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Antenatal Fetal Therapy

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ABSTRACT *Fetal medicine includes assessment of fetal well being , diagnosis and treatment of fetal abnormalities. It is a multidisciplinary branch involving a team of obstetrician, perinatologist, neonatologist or pediatric surgeon, obstetric sinologist and other superspecialists. The branch is still evolving due to problems that are unique to fetal medicine. Fetal therapy includes a series of interventions performed on the fetus aiming towards fetal well being. Certain antenatal fetal disorder in which medical management has got proven benefit includes- antenatal steroid administration in preterm neonates, folic acid supplementation for neural tube defects, triple drug regimen for pregnant women with HIV, Rh isoimmunisation e.t.c. whereas other disorders in which research is still ongoing includes inborn error of metabolism & endocrinal disorders . Surgical management of fetal disorder is particularly outstanding for management of posterior urethral valve, complications associated with twin pregnancy , congenital diaphragmatic hernia and is still evolving*

Fetal medicine includes the assessment of growth , well being, maintenance of fetal health & diagnosis of fetal abnormalities. With improvement in the field of prenatal diagnosisthe fetus is being recognized as an independent individual, and fetal medicine catering the problems of this "unborn patient."

Fetal therapy includes a series ofmedical or surgical interventions performed on the fetus aimingtowards fetal well being. . Perinatal medicine now a days considers the pregnant women & her fetus as two treatable individuals.

Fetal medicine is a multidisciplinary team consisting of the following:

- Obstetrician: Addressing the pregnancy & its complications and performing minimally invasive interventions
- Perinatologist: Addressing prenatal diagnosis, prognosis, genetic counseling.
- Pediatric surgeon/neonatologist: Addressing postnatal management of the diseased fetus & chalking out the treatment plan
- Sonologist: performing diagnosis, assessment of severity ,guiding/performing diagnostic & therapeutic procedures

Problems unique to fetal medicine are:
- Unclear team leadership
- Inadequate skills.
- Maternal beneficence versus fetal beneficence & autonomy
- Decision regarding treatment of viable & previable fetuses

MEDICAL TREATMENT OF FETAL DISORDERS:

1. Neural Tube Defects
- The best known & most extensively studied pharmacologic intervention in perinatology is of folic acid.
- It has been proven that it reduces the incidence of neural tube defects in women with one or more previously affected children as well as in those having no risk factors
- All women should be advised to take folic acid (0.4mg/d) from the time they become pregnant through the first 3 months of pregnancy & 4mg/d especially for women with a previously affected child, beginning at least 1 month prior to conception through 3 months of pregnancy (Rush et al.,1992).

2. Congenital Adrenal Hyperplasia
- Diagnostic test is elevated 17-OHP levels in amniotic fluid
- Current recommendation is to initiate dexamethasone therapy (20mg/kg in 2 or 3 divided doses) (Mercado et al.,1995)
- Therapy should be started as soon as pregnancy is confirmed & no later than 9 wk after the last menstrual period & continued upto term to prevent virilisation
- If the fetus is determined to be a male upon karyotype or an unaffected female upon DNA analysis , treatment is discontinued (New et al., 1989)

3. Thyrotoxicosis
- Fetal thyrotoxicosis is usually seen in infants of mothers with Grave disease or autoimmune thyroiditis.
- Maternal treatment with propylthiouracil (initial dose 300mg/d) to normalize fetal TSH, maternal DIT levels& ultrasound monitoring of fetal thyroid size is recommended (Polak,1998)

4. Hypothyroidism
- Fetal hypothyroidism is linked to maternal hyperthyroidism, use of radioactive iodine, drugs & excessive maternal iodine intake
- Fetal status is usually determined by direct cordocentesis/ amniocentesis & ultrasonography of the gland
- Intra- amniotic instillation of L- thyroxine (250µg every week initiated at 35 week of gestation) causes regression of fetal goiters & normalization of hormone levels (Aslam et al.,2008, Kim et al.,1991).

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5. Methyl malonic acidemia

- Caused due to deficiency of methylmalonyl CoA mutase or its coenzyme adenosylcobalamin.
- Prenatally cyanocobalamin administered empirically orally to the mother at a dose titrated to achieve high maternal plasma B12 levels & normal maternal urinary methylmalonic acid excretion usually is recommended (Evans et al., 1997).

6. Antenatal steroids

- Antenatal steroids has been shown to reduce the risk of RDS, IVH, NEC & death by 55%, 45%, 40% & 35% respectively
- European guidelines on management of RDS recommends a single course of prenatal corticosteroids to all women at risk of preterm delivery from about 23 weeks up to 34 completed weeks' gestation (Sweet et al.,2013).
- A second course of antenatal steroids may be appropriate if the first course was administered more than 2–3 weeks earlier and the baby is <33 weeks' gestation when another obstetric indication arises

8. Maternal HIV infection

- Risk of vertical transmission of infection from HIV- infected pregnant women to her fetus decreases from 20-45% to <5% with the use of triple ART regimen
- Triple ART regimen consists of Tenofovir+Lamivudine+Efavirenz started as early as possible in pregnant mothers (National AIDS Control Organisation [NACO], 2013).

9. Rh isoimmunisation: Occurs if a women who is RhD negative & is exposed to erythrocytes that are RhD positive leading to generation of anti RhD antibody. Antenatal fetal therapy of this condition is both challenging as well as difficult (presented in Table 1 at the end)

SURGICAL INTERVENTIONS FOR THE FETAL DISORDERS

Open fetal surgery is usually possible after 18 weeks of gestation due to size and fragility of fetus, and can be done for up to approximately 30 weeks of gestation due to increased risk of premature labor and, the preferability of performing the surgery ex utero instead. Adequate tocolysis should be achieved before the procedure

Approaches that are currently used for invasive fetal therapy are:

1. Ultrasound- guided vesicoamniotic and, less commonly thoracoamniotic shunt placement, from 16 weeks of gestation till when lung matures optimising postnatal treatment .
2. Fetoscopic techniques: clinical applicable during the ligation of umbilical cords in acardiac twins, selective laser photocoagulation of communicating vessels in twin- to-twin transfusion

1. Obstructive Uropathy

Fetuses with severe obstruction , bilateral hydroureteronephrosis & oligohydramnios should be evaluated for fetal therapy. Fetal interventions may lead to prolongation of gestation to term, but the sequelae of the lesion on renal function may not be preventable (Pereira et al., 2004; Holmes et al.,2001).

- Prior to intervention a cordocentesis should be performed to document a normal karyotype & exclude other major fetal anomalies
- Serial aspiration of urine from bladder under ultrasound guidance, can help in the diagnosis of progressive renal damage especially, <20 weeks of gestation.
- Vesicoamniotic shunt is usually preferred in persistent megacystis along with adequate renal function .However, shunt failure has been reported to occur in 40-50% of cases (Freeman et al., 1997).
- Fetoscopic technique includes, fulgration of posterior urethral valves, placement of shunt &vesicostomy.
- Open surgery has a high mortality rate (45%).

2. Myelomeningocele

Fetal surgical procedure, both open & endoscopic, have been performed to repair myelomeningocele in utero.

- Open surgical procedure is performed at 20-30 wk of gestation &reduces both hindbrain herniation as well as postnatal requirement of shunt placement for hydrocephalus (Johnson et al.,2003; Bruner et al.,2004).
- Kohl & colleagues reported fetoscopic closure of the defect using a Gore-Tex patch

3. Twin- to- Twin transfusion syndrome

- Treatment modalities includes selective fetoscopic laser treatment vs amnioreduction
- In a Cochrane review of TTTS comparing selective fetoscopic laser treatment vs amnioreductionhave shown that selective fetoscopic laser treatmentis preferred over amnioreduction when available (Rossi et al.,2008).

4. Twin Reversed Arterial Perfusion Sequence

- Complicates 1% of monochorionic pregnancy
- Fetal treatment modalities includes umbilical cord ligation in the acardiac twin or a nonviable twin after 21 weeks gestation (McCurdy et al.,1993; Challis et al.,1999).
- Selective laser photocoagulation of the cord circulation,can be performed prior to 21 weeks

5. Amniotic band syndrome

Fetoscopic laser release of amniotic band particularly in cases having a high risk of in utero limb amputation. The procedure is life saving in cases with umbilical cord involvement (Cromleholme et al., 2011).

6. Fetal Hydrothorax

Spontaneous resolution can be seen in 10 % of cases. Various modalities of treatment includes:

- Repeated thoracocentesis: May lead to complete resolution or good outcome despite reaccumulation or may lead to rapid reaccumulation of the effusion & death from respiratory insufficiency (Benacerraf et al.,1986).
- Thoracoamniotic shunt: Indications are not well defined and is done for effusions under tension that recurs after two thoracocenteses& fetal hydrops (Nicolaides et al.,1990).

7. Congenital Diaphragmatic Hernia

Is an anatomic defect in the diaphragm, but in extreme cases may result in profound lung hypoplasia precluding survival (Harrison et al.,1981).The survival using an open fetal surgical approach, was disappointing ,with fetoscopic tracheal occlusion being developed for avoiding preterm labour & complications from tocolysis .Antenatal management of congenital diaphragmatic hernia is challenging & should be approached in a systematic manner (as presented in table 2 at the end)(Flake et al.,2000)

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CONCLUSION

The evolving concept of fetal therapy holds promise not only to change the prenatal history of unborn fetus but also its long term outcome. However, it should not mislead the research for establishing fetal therapy as the standard treatment for any condition. It should develop as an integrated approach by multiple disciplines far beyond the narrow sphere of antenatal fetal therapy. With improved understanding of pathophysiology & molecular aspects of various perinatal disorders the field of fetal therapy will continue to expand & will provide newer & better therapeutic options .

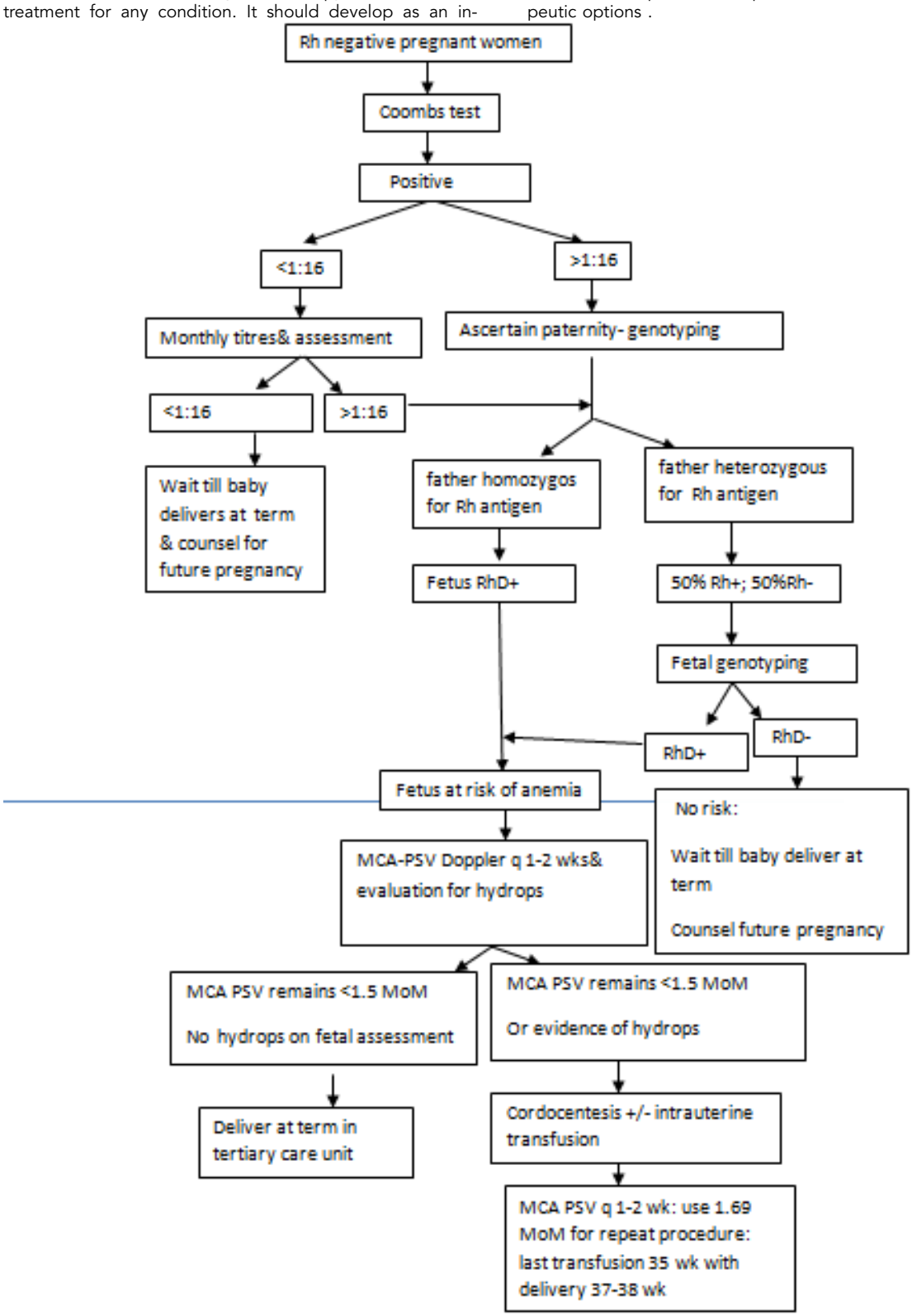

Table 1. Algorithm for antenatal management of RhD- sensitized pregnancy.MCA, middle cerebral artery PSV, peak systolic velocity IUT, intrauterine transfusion MoM, multiples of the median

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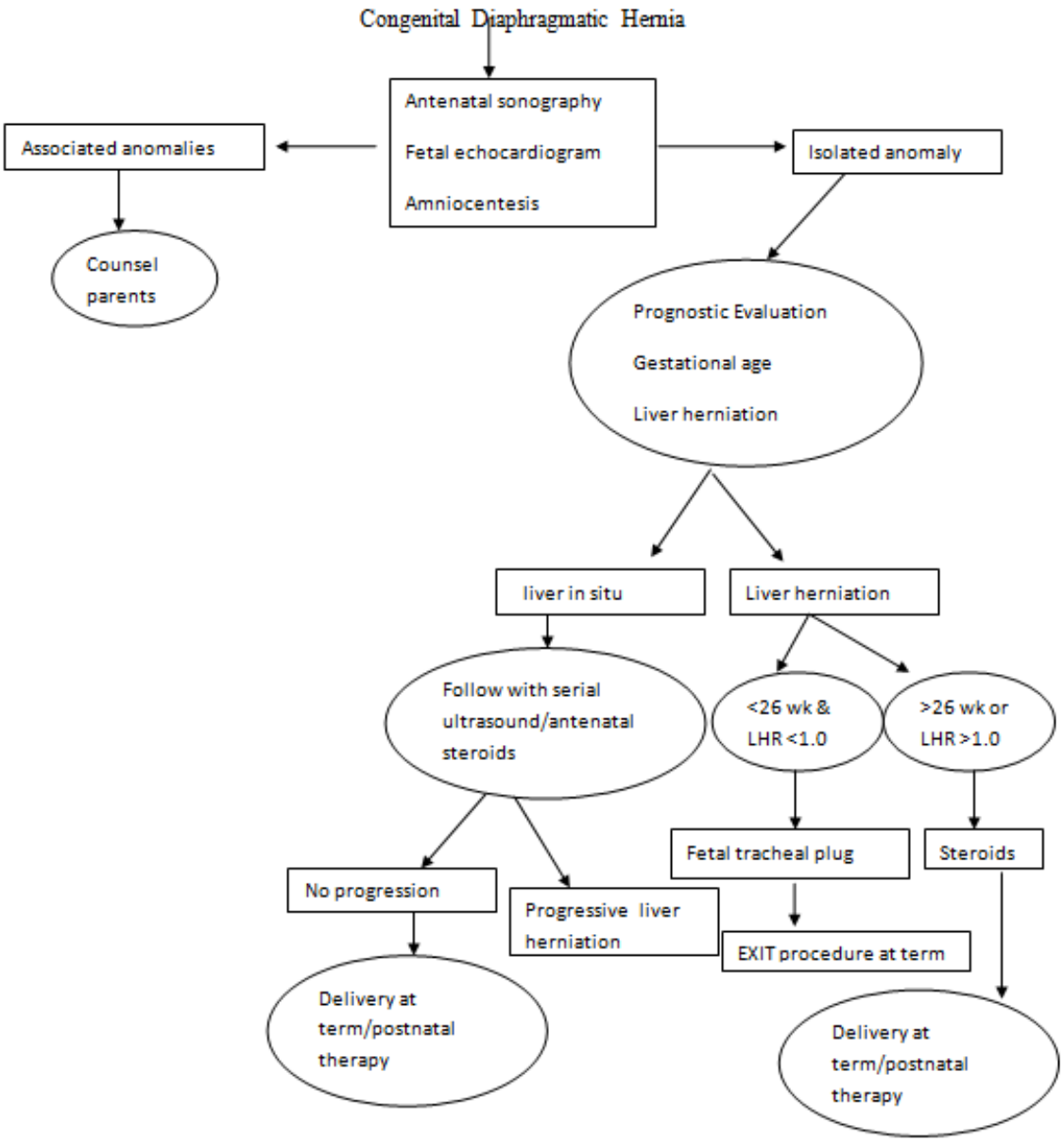

Table 2. Algorithm for antenatal management of congenital diaphragmatic hernia. LHR,lung head ratio EXIT, Ex utero intrapartum treatment

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