Bangladesh J Obstet Gynaecol, 2013; Vol. 28(2) : 92-99

Review Article

Prenatal Management of Compromised Fetus

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Abstract:

Compromised fetuses are those who are at increased risk in intrauterine life due to various factor resulting in increased mortality & morbidity. Fetal compromise in pregnancy is difficult to assess. Diagnostic skills for fetal diseases have improved enormously, but therapeutic approaches remains limited. "The Fetus should be considered as a separate individual and fetal medicine now needs to move into phase of evidence based management. Due to relative rarity of fetal disorder, a multicentre study is needed and this is the challenge for the next decade of fetal medicine.

Keywords: *Compromised fetus, Antenatal surveillance, fetal medicine.*

Introduction:

Fetal tachycardia,Reduced baseline variability, Complicated variable decelerations, Late decelerations, Prolonged decelerations may be associated with fetal Compromse and require

further action. The features very likely to be associated with significant fetal compromise and require immediate management, which may include urgent birth are prolonged bradycardia(< 100bpm for > 5 minutes), absent baseline variability, sinusoidal pattern,complicated variable decelerations with reduced baseline variability, late decelerations with reduced variability. There is no research evidence evaluating the benefits or risks associated with the short term use of maternal facial oxygen therapy in cases of suspected fetal compromise[1]. Fetal compromise in pregnancy is difficult to assess. Many cases have no obvious cause and management has to be aimed at determining the optimum time of delivery.

Antenatal Surveillance of at risk fetuses has become the standard of care for high risk obstetrical population.

Fetal compromisation in intrauterine life is due to maternal, fetal, placental and idiopathic causes. Diagnostic skills with fetal disease have improved enormously, but therapeutic approaches remain limited. Peri-conceptional folate, maternal steroids and fetal blood transfusion are the best examples of preventive, transplacental and invasive treatment developed for more than a decade. Most significant advance in recognition of fetus as a separate individual having their own right[2].

It is also evident that fetal outcome is better in at risk fetus than to low risk one because of increased materno-fetal surveillance. Antepartum unexplained fetal death is by far the commonest cause of death after 20 wks of gestation comprising nearly 40% of deaths in this period[3]. So the main challenge in pregnancy care is to improve fetal surveillance in low risk pregnancies in order to identify the potentially compromised fetus. The emphasis in fetal care is now no longer exclusively on survival but on the quality of that survival[4].

Compromisation in pregnancy are due to genetic, chromosomal & congenital anomaly of fetus, maternal diseases, drugs, infection, endocrine, immunologic & idiopathic causes. In late pregnancy uteroplacental dysfunction (maternal disease, placental factor), fetal anomaly (chromosomal / structural), Congenital infection, Rh- isoimmunization, multiple gestation, postdated pregnancy and premature rupture of membrane(PROM) are the important factors.

All these factor may results in abortion, premature delivery, intrauterine growth restriction (IUGR), intrauterine death (IUD) and birth asphyxia.

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Aim of early detection of at risk fetus is to reduce the incidence of perinatal morbidity & mortality, as 25-75% risk condition are amenable to prenatal modification prior to irreversible damage[4]. Ideally assessment of fetal wellbeing should start before onset of fetal compromise. Optimal time to initiate testing depends on-risk factor & previous obstetric history. Initiate testing at early gestation in pregnancy with multiple risk factor is recommended. Common high risk maternal condition demanding fetal surveillance are hypertension, diabetes, iso-immunization, chronic renal disease, SLE, congestive heart disease, haemoglobinopathies & hyperthyroidism.

Methods of fetal surveillance-

Prenatal testing includes screening and diagnostic tests, which are performed at different stages of gestation and have different risk-benefit profiles.

Screening tests should be safe and minimally invasive, performed in ,low-risk populations to detect conditions in which a timely intervention can alter outcomes. Diagnostic tests are required to confirm a positive screening result.

Prenatal screening tests are for various fetal metabolic, chromosomal, and anatomic defects. Until recently, pregnant women older than 35 were counseled to proceed directly to diagnostic tests rather than to undergo screening tests first because of elevated risk.

The American College of Obstetricians and Gynecologists (ACOG) in 2007 issued prenatal testing recommendations that include offering screening tests to all pregnant women, regardless of age.

A. Prenatal Screening Test

B. First-trimester screening test –Beta human chorionic gonadotropin (â-hCG): Lower value may indicate ectopic pregnancy or threatened abortion

- Pregnancy-associated plasma protein-A (PAPP-A): measured in maternal blood at 11-13 weeks of gestation. Combined with b-hCG (decreased PAPP-A levels and increased b-hCG levels) and ultrasonography for nuchal translucency, more than 80% of trisomy 18 and 21 can be detected.

Second-trimester screening tests-

- Maternal serum alpha-fetoprotein (MSAFP)
- Serum â-hCG
- Unconjugated estriol (uE3)
- Inhibin A
- Maternal hexosaminidase test
- Fetal cells in maternal circulation

The triple screen includes maternal serum AFP (MSAFP), serum â-hCG, and unconjugated estriol (uE3); the addition of inhibin A results in the quadruple screen. The panel findings, along with gestational age, can suggest a number of fetal abnormalities, depending on the results pattern. Maternal weight, race, and multiple pregnancies may affect the risk calculation.

According to ACOG, quadruple screening detect 67% of trisomy 18, 80% of trisomy 21, and 80%-85% of neural tube defects (NTD) and/or abdominal wall defects. The addition of the first trimester PAPP-A and nuchal translucency tests increases detection rates of trisomy 18 to 79% and trisomy 21 to 85%. However, these additions do not improve detection rates for the other conditions[5].

B. Prenatal diagnostic tests

Prenatal diagnosis of fetal disorders and structural malformations is becoming increasingly important for several reasons. Approximately 3% of all pregnancies result in the delivery of a baby with a genetic disorder or birth defect. Minor malformations are found in an additional 7%-8% of neonates.

Diagnostic tests are indicated when the risk of chromosomal anomaly are present or suspected (eg, advanced maternal age, suggestive fetal ultrasonographic findings). Genetic counseling by trained professionals in a timely and sensitive fashion is an essential adjunct to prenatal diagnosis.

First-trimester diagnostic test-

- Fetal ultrasonography-

Fetal ultrasonography in the first trimester is the most reliablemethod of dating a pregnancy, reliably diagnose anatomic abnormalities such as NTDs and abdominal wall defects, congenital diaphragmatic hernia, limb abnormalities, and cardiac defects, screening for nuchal lucency in conjunction with PAPP-A measurements to diagnose trisomy 21[6,7,8].

- Chorionic villus sampling-

Prenatal diagnosis prior to 12 weeks' gestation for detection of a chromosomal anomaly, DNA molecular diagnosis of classic genetic disorders, detection of defects in lysosomal enzymes or mucopoly-saccharidoses and. 21-hydroxylase deficiency causing

congenital adrenal hyperplasia [9,10]. Preimplantation biopsy: in a fetus of parents with substantial risk of a known genetic disorder and in women with repeated miscarriages due to chromosomal translocation[9,10,11,12].

- Early amniocentesis
- Coelocentesis:

Second-trimester diagnostic test-

- Midtrimester amniocentesis
- Percutaneous umbilical blood sampling or cordocentesis
- Late chorionic villus sampling
- Fetal muscle and liver biopsy

Fetal well-being in the third trimester-

- Amniocentesis
- Nonstress test (NST)
- Biophysical profile test: NST with assessment of amniotic fluid volume (AFV), fetal breathing movements, fetal activity, and fetal muscle tone
- Contraction stress test
- Doppler velocimetry: fetal umbilical arterial blood flow velocity or resistance to flow
- Modified biophysical profile(MBBP)
- Fetal kick count

Fetal kick count, non stress test & modified biophysical profile are the screening test.

BPP & CST is a back up test in case of abnormal MBPP. Doppler velocimetry is complementary to BPP.

Antepartum monitoring of fetal heart rate is the most widely used method for fetal assessment in late pregnancy which is a poor predictor of fetal health and is associated with a threefold increase in perinatal death[13]. Assessment of high risk pregnancies by umbilical artery Doppler ultrasonography approximately half the perinatal death rate[7].

Radiologic studies-

Magnetic resonance imaging (MRI): Important adjunct to ultrasonography[5].

Computed tomography (CT) scanning: Limited applications in prenatal diagnosis

Fetal magnetocardiography: Prenatal detection of a prolonged QT interval or Wolff-Parkinson-White syndrome Indications for Diagnostic Tests-

Conditions that increase the risk of chromosomal anomaly include the following:

- Advanced maternal age (>35 y)
- Previous offspring with chromosomal anomalies or birth defects
- Parental balanced translocation, inversion (manifests as recurrent

  pregnancy loss)
- Suggestive fetal ultrasonographic findings
- Positive maternal screening test findings
- Mother having a disease or exposed to drugs, medications, or infections
- Mendelian genetic trait in the parents
- Molecular DNA diagnosis (cystic fibrosis, fragile X)
- Enzymatic activities in villi, amniocytes, or both

Treatments for fetal disorders-

Fetal medicine is a complex undertaking that involves a multidisciplinary team for prenatal diagnosis and fetal therapy. Several issues, including ethical and legal considerations, are particular to fetal medicine; fetal treatment centers may provide solutions to many of these. A multidisciplinary team in fetal medicine generally consists of the following members:

- obstetrician
- maternal-fetal medicine specialist
- geneticist or genetic counselor
- neonatologist
- pediatric surgeon
- obstetric sonologist
- Relevant pediatric subspecialists (eg, cardiologists, cardiothoracic surgeons, neurosurgeons, urologists)

Ethically, the fetus as an individual is thought of in different, the lack of legal clarity further confounds decision making. Important facts are :

- Maternal beneficence and autonomy versus fetal beneficence and autonomy
- Vagaries of the legal status of the fetus as an individual.
- Identifying viable and previable fetuses as candidates for treatment

Fetal disorders that require treatment are-

- Neural tube defects
- Congenital adrenal hyperplasia
- Thyrotoxicosis
- Hypothyroidism
- Methylmalonic acidemia
- Multiple carboxylase deficiency
- Lung prematurity
- Maternal human immunodeficiency virus (HIV) infection
- Immune hydrops
- Fetal thrombocytopenia
- Fetal hemoglobinopathies, immune deficiency diseases, inborn errors of metabolism
- Congenital heart disease
- Certain fetal arrhythmias (eg, sustained supraventricular extrasystoles, atrial flutter), supraventricular tachycardias, and congenital complete heart block

In-utero treatment-

Fetal anaemia and Immune hydrops-

Causes of fetal anaemia are Rh isoimmunization, ABO incompatibility, Fetal infection, haematological disorder. There is hepatosplenomegaly, dilated portal vein, polyhydramnios, placentomegaly, increase flow in portal vein & ductus venosus diagnosed by USG.

Screening for maternal antibody titer, fetal monitoring by serial ultrasound and Doppler assessment of the velocity of blood flow in the middle cerebral artery starting at 16-18 weeks' gestation and repeated every 1-2 weeks until 35 weeks' gestation of at risk fetuses is needed

Serial amniocentesis (10 day to 2 week intervals) with measurement of bilirubin, beginning at 18 weeks, and determine when the result is abnormal from the Queenan and Liley charts.

Serial cordocentesis is indicated for severely affected fetuses for direct measurement of hematocrit (Hct), reticulocyte count, and bilirubin.

Intrauterine transfusions can be performed as indicated based on the results of the diagnostic tests. Direct intravascular transfusions through umbilical vein puncture or a combination of intraperitoneal and intravascular transfusions can be used.

Congenital adrenal hyperplasia

Since the differentiation of external genitalia begins at 7 weeks' gestation, the mothers of all fetuses at risk (those with a previously affected child) are given dexamethasone (0.25 mg PO qid) at 7-9 weeks.

Thyrotoxicosis

Fetal thyrotoxicosis is usually seen in infants of mothers with Grave disease or autoimmune thyroiditis. The diagnosis is made with cordocentesis.

Maternal treatment with propylthiouracil (initial dose 300 mg/d PO, then titrate according to effect) or methimazole is associated with a good fetal outcome.

Hypothyroidism

Fetal hypothyroidism is linked to maternal hyperthyroidism, use of radioactive iodine, drugs, and excessive maternal iodine intake.

Fetal status is evaluated at ultrasonography and by direct cordocentesis.

Intra-amniotic L-thyroxine initiated at 34 wk of gestation has been shown to cause regression of fetal goiters and normalization of hormone levels.

Methylmalonic acidemia

Prenatal cyanocobalamin has been empirically administered orally to the mother at a dose titrated to achieve high maternal plasma B12 levels and normal maternal urinary methylmalonic acid excretion.

Multiple carboxylase deficiency

This disorder is caused by a deficiency of holocarboxylase synthetase

Maternal biotin supplementation may prevent neonatal complications.

Lung maturity induction

Maternal corticosteroid therapy, used to induce lung maturity and surfactant synthesis in the fetus, has been proven effective in significantly reducing respiratory distress syndrome (RDS) in the neonatal period. Controlled studies have shown a reduction from 20.2% to 11.2%. Betamethasone (12 mg IM 24h for 2 doses) or dexamethasone (6 mg IM q12h for 4 doses) is recommended for fetuses at less than 34 weeks' gestation. In 2009 a multicenter, randomized, placebo-controlled trial had shown that the benefit of a single

rescue course of steroids given prior to 33 weeks' gestation outweighs the fetal/neonatal risks.

Maternal HIV infection:

Maternal administration of zidovudine (AZT), started at 14 weeks' gestation, continued throughout pregnancy, and given intravenously during labor, followed by treatment of the neonate for the first 6 weeks, has been documented to decrease the rate of vertical transmission from 25% to 8%.

Fetal thrombocytopenia-

Maternal thrombocytopenia has many causes, many of which do not place the fetus at risk of bleeding.

Fetal hematopoietic stem cell transplantation

Hematopoietic stem cell (HSC) transplantation in utero is an attractive theoretical option for the treatment of congenital disease that can be diagnosed antenatally and improved by engraftment of HSCs.

Diseases theoretically amenable to HSC transplantation are hemoglobinopathies such as sickle cell disease and thalassemias, immune deficiency diseases, and inborn errors of metabolism.

Congenital heart disease

The precise diagnosis of congenital heart lesions with the aid of newer echocardiographic techniques has created the potential for prenatal surgery or interventional catheterization.

Fetal arrhythmias

Most fetal arrhythmias are benign, and 90% are atrial extrasystoles.

Supraventricular tachycardias

These must be treated if they are sustained and associated with hydrops or upon evidence of left atrial preexcitation and a small foramen ovale.

Digoxin is the first-line drug. Propranolol, procainamide, and quinidine have also been used.

Congenital complete heart block

This is associated with major congenital heart disease in approximately 50% of cases.

Diagnoses have included left atrial isomerism, physiologically corrected transposition, atrioventricular canal defects, and ventricular septal defects. This group has a high incidence of congestive heart failure or cyanosis and requires postnatal permanent pacemakers.

Fetal anomaly

Major structural anomaly occur in 2-3% of all pregnancies. It contributes about 20-30% of perinatal morbidity & mortality. Advance in ultrasound technology have contributed greatly in improvement of fetal outcome by diagnosing and evaluation of fetal anomaly at appropriate time.

Following are options for fetal therapy to manage various fetal malformations:

- Termination of the pregnancy
- Elective cesarean delivery
- Preterm delivery
- Prenatal medical treatment
- Prenatal invasive fetal surgery

There is change in overall approach in managing pregnancy with fetal anomaly. The emphasis is no longer on termination but on rapid karyotyping and tertiary referral to fetal medicine centers for intrauterine fetal management. Golden period for anomaly scan is 20-24 wks of gestation. Methodical supervision of all fetal organs by TIFFA (Targeted imaging for fetal anomaly) is indicated at risk condition. In high risk condition TVS at 13-14 wks for early anomaly scan is recommended by some authorities at present.

High risk situations for fetal anomaly screen are increased maternal age, diabetes, consanguinity, drug history, x-ray exposure, history of previous fetal anomaly. Other factors are clinical / laboratory findings of small or large for date pregnancy & screen positive triple test. USG prompter for anomaly scan are abnormal liquor, single umbilical artery & minor aneuploidy marker (eg.echogenic bowel). Benefit of anomaly scan is to reassure the parent and counsel for termination in lethal anomaly, need for additional test and therapeutic procedure in non-lethal anomaly. Drawback of anomaly scan is that all anomaly not recognizable sonologicaly and minor marker may unstable the couple (eg.,Choroid cyst) & operator expertise directly interfere interpretation.

Intrauterine growth restriction (IUGR)-

IUGR refers to a condition in which the fetus is unable to achieve its genetically determined potential size. The clinicians challenge is to identify IUGR fetuses whose health is endangered in utero because of hostile intrauterine environment and to monitor & intervene appropriately. It also includes identifying small but

healthy fetus in order to avoid iatrogenic harm to them or their mother. Early onset IUGR associated with aneuploidy, structural anomaly, congenital infection. While late onset IUGR are associated with severe uteroplacental dysfunction detected after 32 wks.of gestation. Diagnosis of IUGR by history, clinical examination & appropriate investigations (serial USG, Doppler velocimetry).Treatment of IUGR includes rest, avoid stress, smoking, alcohol, drug abuse and low dose aspirin.

Recommendations of 26th RCOG Study Group for fetal surveillance are[14,15]:

1. Smoking cessation programme is effective in increasing mean birth weight (Type I evidence).
2. Nutrient therapy by dietary interventions and supplementation in suspected fetal growth impairment is not effective. (Type I evidence).
3. Fetal movement count in at risk cases may be better practice, but RCT provided no evidence of reduction in intrauterine death (Type I evidence)
4. Routine screening by repeated BPP or Doppler is not effective (Type I evidence).
5. Selective ultrasound is effective in identifying at risk pregnancies(Type I evidence).
6. Measurement of fundal height has quite good specificity and sensitivity in prediction of poor growth (Type IV evidence).
7. Doppler studies to monitor the high risk infant are effective to determine the optimum timing of delivery (Type I evidence).
8. Biophysical profiles are not effective to monitor the high risk infant in improving outcome (Type I evidence).
9. Hospitalization and bed rest for suspected fetal compromise are not effective (Type II evidence).
10. Maternal oxygen therapy should only be used in selective cases(Type I evidence)
11. External cardiotocography is effective in identifying deteriorating fetal condition in at risk preg. Its widespread use is not recommended because of difficult interpretation(Type I evidence).
12. Routine use of calcium channel blockers is not effective in pregnancy with impaired fetal growth (Type II evidence).
13. An accurate early ultrasonic dating of pregnancy is important to avoid unnecessary induction for suspected poor growth(Type V evidence)..
14. Plasma volume expansion for impaired fetal growth is theoretically promising (Type V evidence).
15. Excessive alcohol consumption is associated with increased mortality and morbidity of fetus(Type V evidence)

Once IUGR has been detected, the management should depend on a surveillance plan that maximizes gestational age while minimizing the risk of neonatal morbidity & mortality.

Termination before 36 wks is indicated in evidence of fetal hypoxia, anhydramnios, repeated late deceleration, BPP score <6, fetal cardiovascular decompensation in Doppler study.

Multiple pregnancy-

Twin to twin transfusion syndrome (TTTS) & Twin reverse arterial perfusion (TRAP) are the rare but serious complication of twin pregnancy.

Treatment of Twin to twin transfusion syndrome by serial amnioreduction & laser coagulation of the communicating placental vessels is promising.

But published studies of both procedures are non randomized uncontrolled and need multicentre randomized controlled study for evaluation.

Selective embolization of umbilical cord of acardiac twin in Twin reverse arterial perfusion (TRAP) can be undertaken.

Oligohydramnios-

Oligohydramnios causes fetal anomaly (Pul. hypoplasia, abnormal facies, limb positional defect). Antepartum amnioinfusion prevent pulmonary hypoplasia and relieve cord compression. Intrapartum amnioinfusion dilute thick meconium , reduce the risk of meconium aspiration syndrome and lower the rate of caesarean section has been shown in meta-analysis of published randomized trials. Simple maternal hydration may also increase amniotic fluid volume.

Polyhydramnios-

Polyhydramnios causes preterm labour, maternal oedema, oliguria, dyspnea. In acute symptom (maternal distress) induction of labour at or after 37

wks & indomethacin, amnioreduction before 37wks. Associated congenital anomaly need termination of pregnancy.

Fetal surgery-

Fetal surgery (closed, open, or endoscopic) still be regarded in development phase. Closed surgical procedure for lower urinary tract obstruction and hydrothorax has been done in many centres but no randomized controlled trial is available. Open fetal surgery is associated with increased fetal mortality and maternal morbidity.

Surgical interventions in invasive fetal therapy:

Anesthesia- As new intrauterine surgical techniques have been developed, anesthesia for the procedures has also evolved. It is recommended that fetal analgesia and sedation should be considered for invasive procedures involving direct contact with the fetus after 23 wks of gestation. [7] The major objectives are to ensure maternal and fetal safety. Specific goals are the prevention of maternal hypoxia and hypotension, together with the maintenance of optimal uterine blood flow. Lower doses of epidural and spinal anesthetic agents are needed in pregnant women because of increased epidural pressure and a lower volume of cerebrospinal fluid in the vertebral space.

For surgeries involving direct fetal manipulation, intramuscular fentanyl and pancuronium (a muscle relaxant and vagolytic) administered to the fetus have been tried prior to hysterotomy under ultrasonographic guidance.

Monitoring During Surgery

The parameters monitored during and after surgery include the following:

- Myometrial contractions and intrauterine pressures
- Maternal blood pressure, ECG, and pulse oximetric and blood gas levels
- Fetal pulse oximetric measurement ,heart rate, blood gases and ECG
- Ultrasonographic findings in cases of fetoscopic surgery
- Fetal temperature

Surgical Interventions-

Three approaches are currently used for invasive fetal therapy-

- Ultrasonography-guided vesicoamniotic, thoracoamniotic shunt
- Fetoscopic techniques for ligation of umbilical cords in acardiac twins, selective Laser photocoagulation of communicating vessels in twin-to-twin transfusions, and ablation of posterior urethral valves
- Open fetal surgery

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The surgical inventions are considered appropriate for the following lesions:

- Obstructive uropathy
- Hydrocephalus
- Pleural effusion
- Twin-to-twin transfusion syndrome
- Amniotic band syndrome
- Congenital diaphragmatic hernia
- Congenital high airway obstruction syndrome
- Sacrococcygeal teratoma
- Congenital cystic adenomatoid malformations

Conclusions:

Antenatal surveillance of at risk fetuses has become the standard of care for high risk obstetrical population. Fetal kick count , non stress test & modified biophysical profile are the screening test and BPP & CST is a back up test. In case of abnormal MBPP, Doppler velocimetry is complementary to BPP. Fetal medicine now needs to move into phase of evidence based management including randomized controlled trials. Due to relative rarity of fetal disorder a multicentre study is needed and this is the challenge for the next decade of fetal medicine.

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