress responses have been reported from as early as 18 to 20 weeks.[19]

2. Neuromuscular blocking agent for achieving fetal quiescence prior to intrauterine transfusion and other fetal procedures.

Drugs:
Pancuronium (fetal IM/IV) 0.3 mg/kg (provides long-lasting paralysis; side effects such as a decrease in variability of fetal heart rate, fetal tachycardia and hypertension may occur)
Atracurium (fetal IM/IV) 0.4 mg/kg
Vecuronium (fetal IM/IV) 0.1 mg/kg
Both atracurium and vecuronium have short-lasting agents and fewer side effects compared with pancuronium.

E. Future directions in fetal drug therapy

1. Transplacental antiviral therapy to treat fetal cytomegalovirus infection
2. In utero stem cell therapy for hematological disorders
3. Gene therapy for conditions such as genetic abnormalities and fetal growth restriction

Conclusion

Fetal medical therapy is unequivocally a beneficial strategy. However, it carries potential risks for the mother and/or the fetus. Careful selection of the cases, discussion under the purview of an institutional review board or a multidisciplinary team, strict adherence to standard guidelines and recommendations, and performance by physicians with adequate expertise are therefore mandatory.

Informed Consent
Informed consent was obtained from all women.

Note
It is not an experimental research involving humans or animals.

Conflict of Interest
None declared.

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