KERALA FEDERATION OF OBSTETRICS & GYNECOLOGY

KFOG JOURNAL

Fetal medicine - what an obstetrician should know

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Content

President's *message*

Dr. Aswath kumar
KFOG President

Dear Colleagues and Friends,

Greetings from the Kerala Federation of Obstetrics and Gynaecology (KFOG)!

"The big secret in life is that there is no big secret. Whatever your goal, you can get there if you are willing to work" - Oprah Winfrey

It gives me immense pleasure to present to you the first edition of the KFOG journal for the year 2023. This journal is a platform for sharing our knowledge, experience and research in the field of obstetrics and gynaecology.

I would like to express my sincere gratitude to Dr. Parvathy Deth, the editor of the KFOG journal, for her commendable work in bringing out this edition. I also appreciate the efforts of the editorial board, reviewers, and authors for their valuable contributions.

I hope you will enjoy reading this edition of the KFOG journal and provide your feedback and suggestions for further improvement.

Thank you.

Dr. Aswath Kumar,
President, KFOG

Secretary's MESSAGE

Dr Venugopal
Secretary, KFOG

Dear Colleagues,

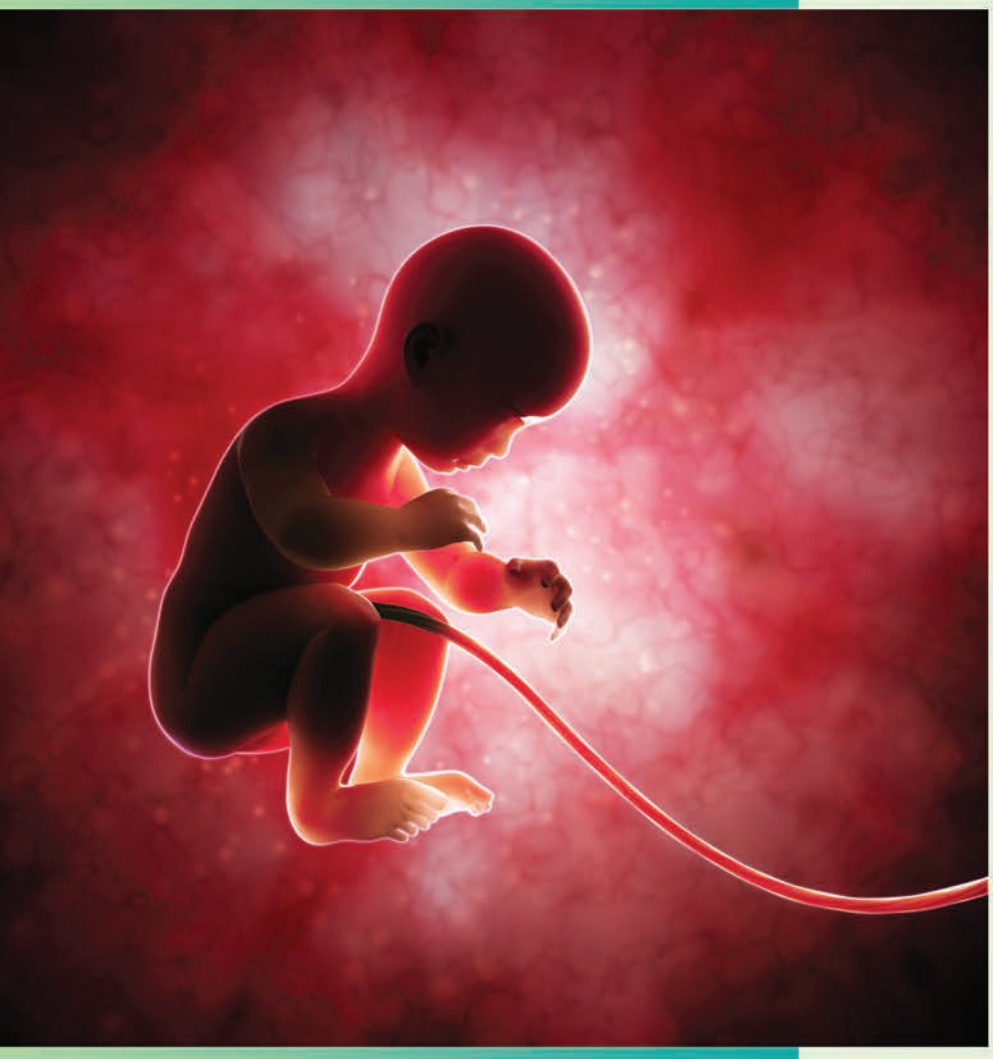
Greetings from KFOG. Hope all of you and family are doing well. Every new editor brings new energy new ideas and refreshing inputs into the KFOG JOURNAL.

Congratulations to Dr Parvathy on taking up the new assignment with great zeal and enthusiasm.

The theme of this journal focused on Fetal medicine is very relevant to day to day practice and I wish to congratulate each contributor for the enthusiasm and effort put into the articles.

I also wish to encourage members of KFOG to contribute in large numbers articles for the future editions of the journal.

After a hiatus there will be print version of the journal and I am sure it will be appreciated by many . Best wishes and happy reading.
Dr Venugopal



Editor's Note

After a long hiatus due to covid, KFOG is back with a printed version of Journal. Since its a new beginning, I thought of starting it in fetal stage- Fetal medicine from an obstetrician's perspective what all to know. Im immensely indebted to KFOG for believing me and handing over me this huge responsibility. My special thanks to Dr Aswath Kumar, Dr VenuGopal, and Dr Fessy Louis for being my three pillars of support. I would like to express my gratitude to each of the authors for sending me the articles with the best content, special thanks to Dr Pio James for coordinating it. Last but not least - CIMAR & FETAL LOUNGE, for making this a reality. I hope this journal will be an academic enlightenment for each one of you.

Dr. Parvathy Deth
Editor,
KFOG Journal

RELEVANCE OF GENETIC TESTING IN PREGNANCY

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For many decades, prenatal genetic testing was offered to pregnant women in certain specific situations. Traditional karyotyping was offered to women at increased risk for chromosomal abnormalities , based on aneuploidy screening using maternal age, serum marker testing, ultrasound or a combination of these. Chorionic villus sampling (CVS) with DNA analysis was offered to couples at high risk for a fetus with dominant or recessive genetic condition. Another situation is karyotyping after the diagnosis of fetal structural anomalies on ultrasound examination.

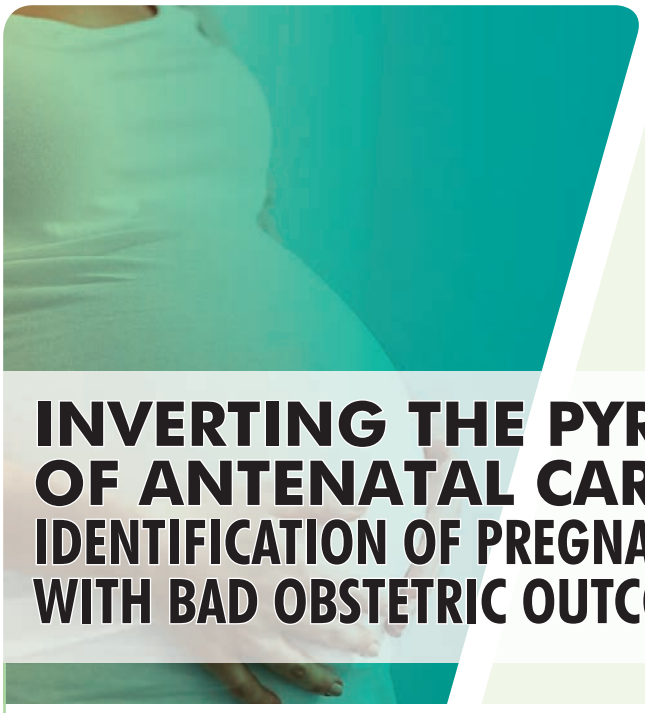
Nowadays prenatal diagnosis plays an essential role in obstetrical care, and with proper planning, it is a boon for obstetricians and prospective parents .Prenatal testing has become more sophisticated with improved level of resolution .

FISH and Qf PCR are targeted tests which detect aneuploidies of chromosomes 13,18 , 21 and sex chromosomes with a turnaround time of 2 – 3 days . Traditional Karyotype has been superceded by chromosomal microarray which identifies copy number variants . Karyotype may not identify chromosomal imbalances of < 10 Mb whereas Microarray can detect submicroscopic deletions and duplications (20-200 Kb). CMA identifies all abnormalities that Karyotype can offer , except for low level mosaicism and balanced translocations . However , the result has to be interpreted carefully since some copy number variants may be present in normal individuals also . Moreover diagnosis of monogenic or single gene disorders is beyond the scope of Karyotype and CMA .

These days, Next-generation sequencing has been used to identify causative genes in many Mendelian disorders. These include panel tests and Whole exome sequencing (WES). WES in prenatal testing has the potential to provide a more precise genetic diagnosis .However since the data is under validation for benefits / pitfalls , it is ideally not recommended for routine use for prenatal diagnosis .

Most forms of prenatal diagnosis require invasive procedures for fetal-sample collection and therefore, although considered safe, these procedures involve a small risk of fetal loss. The most widely used non invasive test or aneuploidy screening methods are combined first trimester screening and second trimester quadruple test .The introduction of cell-free fetal DNA has revolutionized prenatal diagnosis and fetal medicine. It can be offered as a primary first trimester screen , positive first trimester screen , presence of ultrasound markers of aneuploidy in second trimester and in cases of previous child with T21 with a detection rate of 99.7 % for T21 .However , a proper pretest and posttest counseling is necessary.

The birth of a child with intellectual disability or a genetic abnormality is traumatic to the family. Hence determining genetic diagnosis prenatally, helps us to counsel the family about possible fetal outcomes, management options and recurrence risks. Therefore, it is important for the obstetrician to be aware of the genetic conditions, and to use appropriate testing .Referrals to genetic healthcare providers may be done in order to obtain a specific diagnosis.



INVERTING THE PYRAMID OF ANTENATAL CARE- IDENTIFICATION OF PREGNANCIES WITH BAD OBSTETRIC OUTCOME

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Traditionally, , the third trimester has been considered the most important of all trimesters with recommendations that surveillance be more frequent and focussed on this trimester when most complications arise. The first trimester was deemed a period of helplessness. Then came a seminal paper in 2011 by Kypros Nicolaides in which he challenged this notion and proposed a radical different approach to antenatal care. He suggested that instead of waiting for complications to occur, a more proactive and pre-emptive attitude be adopted; that 11-14 week of pregnancy be used as a window of opportunity for screening and early diagnosis of major pregnancy complications.

This would entail using a multi-pronged approach (history, maternal characteristics, ultrasound, and laboratory investigations) to assess the risk status of every pregnancy and use that information to plan further antenatal care i.e., high risk pregnancies are directed towards specialist care while low risk pregnancies are followed up at less frequent intervals. As illustrated below, the late first trimester thus becomes the base of the pyramid upon which the rest of pregnancy care is built.

This concept was inspired by the success of first trimester ultrasound screening for fetal aneuploidy using nuchal translucency (NT) and the realisation that increased NT can be a marker for other fetal abnormalities. With time, more ammunition was added to the screening armamentarium. What seemed a dream in 2011 is more a reality now. Here's a look at what has worked and at what the future might hold.

First trimester estimation of gestational age

Determining the gestational age is one of the most early and vital steps in obstetric practice which influences almost every obstetric decision. Measurement of CRL in the first trimester yields the most accurate assessment of gestational age particularly when the CRL falls between 30 and 84 mm.

Screening for aneuploidies

Fetal aneuploidies, trisomy 21 in particular, are major contributors to perinatal morbidity/ mortality and long-term disability. First trimester combined screening incorporating maternal age and history, gestational age, NT measurement, PAPP-A and

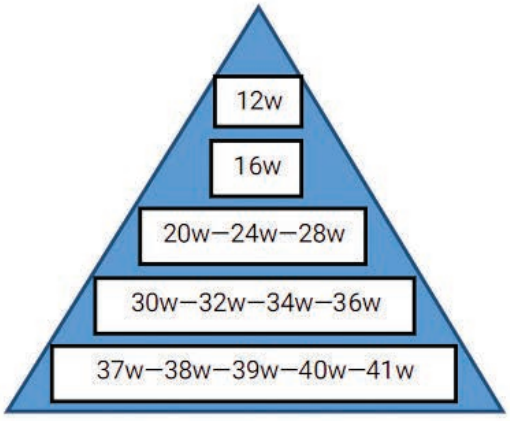

Fig 1: Traditional pyramid of prenatal

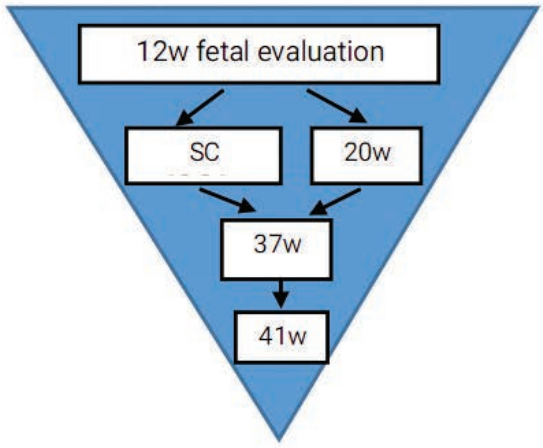

Fig 2: A possible new pyramid. SC-specialist

free beta-hCG has become the preferred screening modality worldwide due to its high detection rate (90% for trisomy 21, about 95% for trisomies 13 and 18), low false positive rate and cost-effectiveness. The performance can be improved further by adding on ultrasound markers like nasal bone, ductus venosus Doppler, tricuspid regurgitation and other serum markers like PLGF and AFP.

In the past decade, NIPT has emerged as a challenger to the combined test because it offers a higher detection rate (>99% for trisomy 21) for a much lower false positive rate (0.1%). The one significant argument against it being used for universal screening is the cost. Most centres prefer to use it in special situations like advanced maternal age or in the intermediate risk group (contingent screening). Many laboratories have also included screening for common microdeletions in their portfolio, but these haven't been validated satisfactorily.

It should be remembered that above mentioned tests are all screening tests; screen positive patients should undergo a diagnostic test like CVS or amniocentesis before concluding that the fetus is affected.

Screening for structural anomalies

The understanding that increased NT is also associated with structural defects (cardiac anomalies, CDH, omphalocele etc.) led to an attempt to diagnose fetal structural anomalies during the 11-14 weeks scan. Recent data suggest that the detection rate for fetal anomlies is around 50%. Higher detection rates can be achieved when transvaginal assessment was a part of the protocol.

Conditions like acrania, alobar holoprosencephaly, limb body wall complex can always be diagnosed at 11-14 weeks; other conditions like open neural tube defects can be diagnosed with careful scrutiny; others like agenesis of corpus callosum still evade detection at this period of gestation.

Early diagnosis of fetal aneuploidies/ anomalies provides the opportunity for early termination of pregnancy which is preferable to midtrimester termination.

Assessment of multiple gestations

Multi-order pregnancies are at increased risk for perinatal morbidity and mortality; this risk is most influenced by chorionicity. Monochorionic fetuses are at double the risk for perinatal mortality than their dichorionic counterparts. First trimester is the best time to determine the chorionicity based upon which, an appropriate plan to monitor and manage these pregnancies can be chalked out. In addition, large differences in the NT of two fetuses or discrepancy in DV flow patten could be early signs of TTTS and could serve as further tools to triage multi-order pregnancies.

Screening for preeclampsia and FGR

Recent years have seen a renewed interest in screening for conditions which arise out of abnormal placentation. First trimester presents a unique window of opportunity in this regard as any intervention to prevent preeclampsia or

FGR must be initiated before 16 weeks ie before the second wave of placentation is complete.

Screening based on maternal characteristics and history alone identifies <50 % of women at risk for preeclampsia which is unsatisfactorily. Throwing mean arterial pressure, mean uterine artery PI and serum PlGF into the mix predicts about 90% of early PE (<34 weeks), 75% of preterm PE (<37 weeks) and 45% of term PE (≥37 weeks), at screen positive rate of 10%.

Treatment with low-dose aspirin (150mg at bedtime) from 12- 36 weeks of gestation effectively reduced the incidence of preeclampsia before 37 weeks by 60%. With good compliance, reduction rates of 75% can be achieved.

Timely administration of low dose aspirin also reduces the incidence of FGR which translates into lower healthcare cost related to prematurity and neurodevelopmental disability.

Screening for preterm labour

Prematurity is the leading cause of neonatal deaths globally. As most spontaneous preterm births occur in women without history of previous preterm birth, screening based on history alone is not effective. Using a combination of cervical length measured vaginally and obstetric history increases the sensitivity of screening. This in turn provides an opportunity to prevent or delay preterm birth.

Natural progesterone given vaginally and cerclage are the two strategies currently proven to prevent preterm births. In asymptomatic women with a cervical length of <2.5mm, natural progesterone 200mg given vaginally reduces the risk of preterm birth before 34 weeks by 35-40%. In those with history of preterm birth, early elective cerclage may be planned if the 11-13 weeks scan demonstrates no major fetal abnormality. Alternatively, these patients may be placed on 2 weekly surveillance and cerclage may be placed when cervical length is <2.5 mm. Both strategies reduce the risk of preterm birth before 34 weeks by 25%. Serial cervical assessment starting at 14 weeks is also recommended in women with history of other risk factors like unicornuate or septate uterus. In twin gestations with cervical length of <2.5mm, vaginal progesterone may reduce the risk PTB at <34 weeks by up to 30%.

Other areas of interest

Screening for SGA without preeclampsia, gestational diabetes mellitus and fetal macrosomia have shown some promise and it is likely that algorithms and protocols will be available for the prediction of these conditions too in the near future.

To conclude, while there may be disagreements regarding the number of visits proposed by Nicolaides, there is no denying that the late first trimester gives us the opportunity to get many things right early on and provides a foundation upon which the right plan of management can be constructed. However, the uptake and implementation of above-mentioned screening programmes have been less than satisfactory, particularly in the peripheries. This may be due to ignorance from both the patients' and the doctors' side, non-availability of laboratory facilities, relatively expensive nature of the tests and social/religious factors. But whatever be the obstacles, we should strive to give our patients the best possible start on their obstetric journey. Well begun is half done.

SCREENING FOR DOWN SYNDROME - THE FACTS

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Introduction:

When we look at the prenatal prevalence of chromosomal abnormalities, approximately 75% is contributed by Trisomy 21/13/18 of which 50% is contributed by Trisomy 21 alone. 50% of Downs syndrome (DS) foetuses will look normal in ultrasound. They live a life expectancy of 45 to 50 years and survive with lots of medical morbidities like severe learning disability, congenital heart disease, endocrinological problems, leukaemia, Alzheimer's disease etc.

Test	Maternal serum markers	Ultrasound markers	Detection rate
1. First trimester Combined test (11 -14 weeks)	PAPPA fβHCG	NT Additional markers – NB,DV,TR	85% with 5% FPR
2. Second trimester Quadruple test (15 – 20) weeks	AFP βHCG Micronised Estriol Inhibin A	Nil	70 – 75% with 5% FPR
3. Non invasive pretanal test(NIPT) (After 11) weeks	Cell free Fetal DNA from maternal blood		99% with < 1% FPR
4. Genetic Sonogram		Strong markers NFT, ARSA, NB Ventriculomegaly	

Table: 1

- Triple Test has a very poor sensitivity. It is obsolete and should not be offered to the patient in the current scenario as Quadruple test with better sensitivity and similar cost is available in the second trimester
- Quadruple test is done after 15 weeks, preferably after 16 weeks or fetal BPD measures >33mm

The definitive diagnostic test to detect DS antenatally is by doing foetal Karyotype. This being an invasive procedure has inherent procedure related complication, which cannot be offered to all.

Hence the importance of screening tests. The challenge of an antenatal screening programme is, therefore, to identify women in whom a risk of DS is sufficiently high to justify such an invasive test and to minimise the risk of miscarrying a healthy baby.

1. Whom to screen?

Every woman who becomes pregnant is at a risk of delivering a DS baby. Though the risk of delivering a DS increases with maternal age, 85% of the babies with DS in the society are born to mothers who are less than 35 years of age.

Therefore, to reduce the prevalence of DS in the community, age should not be considered as a sole criteria to offer DS screening in pregnancy.

2. What are the screening tests available?

Aneuploidy screening test that are available andwidely accepted are shown in Table 1

First trimester combined screening: Maternal age related risk is considered as the background risk. On this background risk, ultrasound foetal markers and maternal serum markers are incorporated to obtain a probability

Fact:

First trimester combined test appears to be the best option to be offered at present as it includes both maternal and foetal markers, done in earlier gestational age, has a good sensitivity and comparatively cheaper. Though NIPT has a higher sensitivity, the cost is a limiting factor.

3. Is it mandatory for all pregnant mothers to undergo Downs Syndrome screening in pregnancy?

DS screening is an optional test that should be offered to all pregnant mothers where the resources are not constraint and if it is easily available. The couple can opt in or opt out from doing the test for many reasons of their own. However it is important that every mother should be offered DS screening in pregnancy.

4. What are the components in DS screening. The components are

A.Pre-test counselling: During a pre-test counselling, it is very important to explain to the patient and give adequate information regarding

(1) What is DS and its clinical significance

(2) Explain age related risk

(3) Explain the test - Scan + blood test

(4) Maternal factors that influence the test

(5) Gives probability only

(6) Explain false positives and false negatives

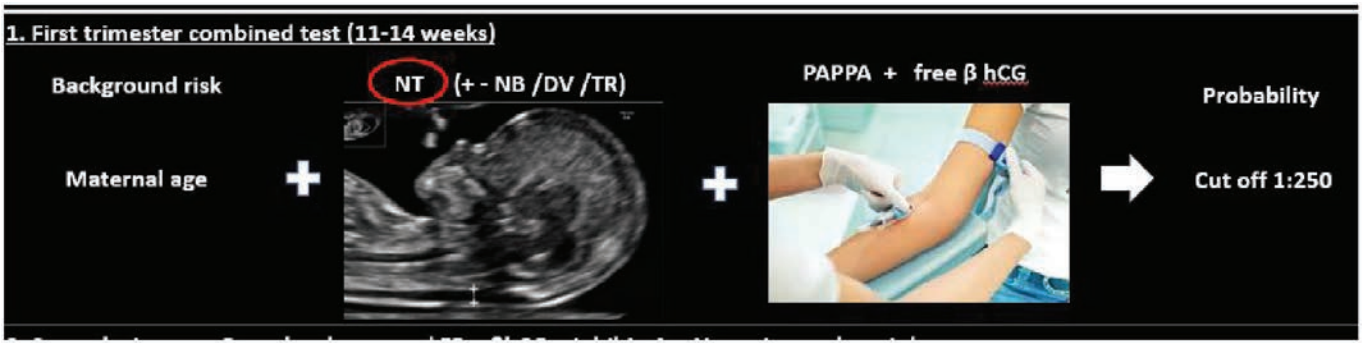
(7) Explain screen negatives

(8) Explain screen positives - Risk cut off 1:250

(9) If the screening test becomes positives, the definite diagnosis can be established only by Invasive testing – Chorionic villus sampling (11-14wks) or Amniocentesis (after 15 weeks). The procedure, complications, turn over time, cost of the invasive procedure should be explained.

Fact:

- Pre-test counselling is best done by the primary obstetrician seeing in the obstetric unit. On an average, it will take at least 10 -12 minutes for counselling each patients.
- In a busy OPD, alternative methods like group counselling by dedicated staff, video demonstration in the OPD or information pamphlets should be provided.



- Couple should be clearly explained that the test is done only for aneuploidy screening (especially DS) and it does not detect any other genetic, morphological or metabolic problems.

B. Collect maternal details

Once the couple opt to undergo screening, the following maternal details are collected from the mother and provided to the lab. 1. Race 2. Correct maternal DOB 3. Method of conception 4. Singleton/Twins 5. Smoking status 6. IDDM 7. H/o DS. 8 Maternal weight - BMI

Providing this information to the lab is the responsibility of the primary obstetrician. These factors can cause variations in the maternal serum analytes (PAPPA, f βHCG). Hence the above information has to be incorporated into the software, so that measurements are normalised for variation for accurate risk calculation.

C. Foetal and Ultrasound parameters:

The accuracy of a screening policy is highly dependant on the accurate measurements of Crown rump length (CRL) and Nuchal translucency (NT) done by a trained personnel with accreditation - trained sonographer/foetal medicine specialist. This is because, even a 5mm error in CRL can change the combined risk by 0.5 – 2.14 times. Inaccuracies in NT as small as 0.5mm will have very significant negative impact on detection rate (decrease18%). Screening should be done only in a structurally normal foetus. Screening should not be performed in a foetus with an NT measurement more than 3.5mm

D. Collect maternal blood for maternal serum markers – PAPPA and f βHCG

E .Accredited lab and quality assurance:

The maternal details, the fetal parameters (NT, CRL), maternal blood analytes normalised for maternal factors (PAPPA, f βHCG) – all the above information are fed on an analytical platform or an algorithm (which is accredited) and the risk is calculated. The lab should be such that it assure quality control, conduct regular audits and calculation of the medians. If there is a shift noted in the median, the lab has to recalculate and readjust the medians of each components periodically for the population to come to a LR.

5. What is the next step once the DS screening report is available

It takes 7 to 10 days to get the report depending upon the lab. The couple is informed to review with the report as soon as they receive it. Post-test counselling should be given. Screen negative pregnancies are reassured and followed up with target scan at 18-20 weeks. Screen positive patients are referred to a geneticist or a foetal medicine specialist for further counselling and confirmatory test ie Chorionic villus sampling (11-14weeks) or amniocentesis (after 16 weeks).

6. What are the common reasons couple opt out of DS screening OR whom are the couple the test is not done?

- Patients for religious or some other reasons, who do not accept termination
- Patients who are not willing for invasive test (confirmatory) even if risk come screen positive
- Couples who are ready to accept a DS baby
- Financial constraints and unavailability of the test nearby.

Summary

Screening for Down syndrome is an optional test that should be offered to all pregnant mothers after a pretest counselling. The couple need to be given an informed choice to opt in or opt out of the screening. Through every point of screening, the clinician is liable to answer their queries. Each and every component of screening is very sensitive for errors and hence accreditations, quality control and standards has to be assured in each level to get the accurate risk out of the screening test. So the obstetrician is liable to know the competency of the imageologist and the Laboratory to whom we send for screening. If not done under strict standards, it will do more harm than good for the patient and the attending clinician.

Screening should be done only in a structurally normal fetus. The best screening modality available is the first trimester combined aneuploidy screening (FTS). If we miss on FTS, second trimester Quadruple test should be offered. Triple test is obsolete and should not be offered as a screening modality. If the couple defer screening, it is very important to document it in the antenatal chart that, screening was offered but the couple deferred testing.

FIRST TRIMESTERS SCAN- A NECESSITY, NOT A FORMALITY

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First trimester scan is done during the 11 – 13+6 weeks period. For many of us, the 11-14 wks Scan is for measuring Nuchal Translucency (NT) and Aneuploidy screening. However it is is beyond that. If appropriately done, it can detect most of the major aneuploidies, major anomalies, and define patient specific risks for most complications.

At present, First trimester screening is considered one of the most integral part of fetal care, not only because of the earlier point of examination but also due to its diagnosing potential. In the current medical practice, no fetal care is complete without a good quality first trimester scan. This a strong statement, however the following aspects will help in justifying this.

Scope of First trimester scan

1. Crown rump length (CRL) – one of the basic measurements during the first trimester scan. Helps in accurate dating which is essential to identify growth disorders and prevent still births, perinatal morbidity, iatrogenic prematurity etc
2. Nuchal translucency (NT)– has evolved from marker for Down syndrome to being a marker for various conditions like other chromosomal abnormalities, genetic disorders, cardiac, pulmonary and skeletal disorders.
3. Multiple pregnancy – the most important factor for the management of multiple pregnancy is the chorionicity. Best time to do it is before 14 wks with a sensitivity of 100% and a specificity of 99.8%. If we assign chorionicity at the anomaly scan, we could go wrong in 14% of the cases. Labelling of twins is also extremely important in identifying them in subsequent follow ups, especially if the twins are discordant. Since the whole pregnancy management revolves around the chorionicity and labelling, it is essential to document it in writing and in the form of image for future references.
4. Screening for common aneuploidies during the first trimester period is well established and well accepted. The high sensitivity and specificity is majorly contributed by the ultrasound parameters like CRL, NT and NB and also biochemical markers like βhcg and PAPP A. The first trimester screening has a sensitivity of around 85 – 90% with a 5% false positive rate. The quality of the whole screening program depends on the quality of the first trimester scan.

5. Screening for structural abnormalities – First trimester scan should be able to detect anomalies like

   Always detectable anomalies: Anencephaly, Alobar holoprosencephaly, body stalk anomaly, exomphalos, gastroschisis, megacystis

   Potentially detectable anomalies: Posterior fossa defects, spina bifida, facial cleft, cardiac defects, renal defects, Limb defects.

   With modern ultrasound equipment and the improved expertise of sonologists, close to 65% of anomalies that used to be picked up only in the second trimester are now being increasingly picked up in the first trimester. It opens a whole lot of options for the parents like testing for chromosomal abnormalities, getting second opinions, prognosticating the abnormality and planning antenatal and postnatal care. All this can be done without worrying about the legal time limitations for termination in India due to the earlier diagnosis. The extra time can help expectant parents to come to terms regarding their child's condition and to reach an appropriate decision.

6. Screening for preeclampsia – Hypertensive disorders in pregnancy are the second biggest cause of maternal mortality in our state after hemorrhage, The detection rate for preeclampsia with maternal factors alone is very poor. Screening for preeclampsia with a combination of Mean uterine PI, maternal blood pressure, biomarkers (PAPPA and PLGF) has a sensitivity of 90% and 75% for the prediction of early and preterm preeclampsia, respectively, with a 10% false-positive rate. Any doubts about the usefulness of screening for pre-eclampsia were laid to rest when the ASPRE trial performance results were finally published. If screen positive, Aspirin prophylaxis started in the first trimester can help to delay the onset and risk reduction of this major comorbidity.

7. Screening for open neural tube defects – Intracranial translucency has helped shift the diagnoses of Open spina bifida from second trimester to first trimester.

Advantages of First trimester scan:

By doing a meticulous First trimester scan, every single antenatal woman can be stratified based on her specific risk for developing maternal or fetal complications. Accordingly, the great majority of antenatal women will be classified as low risk in whom the number of antenatal visits could be substantially reduced to as low as just two visits more for the rest of her pregnancy. The small proportion of high risk women can therefore receive better, specialised prenatal care.

Limitations:

First trimester scan relies heavily on ultrasound expertise of the operator right from getting a good CRL , a good NT, dedicated anatomical survey of the fetus to accurately measuring uterine artery. However it warrants adequate training and a learning curve for expertise. At present a dedicated first trimester scan is only available in very few centers in our state.

Conclusion:

The objective of a First trimester scan should not be only to confirm, localization, number, viability, and dating of pregnancy. However, its manifestations are many fold. In clinical practice, the obstetrician should know to whom we are sending for the first trimester scan. It should not be prescribed for a formality to be done by a random imageologist. Obstetricians should be aware of the expertise around to get the maximum benefit out of the first trimester scan. If there is no expertise around, the best way to overcome this is to get trained ourselves.

DOPPLER IN FETAL GROWTH RESTRICTION

Dr. Jyothi Mancheri
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Doppler studies of the various vessels have contributed enormously in the field of obstetrics. Fetal growth restriction (FGR) contributes to 40% of all intrauterine fetal demises and 25% of all perinatal morbidity. If we follow the standard definition of estimated fetal weight (EFW) less than 10 percentile as the criteria for FGR diagnosis, more than 2/3rd will be constitutionally small. Doppler studies of various vessels are used to improve the detection and management of pathologically growth restricted fetuses. Major vessels studied in relation to growth restriction are uterine artery, Umbilical artery (UA), Middle cerebral artery (MCA), aortic isthmus and ductus venosus (DV). Other parameters, which are widely studied but not part of the accepted guidelines as of now, are umbilical vein and cardiac function evaluation. Use of Doppler has shown 38% reduction in overall perinatal deaths (Neilson JP et al 2005)

Umbilical Artery :

Umbilical artery is the much-studied vessel in relation to FGR. For the diagnosis, prognosis and management of early onset FGR umbilical artery Doppler changes is the most widely used Doppler parameter.

When there is placental damage, umbilical artery Doppler shows a definite, chronological change. When the placental involvement is 30% or more, there will be increased resistance in the umbilical artery PI. When it is >50%, absent diastolic flow and >70% reversal in the end diastolic flow.

When there is placental dysfunction, there will be fetal hypoxia, leading on to compensatory changes in the foetus like preferential shunting of blood to brain, heart, adrenal and spleen. There will be decrease in blood flow to organs like kidneys, liver, muscle and bowel. It will manifest as decreased urine production and oligohydramnios, bowel ischemia, cerebral vasodilatation and low resistance in middle cerebral artery etc. In extremely preterm fetuses as the tolerance to hypoxia is high the compensatory changes and the changes in the umbilical artery will be seen in a chronological pattern.

In late onset FGR, this pattern is not seen as near term fetuses have minimal tolerance to hypoxia. Even before the placental damage is 30%, fetal compromise may happen. Hence we cannot rely on the umbilical artery Doppler changes alone to diagnose, prognosticate or manage late onset FGR.

Middle Cerebral Artery Doppler :

MCA Doppler is mainly used in the management

of late onset FGR. MCA vascular resistance is almost constant throughout pregnancy. Placental resistance drops with gestation hence Cerebro placental ratio (CPR), the ratio of PI of MCA to UA, increases with gestation. As previously mentioned, when there is fetal hypoxia, the preferential blood flow to the fetal brain is reflected as the low resistance in middle cerebral artery blood flow. This will be evident as low pulsatility index in MCA. When there is placental dysfunction, MCA PI will start dropping and the umbilical PI will start increasing. CPR will be abnormal even before the individual parameters are abnormal; hence it is a better predictor of fetal hypoxia. In general CPR of less than 1 is considered as abnormal. When hypoxia is severe, MCA PI tends to rise, which reflects development of brain edema. MCA Doppler is used in the Barcelona staging of FGR as well as in timing of delivery of fetuses with late onset FGR.

Uterine Artery :

Uterine artery blood flow indices have been used as a screening tool for FGR. Uterine artery pulsatility Index (PI) along with maternal blood pressure, Serum levels of PAPP-A, PLGF, and HCG will predict 52 % of the early onset FGR and 20% of late onset FGR. (FMF UK)

Mean Uterine PI of more than 2.35 in the first trimester and 1.44 in the 2nd trimester is roughly taken as cut off for categorizing patients in to high risk for FGR. Increased uterine PI along with SGA is most likely related to placental or uterine cause for FGR. 3rd trimester uterine artery Doppler resistance has been shown to be associated with abnormal CPR. Uterine artery Doppler PI is incorporated in the Barcelona staging protocol as one of the criteria for distinguishing SGA from FGR

Aortic Doppler:

This vessel reflects the balance between the impedance of the brain and systemic vascular systems. In hypoxic fetus due to redistribution of blood flow, there is increased vasoconstriction and peripheral resistance and rise in RI and PI values. In the presence of severe hypoxia, diastolic flow reverses. This has strong association with both adverse perinatal and neurological outcome. AoI precedes Ductus Venosus abnormalities by 1 week

Ductus venosus Doppler:

In early onset FGR the final stage of compensation is fetal academia. This will be reflected as the changes in the ductus venosus flow. This is part of the cardiac compromise and the final warning before fetal demise. In about 50% of cases, abnormal DV precedes absent STV in cCTG. In about 90% of cases DV flow is abnormal 48– 72 h before the biophysical profile is abnormal. Absent or reversed velocities during atrial contraction are associated with very high perinatal mortality Hence DV abnormality is used as the cut off for timing the delivery

Application of Doppler

Role of Doppler in diagnosing FGR- Delphi consensus

In order to distinguish between SGA and true FGR apart from severe

smallness and poor growth velocity, UA and MCA Doppler studies are included in Delphi consensus.

Role of Doppler in staging and management of FGR

As per the Barcelona protocol Doppler parameters

	Early onset FGR (<32 weeks)	Late onset FGR (After 32 weeks)
Solitary	3 solitary parameters AC/ EFW < 3rd centile, Umbilical AREDV	2 solitary parameters AC/ EFW < 3rd centile
Contributory	4 contributory parameters • AC or EFW <10th centile with • PI>95th centile in either the UA or uterine artery	4 contributory parameters AC/EFW <10th centile with Crossing centiles by >2 quartiles on growth charts, CPR <5th centile Umb PI > 95th centile

Stage	Pathophysiological correlate	Criteria	Monitoring	GA/mode of delivery
I	Severe smallness or mild placental Insufficiency	EFW <3rd centile CPR <p5 UA PI >p95 MCA PI <p5 UtA PI >p95	Weekly	37 weeks LI
II	Severe placental insufficiency	UA AEDV Reverse AoI	Biweekly	34 weeks CS
III	Low-suspicion fetal acidosis	UA REDV DV-PI >p95	1 – 2 days	30 weeks CS
IV	High-suspicion fetal acidosis	DV reverse a flow cCTG <3 ms FHR decelerations	12 h	26 weeks CS

All Doppler signs described above should be confirmed at least twice, ideally at least 12 h apart. GA = Gestational age; LI = labor induction; CS = cesarean section

of umbilical, MCA, DV and uterine artery Doppler studies will help to assess the severity of growth restriction and plan the follow up and timing of delivery.

Conclusion:

Doppler study of the fetal and uterine vessel has made tremendous progress in the field of fetal growth restriction. Before 30 weeks Umbilical artery Doppler is used to diagnose and monitor FGR and DV flow assessment helps to time the delivery. After 30 weeks, UA and MCA with uterine artery Doppler will compliment biometry in diagnosing, monitoring and timing the delivery. FGR being the commonest cause of unexpected fetal demise and the diagnosis is still not 100% more work is needed in this field to reduce the morbidity and mortality related to FGR.

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   J. Gordijn Ultrasound Obstet Gynecol 2016

INTERVENTIONS IN COMPLICATED MONOCHORIONIC TWINS TO IMPROVE OUTCOME

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INTRODUCTION

The incidence of monozygotic twinning unlike the dizygotic is stable, similar across countries, unaffected by artificial reproductive techniques, advanced maternal age or other factors. However, despite forming only 20% of all twins, the monochorionic (MC) twins have a higher rate of perinatal mortality due to higher risk of complications secondary to their placental sharing. Additionally, the monochorionic monoamniotic (MCMA) which forms 5% of MC, are at further risk of perinatal mortality due to twin related congenital abnormalities and cord related complications. Hence, a timely fetal intervention in these complicated pregnancies can result in improved neonatal survival rates.

Indication for intervention in MC Twins

The complications unique to MC pregnancy include Twin to twin transfusion syndrome (TTTS), Twin anemia polycythemia sequence (TAPS), Twin reverse arterial perfusion (TRAP) sequence, monoamniotic pregnancy and conjoined twinning. Complications like TTTS, TAPS, TRAP are primarily due to the abnormal placental vascular anastomoses connecting the two fetal circulations.

(i) TTTS occurs due to deep arteriovenous (A-V) anastomoses seen in 15% 25% of MC twins while clinically significant TTTS occurs only in 1% of MC. Untreated severe TTTS has a poor prognosis with a perinatal mortality rate of 90%. In those before 26 weeks of gestation, there is a higher risk of fetal loss, and severe handicap in the surviving twin. Indications for intervention in TTTS include, TTTS stage 1 with progressive polyhydramnios, short cervix, maternal distress or cardiac compromise in the recipient and Stage II, III TTTS .(figure 1)

(ii) TAPS is a form of chronic feto-fetal transfusion, characterized by inter-twin hemoglobin differences in the absence of amniotic fluid discordances. TAPS may occur spontaneously (5%) or post laser treatment for TTTS (2-13%). Even though intrauterine transfusion (IUT) can result in temporary symptomatic treatment for the donor, the only causal treatment is fetoscopic laser coagulation of the anastomotic vessels. (figure 2)

(iii) TRAP sequence seen in 2.6% of MC pregnancies, is an acute difference in arterial pressures between twins, resulting in a unidirectional flow in the reverse direction. The perfusion of the acardiac twin results in high-output cardiac failure in the pump twin, which is a poor prognostic factor requiring intervention. Others include abnormal doppler indices of the pump twin and the ratio of the weight of the acardiac twin to the weight of the pump twin > 0.7 (figure 3)

(iv) Selective fetal growth restriction (sFGR), in MC twins is when one fetus has estimated fetal weight (EFW) < 10th centile and the intertwin EFW discordance is > 25%. This could be structural anomalies, viral infections, chromosomal abnormalities, or due to unequal sharing of the placenta and vasculature. sFGR, are classified based on the pattern of end-diastolic velocity at umbilical artery doppler. (table 1) The survival rate in Type-I sFGR is greater than 90%. Type-II sFGR is associated with a higher

Types	Pattern of end-diastolic velocity of umbilical artery Doppler
Type I	Umbilical artery Doppler waveform has positive end-diastolic flow
Type II	Absent or reversed end-diastolic flow (AREDF)
Type III	Cyclical/intermittent pattern of AREDF.

Table 1: Types of selective fetal growth restriction in MC twins

risk rate of complications, (IUD of either twin is seen in up to 29% and risk of neurological sequelae in up to 15% of cases born prior to 30 weeks). Type-III sFGR is associated with a 10– 20% risk of sudden death of the growth-restricted fetus, and up to 20% risk of neurological morbidity in the survivor. If there is a substantial risk of fetal demise of the co-twin before 26 weeks, a selective termination may be considered to protect the cotwin.

Type-I sFGR managed expectantly have good perinatal outcome. However, fetoscopic laser ablation in Type-II or -III sFGR resulted in higher rate of mortality but lower morbidity than expectant management. There is lack of evidence on data on the outcome following selective reduction in the prenatal management of sFGR. Hence management of these cases should be individualized based on the gestational age at diagnosis, severity of discordance and the type of Sfgr.

(v) Single fetal demise- can result in sudden hypotension in the survivor from immediate exsanguination through the vascular anastomoses in to the dead fetus resulting in ischemic/hypoxic lesions in the survivor. This can result in 15% risk of fetal death and 25% risk of neurologic handicap and preterm delivery of 68%. In SFD before 24 weeks, delivery is recommended. If beyond 24 weeks, the pregnancy is best terminated on attainment of lung maturity in the survivor. Later in gestations, SFD could theoretically trigger coagulation defects in the mother requiring a baseline coagulation profile in the mother and a follow up. Anemia in the survivor may need an intra-uterine blood transfusion. Hence a fetal blood sampling helps to rule out fetuses that are not anemic and hence unlikely to develop a cerebral lesion.

Methods of fetal intervention -

The antenatal management of these complications in MC pregnancies involves, fetoscopic laser ablation, thus salvaging both the twins, or by selective fetal reduction by procedures like bipolar cord coagulation, radiofrequency ablation or interstitial laser ablation.

1.FETOSCOPIC LASER ABLATION

Indications

1. TTTS - In stage 1 with progressive polyhydramnios, short cervix, maternal distress or cardiac compromise in the recipient, Stage II, III

2. In selective fetal growth restriction type 2 or 3 to salvage both the babies

3. TRAP

This is based on the principle of interruption of inter-twin vascular anastomoses (the AA, AV, VV) by laser ablation under local anesthesia, using a 2 mm fetoscope with the laser machine is set at 20 - 40W power and the laser is fired at short bursts of 3-5 seconds, till the anastomotic vessels are blanched following which all the ablated areas are connected by the Solomon's technique (equatorial laser dichoronisation), which reduces recurrence of TTTS (seen in 14%) and post-laser TAPS (seen in 13%)

Follow up- is weekly for 2 weeks to assess for fetal anemia, presence of fetal bladders, liquor, dopplers and interval growth. Further follow up is fortnightly till delivery between 34 to 36+6 weeks

The Eurofetus consortium randomized trial concluded that, fetoscopic laser coagulation is more effective first line treatment than serial amnioreduction for severe TTTS diagnosed before 26weeks and it was further concluded by Cochrane review that it should be considered the treatment for all stages of TTTS to improve the neurodevelopmental outcome. Amnioreduction can be considered in those diagnosed after 26weeks.

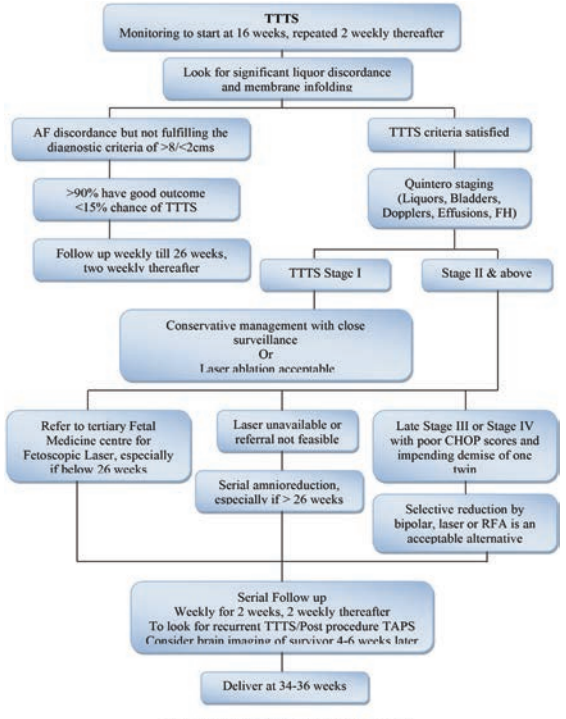

Figure. 1. Management algorithm – TTTS

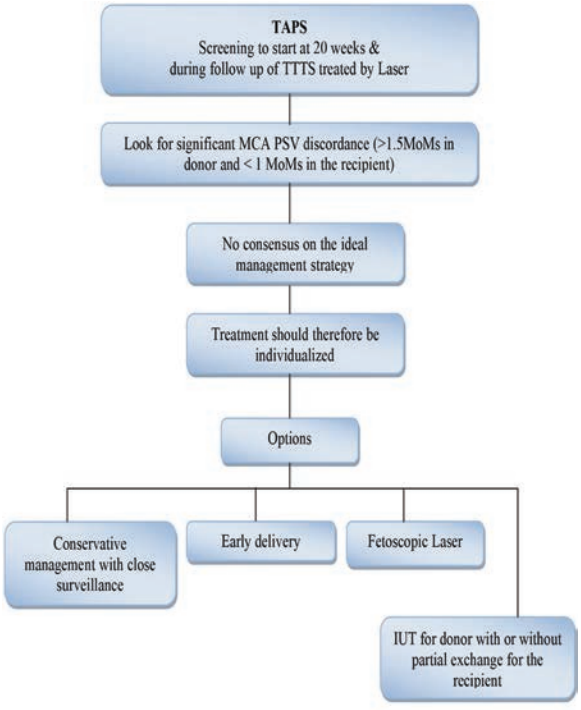

Figure 2. Management algorithm – TAPS

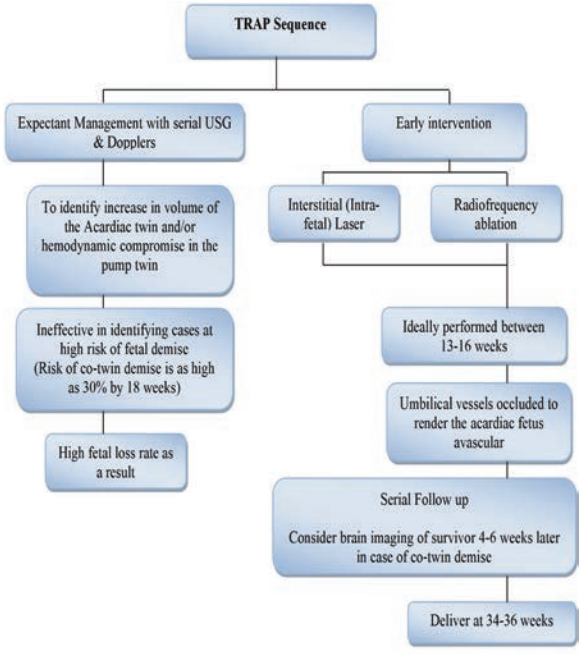

Figure 3. Management algorithm – TRAP sequence

2. SELECTIVE FETAL REDUCTION

"Selective termination" involves reduction of a fetus with severe defects or one that is expected to die later in the pregnancy, or that would threaten the life of the survivor.

This is done by by bipolar cord coagulation, intra-fetal laser ablation or radiofrequency ablation (RFA) of the interstitial cord vessels.

Indication: Monochorionic twins with

a. Discordant anomaly in one of the twins

b. Severe selective FGR- type 2 or 3

c. TRAP with Pump twin compromise

d. TTTS with cardiomyopathy in the recipient

a. RADIOFREQUENCY ABLATION (RFA) - This is usually done between 16-24weeks of gestation using a 17G RF needle introduced to the fetal abdominal cord insertion under ultrasound guidance, to cause coagulation of an area of 2cm diameter and a complete cessation of blood flow in the down- stream portion of the cord.

b. BIPOLAR CORD COAGULATION- is done under ultrasound guidance using a 3mm bipolar forceps, grasping the umbilical cord and coagulating with a power set at 40W applied in short bursts of 10sec. At least 2 different sites on the cord are coagulated. Cotwin is monitored after the procedure by MCAPSV and amnioreduction is considered if polyhydramnios.

c. INTERSTITIAL LASER ABLATION- of the intra-abdominal portion of the umbilical cord using an 18G 15cm large bore needle, which allows 600micron diameter laser fiber through it to coagulate the umbilical cord vessels resulting in cessation of cardiac activity. This procedure is done in fetuses is less than 19 weeks of gestation.

Follow up- After the procedure, follow up is weekly for 2 weeks and a neuro sonography of the survivor is recommended after 4 weeks. Post procedure, the pregnancy is managed as singleton.

Outcomes following fetal intervention

Fetoscopic laser in severe TTTS resulted in higher likelihood of survival of at least one twin to 28 days of age in 76 %. And on follow up, at 6 months of age, these infants had a lower incidence of cystic periventricular leukomalacia and were less likely to have neurologic complications. Perinatal outcome of complicated MC twins remained same with RFA or BPC with similar survival rate of 88.9% and 76.5% respectively.

However, RFA appeared particularly useful in sFGR and in those requiring selective termination later in gestation and beyond the period of viability.

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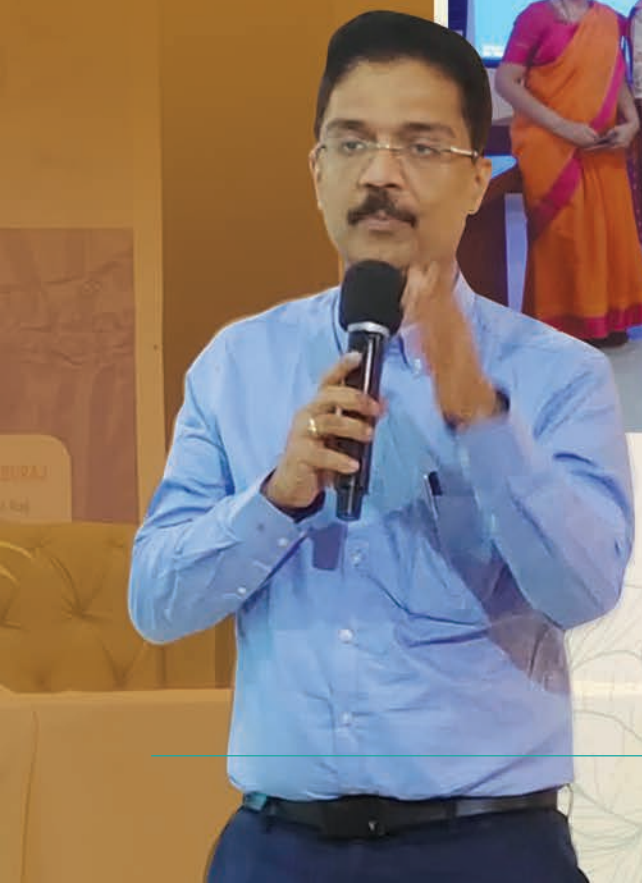

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