PRINCIPLES, PROTOCOLS & PRACTICES

ICOG CAMPUS

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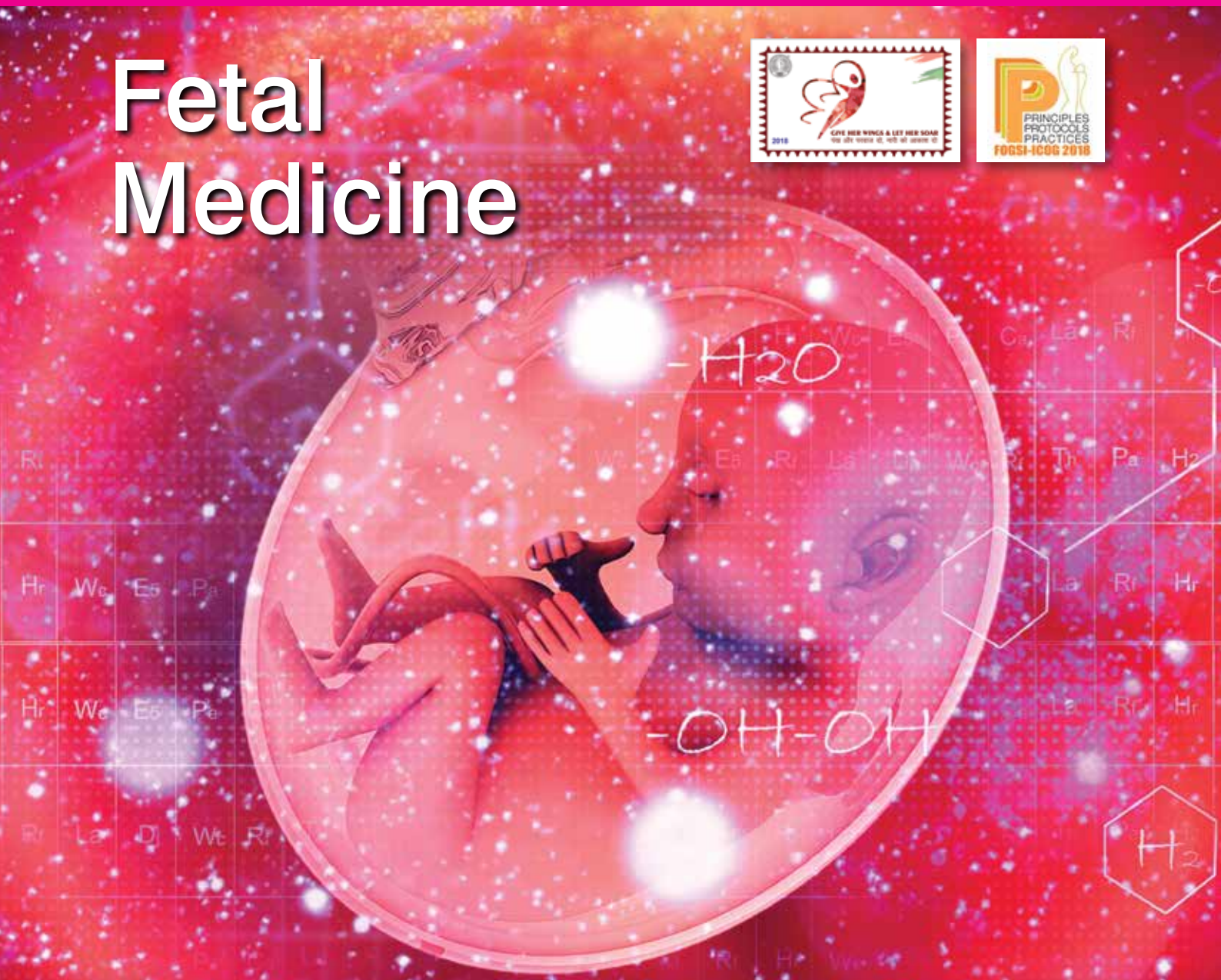
Fetal Medicine



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Dear Friends,

The concept of treating the fetus as an individual patient is the basis of the science of Fetal medicine. Ever since this has become an integral part of Obstetric care there is no doubt that the potential of improving perinatal outcome has increased tremendously. What started as a very specialised service limited to few high – end organisations has now permeated to many layers of the Obstetric care units and it is heartening to see the acceptance of Fetal medicine by most Obstetricians. Like any other science, there has been progress in technology in Fetal medicine and the need for constant updating cannot be undermined. This newsletter has been compiled with the aim of bringing to its readers the latest developments in most aspects of fetal medicine.

This year ICOG is committed to develop standard practice protocols to help improve the ObGyn specialist all across the country and as the chairperson of ICOG I hope you all will help us actively by contributing further towards "PPP – Principles, Protocols and Practice" in every subspecialty of ObGyn. Happy Reading!!

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DR. JAIDEEP MALHOTRA

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Dear Fogsians,
Greetings.

"Every life is different; being pro-life is not only about saving the fetus, being pro-life is about all the stages of life."
– Nat Hentoff

The journey of the little Zygote implanting in utero and the transformation into a complete human being in a short span of nine months is most fascinating. This journey is also not always smooth sailing and there could be many minor to major defects in the formation period. Today we are very lucky that we have many diagnostic modalities available to us for screening and diagnosing these abnormalities.This year with FOGSI dedicating itself to Adbhut Matrutva, we cannot forget Adbhut Sattva or the Fetus cannot be forgotten or overlooked.

We all now have accepted the fact that Fetal medicine is an inseparable part of Obstetric care – both in high risk and low risk situations. It is imperative for all Obstetricians now to allocate specific tests for fetal wellbeing and screening for specific fetal problems. In this era of "Fetal therapy" it is heartening to see that fetal problems are finding vital solutions and don't always warrant terminations!

This ICOG newsletter has amalgamated many interesting articles about recent advances in fetal screening, diagnosis and treatment.

I am sure, you all will find it very informative and enriching reading.

SECRETARY'S MESSAGE

DR. PARAG BINIWALE
MD, FICOG

Secretary, ICOG

Dear Friends,

The face of antenatal care has undergone a paradigm shift in the last couple of decades with the advent of the science of Fetal Medicine. Obstetrics has now diversified into a dual care pathway addressing the needs of the mother and the fetus as two individual patients rather than a common entity which invariably resulted in compromising the interests of one in favour of the other if there ever was a crisis. Given the fact that risk profile of Obstetric patients is changing towards the more challenging end of the spectrum, one is relieved that we are today able to do justice to the needs of both the mother and her fetus thanks to this new breed of "Fetal medicine" specialists who dedicate their attention to the fetus in utero and help the Obstetrician plan care better to optimise the final outcome of pregnancy. This edition of the newsletter is based on updates in various aspects of Fetal medicine which directly or indirectly help in improving Obstetric services. The ICOG newsletters have always aimed at keeping a balance within all subspecialities of ObGyn and this edition continues the tradition as such. Wish you all a happy reading!

Our team has put in a lot of efforts to bring this issue. I express my sincere thanks to them, especially Dr. Chinmayee Ratha. Do give your feedback so that we will bring in more & more scientific material to help you in day to day patient management. Happy reading!!!

FROM EDITOR'S PEN

DR. ASHOK KUMAR
MD, PhD

- FAMS, FICOG, FICMCH
- Director Professor:
  Department of Obstetrics and Gynecology
- Maulana Azad Medical College &
  Lok Nayak Hospital

Dear Friends,

Very Warm greetings to all!

Pregnancy is considered as a unique physiological normal phenomenon in a woman's life; however, pre-existing illness and unexpected diseases may affect the mother and fetus. This issue has paid attention to this well advanced subspecialty "Fetal Medicine "so as to take care of needs of unborn baby.

Advancing age of conception and rising trends of artificial reproduction techniques has led to an increase in the incidence of dizygotic twining and advanced multiple gestations. The aim of prenatal and perinatal care is to prevent, detect and manage problems that adversely affect the pregnancy and its outcome. Early diagnosis and detection of such abnormalities can help in early intervention or early termination of pregnancy which has considerable medical and psychological benefits. Clinicians should be aware of the advances made in the specialty and the possible available options so that timely referral is planned for targeted action by the experts of the field.

This issue has been prepared by Dr. Chinmayee Ratha to highlight the current practices in aneuploidy screening in India, principles and protocols to be followed for common fetal intervention. A special section of this issue is dedicated to multiple fetal gestation and fetal reduction in advanced multiple gestations. It also addresses planning of fetal care in pregnancies conceived by assisted techniques.

Happy reading.

FROM ISSUE EDITOR'S DESK

DR. CHINMAYEE RATHA
MBBS, MS - Obstetrics & Gynaecology, MRCOG, FIMSA, FICOG

- Fetal Medicine Consultant – Navodaya Hospital

Dear Friends,

Education, they say, is the best form of health care. When we share our knowledge and educate our peers, we build and edifice of learning which moves care standards from one plane to another – always towards betterment and progress. This is true for every science in this world and so it is for Fetal medicine -"the science of tomorrow".

The fetus - our "unborn" patient is the citizen of tomorrow!! This "unborn" individual shares centre stage in the care paraphernalia of the present day pregnancy care where both mother and her fetus are treated as separate patients. With years of study, research and publications, the understanding of the basic physiology of fetal development and function we now have clarity on many fetal conditions that remained largely enigmatic in the past. Every day we are defining some conditions better, understanding more of the pathophysiology of fetal ailments and finding some solutions to persistent problems – all this is exhilarating in its pace and potential and awareness is the first step to achieving the benefits of advancements. I am thankful to the ICOG for publishing the newsletter "ICOG campus" and allocating this entire edition to various topics on Fetal medicine. I am sure most of you would have read the previous edition which had a conglomeration of many interesting topics including NIPT,FT scan, IUGR etc (Ref:ICOG campus April2017 issue) . In this edition we have tried not to replicate old topics but to focus on some newer aspects and help the readers move a step forward in understanding this subject.

Screening for aneuploidies has been a core topic in Fetal medicine through the decades and the concepts are complex and ever evolving. There is a dire need for every practitioner to learn and relearn the views of screening which are most relevant to our times and our people. The article in this issue does exactly that and

hopes to focus the reader's thoughts towards a clearer perspective.

Early pregnancy assessment is a vital issue and "well begun is half done " anyway – we have put together the basic of early pregnancy assessment from the fetal medicine standpoint. With a collection of interesting articles on interesting clinical cases we hope it will make for an enriching reading experience. There is a small section of MCQs at the end to test your alertness at reading – a self learning exercise!

Fetal interventions are very exciting and have a futuristic note to them but its heartening that at present many such interventions are possible within our country and we have a review on the "PPP" of such interventions in our country.

Multifetal gestation is another area which requires extensive clarity as all Obstetricians are seeing more and more such cases. We hope the beautifully written review on multiple pregnancy assessment will make life easier for all readers.

There is an article on Multifetal pregnancy reduction which is needed to reduce higher order multiples or abnormal foetuses and awareness is sparse amongst doctors as to the how, why and when of this procedure.

We also put together an article on planning fetal care in pregnancies achieved by assisted reproduction techniques because sometimes there are novel factors affecting the final care plan in such pregnancies – at least one thought from this angle will help smoothen out the final common pathway.

As we make more progress, we realise that basics really don't change – but things appear different nevertheless. The change is in the "vision"- its how broadly you think before you put together the final take home messages. Our authors have put in a lot of effort summarising complex material for you and I hope you make use of this unique learning opportunity and share your feedback with us.

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PRINCIPLES, PRACTICES AND PROTOCOLS OF ANEUPLOIDY SCREENING IN INDIA

Dr. Manikandan Krishnan

Transitive verb
"to examine usually methodically in order to make a separation into different groups"[1]

Introduction

The advances in foetal medicine practice in the past few decades have made it possible to identify a vast majority of foetal chromosomal numerical abnormalities prenatally. However, it requires a systematic and dedicated screening program in the first place, backed up with adequate resources to perform and interpret the diagnostic tests. The setting up of a foetal aneuploidy screening program requires a thorough understanding of the principles of screening, the pros and cons of component tests, creating and sustaining awareness of the problem among the clients, constant monitoring of the quality of the screening tests, and regular adaptation to ongoing improvements in the clinical practice. This article will discuss the principles of screening as applied to prenatal aneuploidy screening and the available protocols commonly practiced.

Principles of Screening

Wilson and Jungner[2] published the principles of screening for disease on behalf of the WHO as early as 1968. They accepted the definition of screening as proposed by the "The CCI Conference on Preventive Aspects of Chronic Disease held in 1951":

"the presumptive identification of unrecognized disease or defect by the application of tests, examinations, or other procedures which can be applied rapidly. Screening tests sort out apparently well persons who probably have a disease from those who probably do not. A screening test is not intended to be diagnostic. Persons with positive or suspicious findings must be referred to their physicians for diagnosis and necessary treatment."

It is important to understand the difference between a 'screening programme' and a 'screening test' as we often find these two concepts being erroneously interchanged in academic discussions.

Screening program versus screening test

A screening program is a comprehensive policy, usually adopted by the healthcare delivering agency in order to fulfil the community requirements. Screening tests are employed within a screening program as a tool to identify the subset of the screened population that should then undergo the diagnostic testing. Usually, screening tests are done when diagnostic tests are costly, difficult to perform, or have a significant risk associated with it.

Wilson and Jungner's principles of screening

- The condition sought should be an important health problem.
- There should be an accepted treatment for patients with recognised disease.
- Facilities for diagnosis and treatment should be available.
- There should be a recognisable latent or early symptomatic stage.
- There should be a suitable test or examination.
- The test should be acceptable to the population.
- The natural history of the condition, including development from latent to declared disease, should be adequately understood.
- There should be an agreed policy on whom to treat as patients.
- The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.
- Case-finding should be a continuing process and not a "once and for all" project.

Box 1

Prenatal Screening for Aneuploidy

Foetal chromosomal abnormalities are in general rarer compared to foetal structural defects – in the order of about ten-fold. However, they may have profound implications on the quality of life of the individual and the parents. The most common non-gonosomal chromosomal abnormality among live born infants is

Trisomy 21, or Down Syndrome (DS) occurring in about 1 in 9623to 1 in 12304 births in India, less common than congenital structural defects5. The next most common aneuploidies at birth such as Edward syndrome and Patau syndrome are rarer than DS. Unlike structural defects, DS is unlikely to be diagnosed with certainty by ultrasound alone. DS foetuses do not show any pathognomonic sonographic criteria. Only about half of the foetuses with DS will even show some markers on ultrasound and these are again quite non-specific. Therefore, ultrasound examination of the foetuses cannot be used as a diagnostic test nor be a useful screening test in the detection of DS. On the other hand, the vast majority of the foetuses with Edward or Patau syndrome show defects that are detectable sonographically and hence ultrasound examination itself can serve as a good screening tool in the detection of these less common albeit more severe chromosomal abnormalities.

The only definitive way of diagnosing a chromosomal abnormality in the foetus is by karyotyping the foetal cells obtained by direct testing – chorionic villus sampling, amniocentesis, or foetal blood sampling. This diagnostic test-foetal karyotype - is costly, labour intensive, and is associated with the small but ominous risk of pregnancy loss. Therefore, it is impractical to apply direct testing to all pregnancies to detect Down Syndrom foetuses.

Prenatal screening for aneuploidy essentially is screening for DS and it involves systematically segregating pregnant women into high and low-risk categories. The high-risk category is then offered the diagnostic test.

Setting up a screening program

Box 2 enlists the components of a screening program. A screening program can be set up at hospital level, local level, regional level or at national level. The most important point is the uniformity in the application of screening. Until national organisations come up with comprehensive screening guidelines, it is the responsibility of the individual hospitals to define a screening program and adhere to it. In this way, a large proportion of the confusion amongst practitioners and patients will be removed. At the core of the screening program is a program director who reviews the policies and components and takes up

Components of Screening Program

- Definition of included population
- Mechanism for pre-test and post-test counselling
- Mechanism for population awareness about the condition and the programme
- Information about the screening tests and diagnostic tests to be used in the programme
- Information on the 'screen-positive' threshold to be used
- Mechanism for auditing and quality control of various components of the programme

Box 2

Minimum mandatory information to be conveyed about the screening program to women

Eligible Clients
- Who all are offered in your set up?

Importance of the condition
- Brief review about Down Syndrome, accurate and in lay-man's language

Test offered
- Describing the actual test offered at your centre

Interpretation of results
- Describing the concepts of screen positive and screen negative; informing the screen positive cut off

Performance of the Screening Program
- Detection Rate (DR): What proportion of Down Syndrome foetuses will be picked up by the screening program
- False positive rate (FPR): What proportion of women undergoing screening will be flagged as screen-positive
- Odds of being Affected given a Positive Result (OAPR): The odds of the foetus having Down Syndrom when the woman is screen positive

Diagnostic test
- Describing the actual procedure of a diagnostic test offered at your centre: chorionic villus sampling, amniocentesis, or foetal blood sampling

Procedure related loss
- Accurate and centre-specific loss rate to be communicated; in expert hands, this is lower than 0.5% for amniocentesis and about 0.5% in CVS.

Quality control
- Information about how quality control is achieved on an ongoing basis

Box 3

the responsibility of running the program.

Ideally before launching the screening, a systematic effort should be made to educate the masses. Box 3 lists the items patients need to be educated about as part of the screening program. In practice, this patient education should be an ongoing process and part of the pre and post-test counselling that every patient should receive.

Protocols and Practical issues

None of the available screening tests for DS and other aneuploidies can be described as desirable. Table 1 lists the available tests and the various attributes. The detection rates provided are for a fixed false positive rate of 5%. There are only a few large scale validation studies from India for the screening tests – Kaur et al from Chandigarh[6] and Manikandan et al from Chennai[7] provide performance results of the second and the first trimester screening test.

The test protocol followed in any centre should be based on the expertise and resources available locally or regionally. For example, NT expertise is limited and also requires the patient to travel to the place of ultrasound centre. Serum screening partly overcomes this limitation in that the blood sample can be transported to a referral lab from the physician's office. Centrifugation of the blood sample and sending across the serum sample partially mitigates the transport associated false elevation of the analytes especially ß-hCG.

Suggested Practice Model for India

Although individual centres would like to offer cutting edge technology, depending on the availability of expertise and patient affordability, it is also essential to project a minimum standard that is to be followed all over the nation uniformly. Standardisation of practice would lead to less medico-legal hassles such as the one that recently went viral in social media. In considering the model in a country as diverse as ours, we need to consider the availability of expertise: in general, expertise in ultrasound is more localized than expertise in laboratory since the latter can be overcome by logistic support that is offered by the commercial labs.

Screening Test	Components	Period of performance	Detection Rate	Drawbacks	Remarks
First trimester serum screening: "double marker test"	Free beta hCG and PAPP-A	Weeks 10 13+6 or CRL 33 84 mm	60%	In practice, very low discriminatory value. Cannot be done in multiple pregnancy	To be highly discouraged
Nuchal scan	Nuchal translucency (NT)	CRL 45 84 mm	75-80%	Requires a committed team of skilled operators	The most cost-effective method
Combined screening test	NT, Free b-hCG, PAPP-A	CRL 45–84 mm	90%	Expertise for NT	Standard of care in many countries offering DS screening
Triple screening test	AFP, ß-hCG, UE3	BPD 32–52 m	65–70%	Transport of blood or serum may result in higher false positives	Supplanted by the QST due to a combination of higher DR and lower FPR
Quadruple screening test	AFP, ß-hCG, DIA, UE3	BPD 32–52 mm	80%	Transport of blood or serum may result in higher false positives	Standard of care in case of missed combined test
Integrated test	NT, PAPP-A at first trimester ß-hCG, AFP, DIA, UE3 at second trimester	As per each visit	94%	Clinical dilemma in partial reporting, patient anxiety awaiting results, lost to follow up	Not a practical policy even in countries with robust health care system
NIPT	Cell free foetal DNA from maternal blood	9-18 weeks	99%	4% no call rate so effectively 95%; high cost; performance not yet widely validated in low risk population	Can be used as a second line screening for selected cases of screen positive at a higher centre

With NT expertise available

In places where NT expertise is available within a reasonable distance, a screening model based on NT and biochemistry should be the standard procedure. This should be offered to all women. The advantage of this model is the concomitant identification of about 60% of all the major/lethal foetal abnormalities before the end of the first trimester. In addition, this visit will allow screening for, and prevention of, early onset preeclampsia[8].

Where NT expertise is unavailable

According to the FMF website,[9] as on January 2018, there are about 2366 healthcare professionals that have completed the online theory course on NT, 531 that have been awarded the certificate of competence in nuchal translucency scan, and a mere 118 practitioners who have successfully been audited. Therefore, it is obvious that our efforts should be towards motivating the practitioners of obstetric ultrasound, be it obstetricians, sonologists or radiologists, to obtain the relevant competency and to maintain the quality through regular audits. National bodies may themselves form auditing policies and committees to monitor competency. However, this is an intermediate-term goal. In the interim, the vast majority of the population would not have access to NT expertise or would be exposed to suboptimal NT assessment. As obstetricians are the primary physicians for the mothers, it is our responsibility to get the correct NT measurement as per protocol.

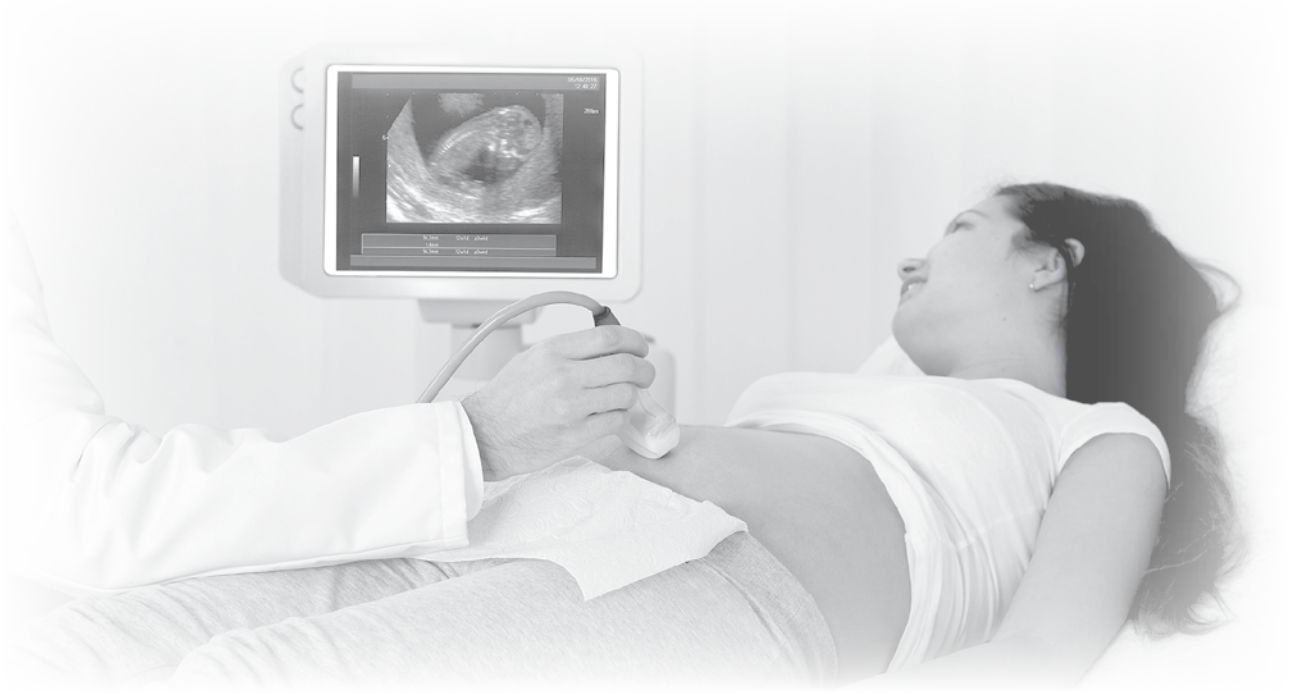
A large number of obstetricians would therefore not have access to quality NT measurements. In such a situation, the next best option for screening would be the quadruple screening test at around the 16th week of pregnancy. This gestational age is important since if the test returns screen-positive, there is sufficient time to perform a foetal karyotype before the legal limit of 20 weeks is met.

Ethical Considerations

Of late, we see a number of arguments against screening for Down Syndrome, circulated unilaterally among the public and sometimes targeted towards the medical community. Screening for DS should not stigmatise people actually living with the disease. This is particularly important since prenatal screening does not offer any therapy for DS, rather termination as the only alternative to continuation of pregnancy. Every pregnant woman has the right to know about the screening tests and the condition for which the screening test is performed. Participating in DS screening should entirely be an informed choice by the pregnant mother and her partner. To make this informed decision, accurate pre-test counselling or information should be provided to the couple.

Concluding remarks

At the forefront of DS screening should be a thorough understanding of the principles of screening. A clearly defined screening program that is relevant and appropriate to their local situation, as outlined above, should be followed by practitioners. The views and desires of the couple about participating in the program should be given importance and documented.



EARLY PREGNANCY ASSESSMENT FROM FETAL MEDICINE PERSPECTIVE

Dr. Chinmay Umarji

Aims and objectives

- To give a clear picture, to a generalist, of what to expect at the first trimester scan.
- To establish the minimum standard of care for scanning of twins and appraise a generalist of the variations.

Early Pregnancy Assessment - the basics

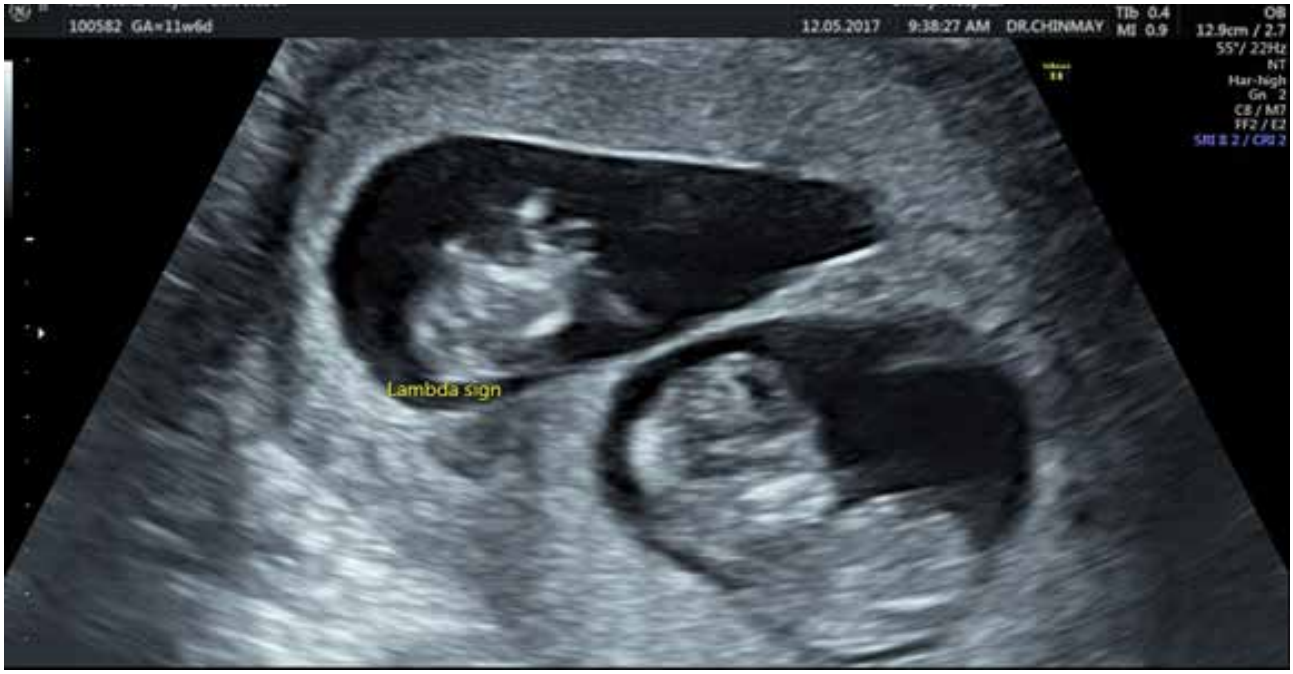
1. History is mandatory, assessment should always be trans-vaginal, unless contraindicated.
2. Non-viable foetus should be diagnosed if the CRL is 7 mm or more in the scan; the gestational sac diameter is 25 mm or more without visible heartbeat; two consecutive scans suggest no obvious growth.
3. Avoid pulsed wave Doppler, use M-mode.
4. Use of guidelines and dedicated EPAU improves the performance.
5. Detection rate of Trisomy 21 on combined test is 92 96% when a systematic scanning is coupled with standardised biochemical assessment. Risk stratification of a patient for preeclampsia, FGR and premature deliveries can be performed simultaneously without any additional costs.

Pregnancy assessment before 11 weeks helps in dating and viability, diagnosis of multiple pregnancies,, chorionicity and amnionicity and is also the best time period to plan blood sampling and NT scan. Beware- the natural anatomical variants may sometimes mislead at this stage (e.g., mid-gut herniation, pericardial effusion, hyperechogenic bowel).[1]

Early diagnosis of foetal anomalies cannot be overstressed with gestational age limits of the MTP act and the obvious ease of action with an early diagnosis.

With the advent of human understanding and better ultrasound machines, it is possible to diagnose fetal anomalies much earlier than before.[2] The 2D imaging is the mainstay of the diagnosis; however, 3D/4D techniques have further helped to accelerate this transition to a limited extent, so far.

In early pregnancy assessment, the first ultrasound should always be performed in the context of the history. The logical conclusion of any anomalies found should not be termination but cytogenetic analysis. This not only helps in identifying the cause but also helps to postulate the risk of recurrence sometimes, in additional



investigations. The newer techniques, like array cGH, have significantly reduced the culture failures associated with karyotyping. Karyotyping, now, has a role only in suspected aneuploidies, triploidies etc.

Advantages

Early ultrasound might be more accurate than second trimester ultrasonography in the detection of malformations associated with oligohydramnios and anhydramnios which lead to poor visualisation at later gestation, necessitating amnio-infusion.

Early detection of anomalies provides adequate time for investigation and action before the crucial limit of 20 weeks.

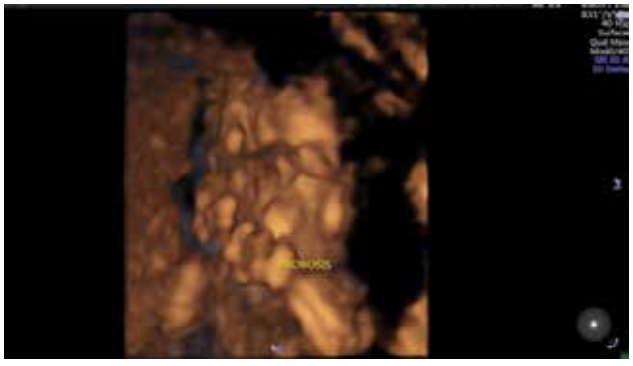
In multiple pregnancies, the early ultrasound helps in the diagnosis of location, viability of each foetuses and the chorionicity. The diagnosis of chorionicity is difficult with advance gestation; however, the first trimester sonographic signs (viz."Lambda" sign for dichorionic and "T" sign for monochorionic-diamniotic twins) make it much easier to make an accurate diagnosis. These should be specifically noted and a print should be attached to the patient's notes at the time of early pregnancy scanning.[3]

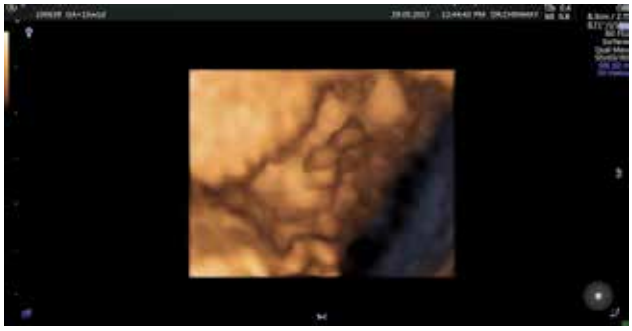
The early detection of anomalies: Foetal anatomy is best seen by a trans-vaginal ultrasound which should be offered to every woman.

Acrania, holoprosencephaly and limb-body wall complex can be diagnosed on a trans-vaginal ultrasound, as early as 8 weeks of pregnancy. However, repeat scans two weeks later are a must before the final diagnosis.[1]

By scanning at 11–14 weeks, the anomaly detection rates are as high as 84%.[4] Acrania and alobar holoprosencephaly can be almost always diagnosed at this stage.

Probosis, retrognathia, cleft lip can be diagnosed; however, they are considered optional for routine scanning.[5]

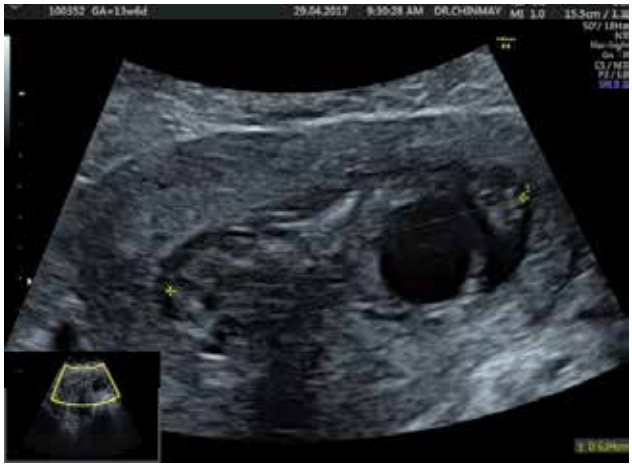


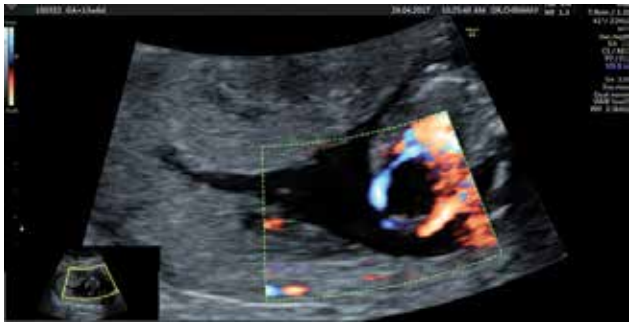


Spina bifida may be diagnosed by the direct sign of break in the continuity of the overlying skin and vertebrae or by the indirect signs of a deranged BPD/TAD ratio and BPD at 11 14 weeks; also lemon and banana signs.[7]

In the chest: Diaphragmatic hernias are easy to diagnose, especially, on the trans-vaginal scan. Pleural effusions can be seen and as they are associated with aneuploidies, karyotyping must be offered at this stage. Developmental malformations of the lungs can rarely be seen at such an early scan.

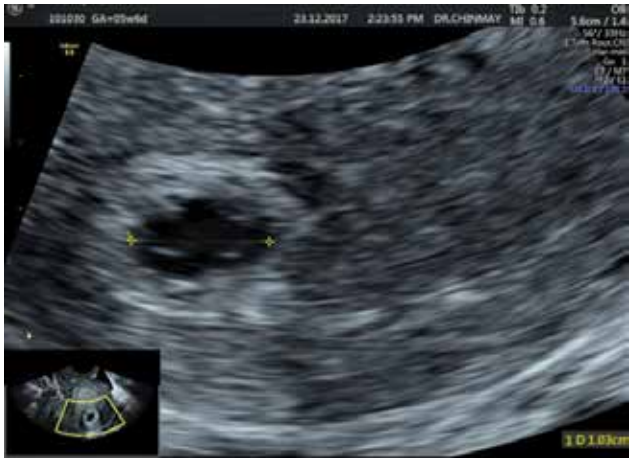
Abdomen may show anterior wall defects as seen by abnormal cord insertion, absent stomach bubble, absent bladder bubble or megacystis (bladder > 7mm)[8].

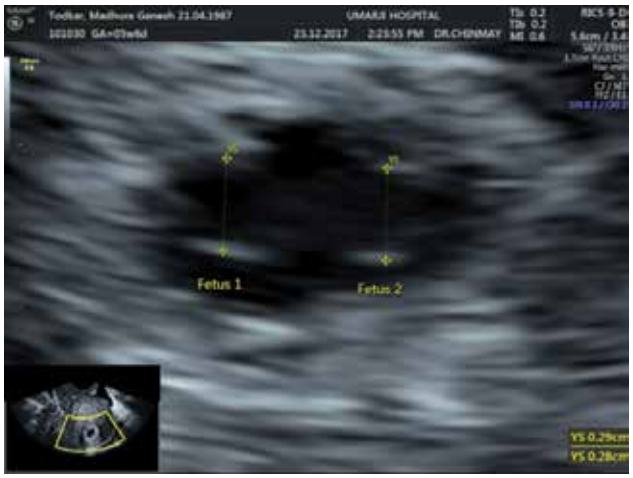


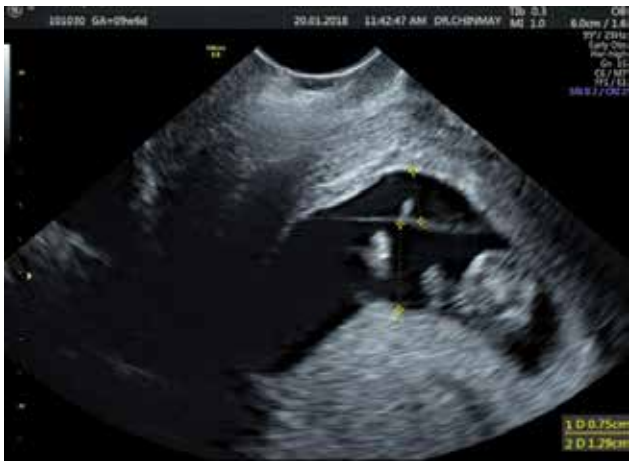


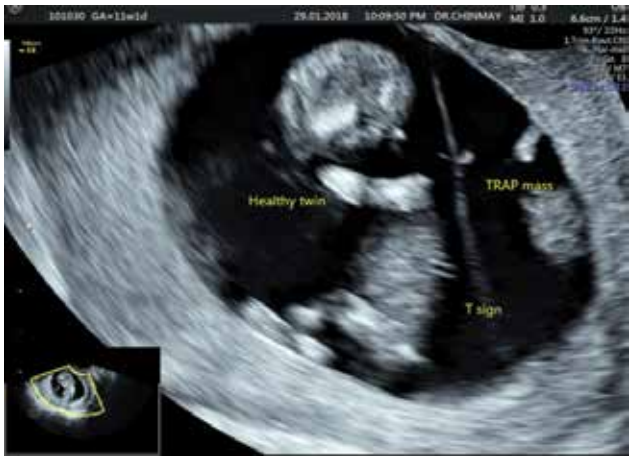
SUA can also be diagnosed at this stage.

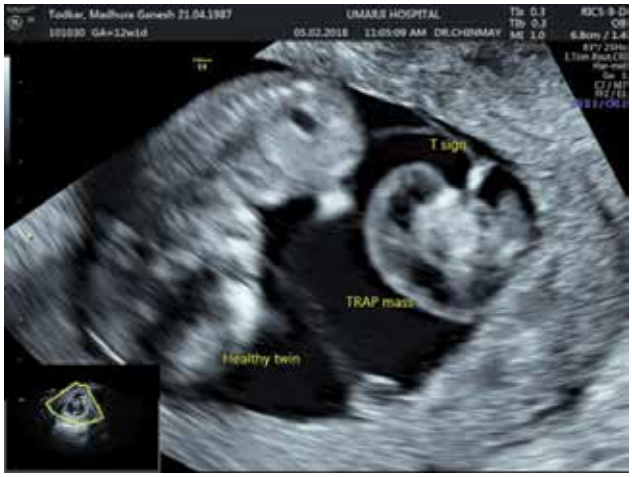
In twin and higher order gestation, the dating, identification of chorio-amnionicity and viability is important. This is best achieved at 11-14 weeks scan.





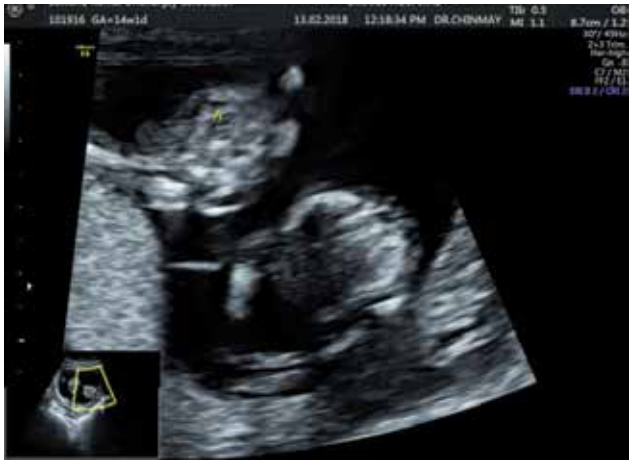


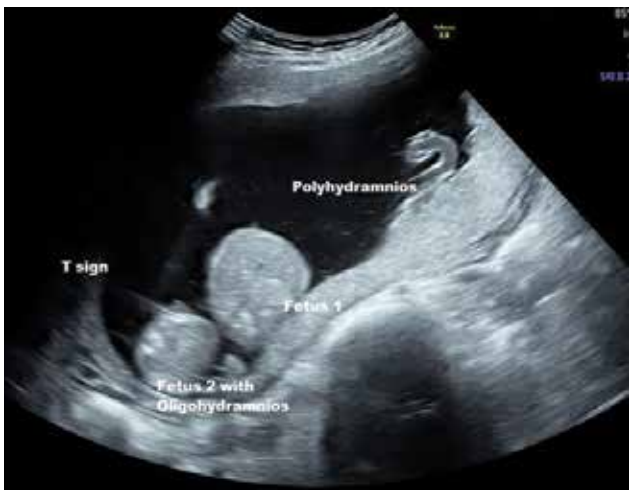




As many as 20-30% twins have a vanishing twin syndrome. The vanishing twin in early pregnancy usually has excellent prognosis for the surviving foetus.[9]

The monochorionic twins, thus diagnosed, need more frequent scanning (every 2 weeks) for early diagnosis of TTTS and they need early delivery at 36 weeks to reduce the risks of still birth. A dichorionic twin pregnancy should be offered monthly growth scans and delivery should be at 37 weeks.[10]





However, a foetal demise in the later gestation increases the risk of preterm deliveries and thus suboptimal outcomes, for the surviving foetus.

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4. R. Becker et al, "Detailed screening for fetal anomalies and cardiac defects at the 11–13-week scan." *Ultrasound Obstet Gynecol*. **2006**, 27 (6)613–618.
5. ISUOG Practice Guidelines: performance of first-trimester fetal ultrasound scan. *Ultrasound Obstet Gynecol*. **2013**, 41: 102–113.
6. E G Simon et al. "BPD:TAD ratio <1, potential marker for open spina bifida". *UOG*. **2016**, 45:267 272.
7. Chaui R. Intracranial translucency. *Ultrasound Obstet Gynecol*. **2009**, 34: 249–252.
8. Nicolaides K.
9. Khalil, A. *ISUOG*, March **2017**.
10. NICE clinical guidelines: Multiple pregnancy: Management of twin and triplet, 2011.

MCQs:

1. Which one of the following is abnormal at 10 weeks scan:
   a. Exomphalos
   b. Hyperechoic bowel
   c. Pleural effusion
   d. Pericardial effusion
2. In multiple pregnancy, the following is true
   a. Diagnosis of chorionicity is easier at 18 weeks scan than at 11 weeks
   b. In dichorionic pregnancy scans should be offered every 2 weekly
   c. Foetal demise at 24 weeks increases the risk of preterm labour as compared to a foetal demise at 12 weeks and thus potentially has worse prognosis for the surviving twin.
   d. The risks of twin to twin transfusion syndrome are increased in dichorionic as compared to monochorionic pregnancies.
3. Now algorithms exist to predict the risks of the following, except:
   a. Preeclampsia prediction in singleton pregnancy
   b. Premature delivery prediction in a twin pregnancy
   c. Trisomy 21 prediction in a twin pregnancy
   d. Foetal growth restriction in a singleton pregnancy
4. In the first trimester scanning of twin pregnancies, the following is true
   a. Dating is done by the CRL of the bigger twin
   b. The vanishing twin before 14 weeks increases the risk of anomalies in the surviving twin
   c. Increase in NT could only be due to aneuploidies.
   d. A T sign indicates dichorioonicity and thus better prognosis.
5. The following ultrasound findings can be diagnosed at 11 weeks scan, except
   a. Acrania
   b. Lobar holoprosencephaly
   c. Absent corpus callosum
   d. Limb-body wall complex.

PRINCIPLES, PRACTISES AND PROTOCOLS FOR COMMON FOETAL INTERVENTIONS


Dr. K Aparna Sharma


Dr. Ritika Bajaj

It was the advent of real time ultrasound in the late 1970s which led to a better understanding of foetal pathology and eventually paved the way for interventions to diagnose and manage foetal diseases in intrauterine life. Foetal interventions can be diagnostic or therapeutic. We will be discussing these in this article:

Fetal Interventions	
Diagnostic	**Therapeutic**
Amniocentesis	Intrauterine fetal transfusion
Chorion Villus Sampling	Fetal reduction techniques – Intracardiac KCL and Radiofrequency ablation
Cordocenetesis	Amnioreduction and Laser for TTS

To understand these procedures it is important to ask some basic questions:

WHY? WHAT? WHEN? HOW?

Diagnostic Procedures

1. Amniocentesis

Amniocentesis is a process of withdrawing amniotic fluid from the cavity for diagnostic or therapeutic purposes.

1.1 What are the Indications for amniocentesis?

Diagnostic	Therapeutic
Chromosomal analysis: Most Common indication following a screen positive on combined screening in first trimester or quadruple in second trimester. May also be done as confirmatory test following a positive cell free foetal DNA test result.	To remove excess amniotic fluid, such as in symptomatic polyhydramnios or twin-to-twin transfusion syndrome
Biochemical disorders- Gaucher's/Hurler's Syndrome	
Intra-uterine Infections	
Sex determination – X linked disease, CAH, DMD	
Rh isoimmunisation - Rh group, haemolysis Infrequent now with availability of non-invasive screening tests.	

1.2 What Pre-procedure Counselling should be offered to the couple?

The couple should be told about the purpose of the procedure (clear indication/ severity of the disorder), the potential complications including technical problems that might necessitate a second procedure. The genetic risk versus the procedure related risk & test accuracy should be weighed before deciding to undergo the test. They should be told about the time required before results will be available and the accuracy and limitations of the diagnostic test(s) planned, including possible inability to make a diagnosis. Alternatives that may yield the same or similar information but less invasive should be told. It is imperative to understand whether termination would be warranted following confirmation of the affliction and whether termination is acceptable to the couple.

1.3 What are we looking for in the amniotic fluid?

Most of the cells floating in amniotic fluid are epithelioid but fibroblastoid and amniotic fluid-specific cells are also present. At 16 weeks there are more than 200,000 cells/mL of which only 3.5 ± 1.8 cells/mL are capable of attaching to a culture substrate and yielding colonies. Before 15 weeks there is a significant decline in cloning efficiency (fewer than 1.5 clone forming cells/mL fluid).

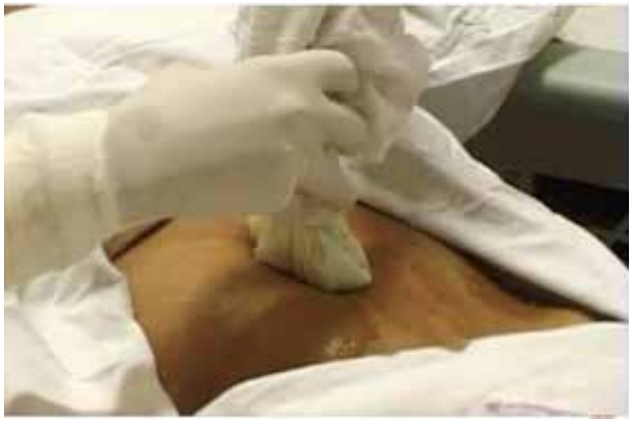
1.4 What is the optimal gestation for performing Amniocentesis?

It is technically possible at any gestational age after approximately 11 weeks of gestation. Optimally it should be performed at 16 17 weeks of gestation. Before 15 weeks (i.e., early amniocentesis) it is associated with

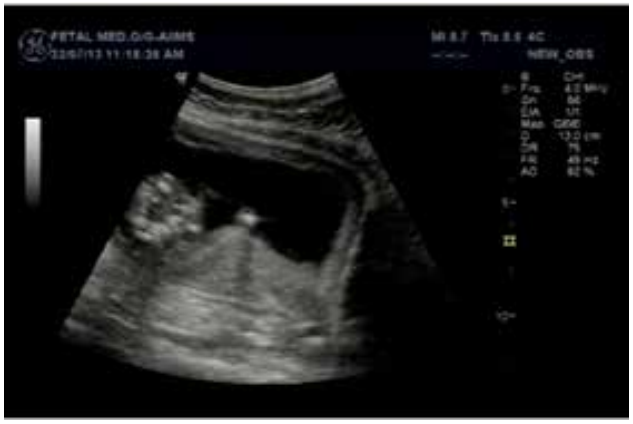
higher foetal loss and complication rates, including culture failure.

1.5 How is amniocentesis done?

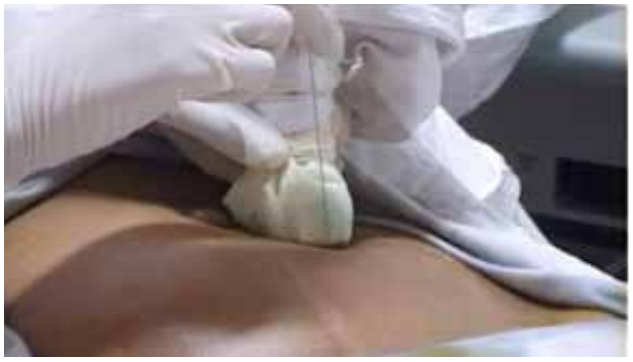
- Site selection: Avoid placenta as far as possible. Although some studies have suggested an increased rate of foetal loss in trans-placental procedures, this has not been substantiated. Also, the lateral quadrants of abdomen should be avoided.
- Needle specification: a 22G spinal needle should be used.
- Local anaesthesia usually not necessary. In a study by Dadhwal et al it was found that risk factors for pain at amniocentesis include maternal anxiety, history of menstrual cramps, previous amniocentesis and needle insertion into the lower part of the uterus.



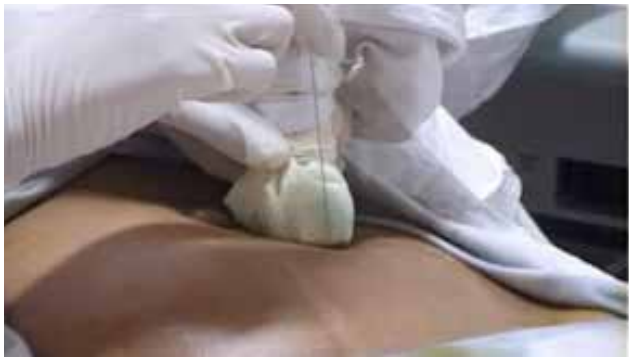
USG guided site selection



Chose a placenta free area



Needle insertion



Needle tip avoiding fetal parts

Discard first 2 ml

Take about 16 ml

1.6 What are the components of the post procedure care?

The foetal heart rate should be assessed sonographically. Transient uterine cramping, spotting, and vaginal loss of a few drops of amniotic fluid may occur immediately after the procedure. Limitation of activity after the procedure is unnecessary. Nonalloimmunized Rh(D) negative women should receive Rh(D) immune globulin after the procedure to prevent Rh(D) sensitization. The American College of Obstetricians and Gynecologists (ACOG) recommends a dose of 300 mcg.

1.7 What are the possible complications of the procedure?

a) **Dry tap:** Foetal membranes may have tented over the needle tip. It is seen more often with insertions prior to 15 completed weeks of gestation due to incomplete physiological 'fusion' of the amnion, chorion, and decidua parietalis.

b) **Bloody tap:** It is seen in <1% when done under ultrasound guidance blood is almost always of

maternal origin and does not adversely affect amniotic cell growth.

c) **Foetal loss:** In general, procedure-related rate of loss of 1/300 to 1/500 is usually cited. Most foetal losses occur up to four weeks following amniocentesis. Operator experience, number of punctures, maternal body mass index (BMI) ≥40 kg/m2, vaginal bleeding during the current pregnancy and history of abortion (spontaneous or induced) are some of the factors which increase the risk of abortion.

2. Chorion Villus Sampling

2.1 What are the Indications for CVS

CVS can be done for all indications of amniocentesis:
Cytogenetic analysis
Metabolic: in born errors of metabolism
Molecular: haemoglobinopathies, haemophilia, muscle dystrophy
The preoperative counselling should be done as described for amniocentesis.

2.2 What is the optimal gestation for performing Amniocentesis?

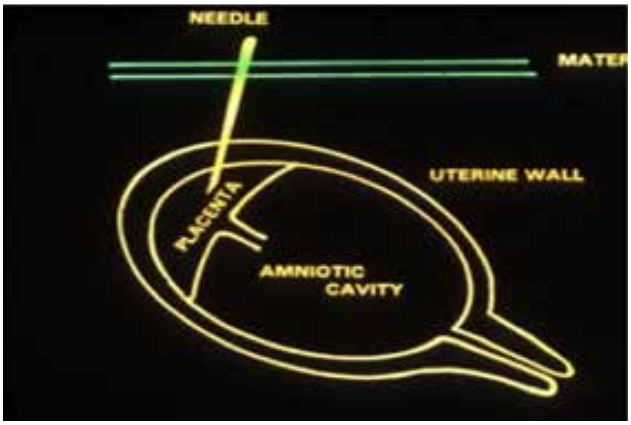
CVS can be done after 10 weeks. Therefore it can be performed at earlier gestations than amniocentesis.

2.3 What is the advantage of CVS over amniocentesis?

- Biochemical or DNA analysis can usually be carried out directly on villi obviating the need and delay of a cell culture as required after amniocentesis.
- Yield of cells and DNA from CVS is much greater than 20 ml of amniotic fluid
- Provides a shift towards first trimester screen and option of termination with more privacy

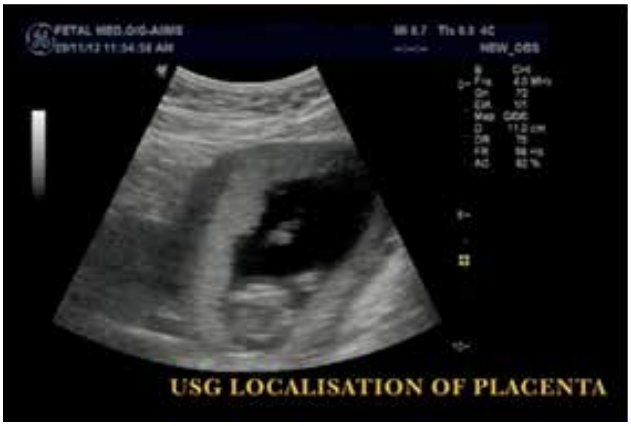
2.4 How is CVS done?

- Gauge 18 disposable spinal needle of adequate length (7.5 15mm) used.
- The needle passed through anterior abdominal wall into the substance of the chorion frondosum under continuous ultrasound guidance by freehand/needle guide technique.
- The stellate is withdrawn and 20 ml syringe is attached.
- Gentle up & down movements with continuous negative pressure are made taking care to avoid puncturing foetal aspect of amniotic membrane by U/S control with continuous needle tip visualization.

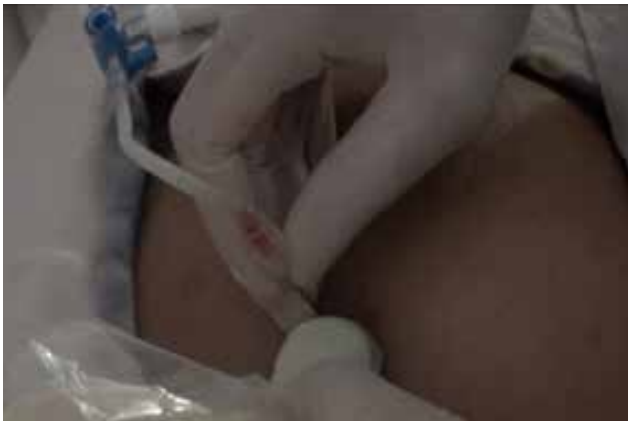


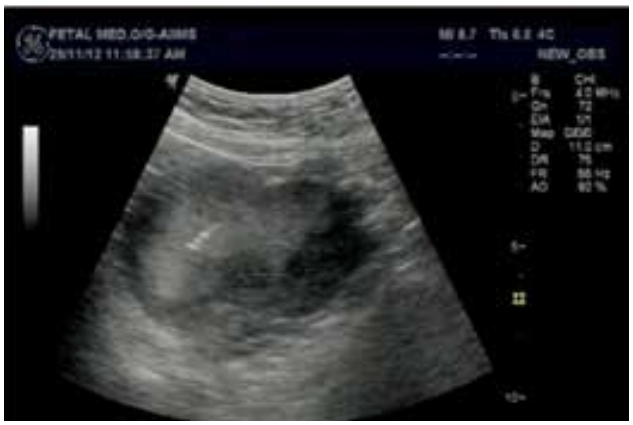
Pictorial depiction of CVS

The CVS set



USG localisation of placenta


Attaching the suction



Needle in the placenta

Chorionic villi in the media

2.5 What are the post procedure instructions?
A single shot of antibiotic can be given although the practice varies from centre to centre. There may be mild spotting for 3 5 days or slight pain for 1 2 days. Restricted activity may be advised for 1 2 days. Abstinence is advised for 2 weeks. Patient is advised for follow-up ultrasound after 1 2 weeks with the report. Failure to obtain sample can happen in 1%. Mosaicism may occur in 1 2% in CVS and 0.0.2% in amniocentesis.

2.6 What are the complications?
Foetal loss rate of CVS has been reported to be 0.7% within 2weeks. Total pregnancy loss rate after trans-abdominal CVS is comparable to amniocentesis, trans-cervical CVS is slightly higher.

3. Cordocentesis
It is the process of obtaining blood from the umbilical cord of the foetus. This test is technically more difficult and the complication rates are also higher.

3.1 What are the indications for cordocentesis?
Cordocentesis is performed for diagnosis of:
- Chromosomal abnormalities
- Single gene defects
- Anaemia, thrombocytopenia
- Infection

3.2 How is cordocentesis done?
Placenta and cord insertion are localised. Using USG guided freehand technique, umbilical vein is punctured and sample taken for foetal blood sample.

3.3 What are the complications?
- Foetal loss rate of 0.2 9.9% has been reported.
- Bradycardia may result from the handling of the cord
- PPROM/PTL
- Cord haematoma
- Chorioamnionitis
- Umbilical thrombosis
- Foetal-maternal haemorrhage.

Therapeutic Procedures

4. Intrauterine Transfusion (IUT)

4.1 What are the indications for IUT
The primary indication of intrauterine transfusion (IUT) is foetal anaemia. It can be due to various causes such as
- Rh isoimmunisation (most common),
- Sensitization to other blood group antigens (Kell, Duffy),
- Parvovirus B19 infection,
- Foetal or placental tumours,
- Foetal arteriovenous malformations,
- TTTS or foeto-maternal haemorrhage.

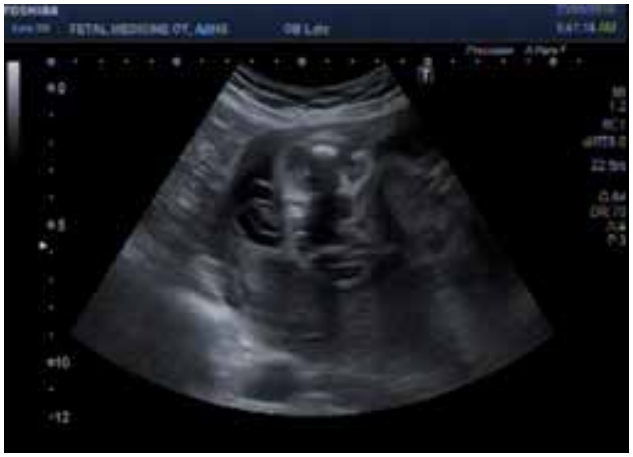
Middle Cerebral Artery-Peak Systolic Velocity>1.5 MOM indicates that the pregnancy is at risk of significant foetal anaemia and mother is offered IUT.

4.2 What is the pre-procedure counselling?
Patient is counselled regarding the benefit of IUT and risks associated such as preterm labour, PPROM, chorioamnionitis, cord accidents (cord hematoma, haemorrhage from the cannulation site, umbilical artery spasm) and requirement of emergency caesarean section if a viable foetus develops severe bradycardia.

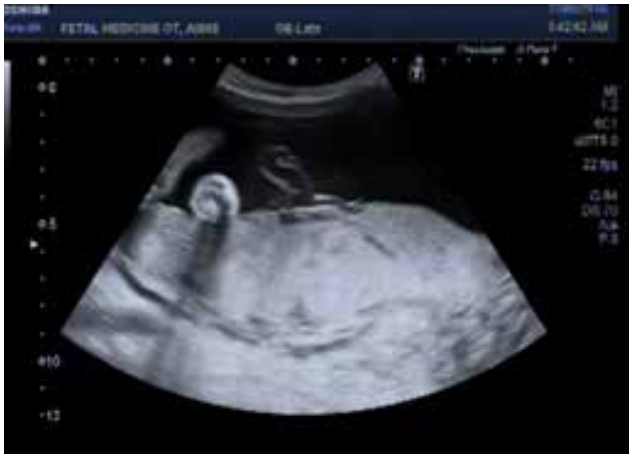
4.3 How is the procedure performed?
- Steroid cover (in viable foetus) is given.
- O negative, leucocyte depleted, irradiated blood with haematocrit of about 80% and cross matched with maternal blood is used.
- The volume of blood to be transfused is calculated using the formula – Vfetoplacental× (Haematocritfinal -Haematocritinitial)/Haematocrittransfused blood. Vfetoplacentalis calculated by Mandelbrot formula wherein fetoplacental volume (ml) = 1.046 + foetal weight (g) X 0.14. If the foetus is hydropic, about half of the calculated volume is transfused in one setting.
- A single dose injectable antibiotic and intramuscular progesterone is given preoperatively.
- Ultrasound is done to assess the placenta and cord insertion site. Mapping of needle path is done to enter at cord insertion (preferably) or free loop if

insertion site IUT is not feasible.

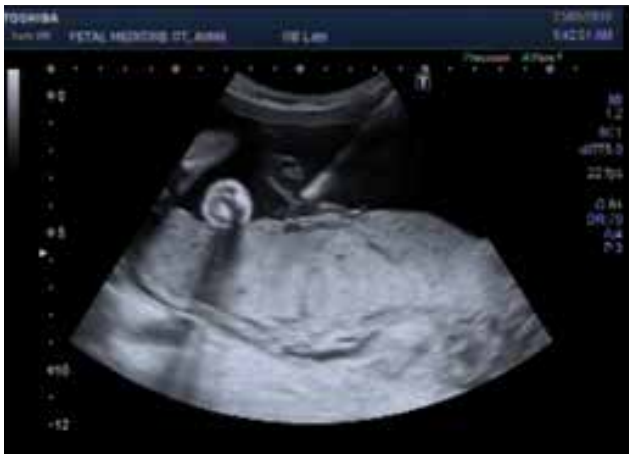
- Foetal paralysis is obtained using injection pancuronium or vecuronium intramuscularly or into the umbilical vein depending upon the position of placenta and accessibility of cord.
- A long 20G needle is introduced under continuous ultrasound guidance using free hand technique.



Giving pancuronium into fetal thigh



Localising the cord insertion



Needle puncturing the cord

Blood being transfused

- After this, blood for post transfusion haematocrit is aspirated after discarding the first 2 3 mL.
- Foetal heart is monitored on CTG for about one hour after the procedure.
- Following first IUT, the rate of fall in haematocrit is estimated to be 1% per day.
- After 34 weeks, the risk of procedure outweighs the risk of delivery and a preterm delivery may be indicated if needed.

With the use of IUTs, perinatal mortality in severe cases has decreased to less than 10%.

5. Foetal Reduction By Intracardiac KCL

5.1 What are the indications for foetal reduction by intracardiac KCL

Intracardiac KCL instillation is used in multichorionic placentation in cases of multi-foetal pregnancy reduction (MFPR) to reduce a higher order multiple pregnancy to twins or singleton and selective feticide in multiple pregnancy affected with a foetal anomaly.

5.2 What is the pre-procedure counselling?

After appropriate counselling of the couple, a written informed consent explaining a 5 6% risk of complete pregnancy loss is taken.

5.3 What is the ideal time for performing the procedure?

It is usually performed after 11 weeks as by then most spontaneous losses would have occurred and ultrasound can be done to screen for foetal aneuploidies (NT, NB, DV Doppler, TR) and a few structural anomalies can be detected.

5.4 Which foetus should be reduced?

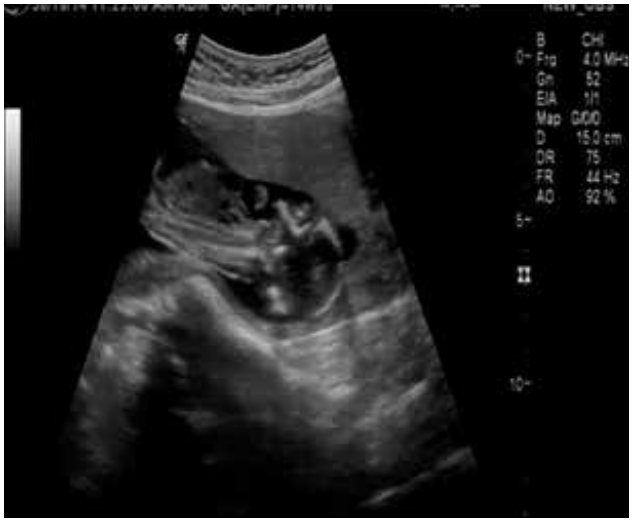
Most easily accessible foetus (usually closest to anterior uterine wall or fundus) or one with the smallest CRL, highest NT or any marker for aneuploidy is selected for termination. Wherever possible, the foetus closest to the cervix is avoided because of a hypothetical

increased risk of infection.

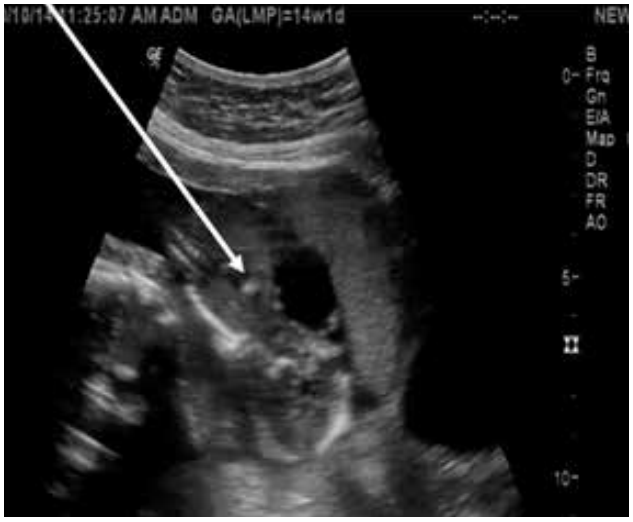
5.4 How is the procedure done?

- A single dose of injectable antibiotic and intramuscular progesterone injection can be given before the procedure.
- Amniotic cavity of selected foetus is entered transabdominally under ultrasound guidance using a 22G needle avoiding a transplacental entry if possible.
- After entering foetal heart, foetal blood is aspirated to confirm correct needle placement and 1 2 ml KCL (2 mEq/mL) is injected.
- Cardiac asystole is obtained as KCL enters the coronary circulation. Further dose may be required if asystole does not occur after initial injection.
- Needle is withdrawn only after asystole is observed for one minute.

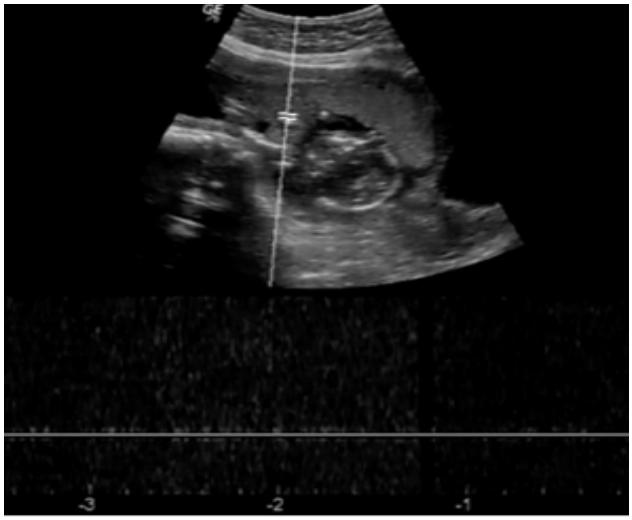
A check scan preferably on the following day to avoid missing a failed attempt is recommended.
Complications can be PPROM, accidental entry into non-targeted sac or complete pregnancy loss.



Localising the fetus



Needle in fetal heart



Documenting Asystole

Intracardiac KCL is avoided in monochorionic placentation as it can enter into the co-twin's circulation due to placental vascular anastomosis and causing foetal death.

6. Foetal Reduction in monochorionic twins

6.1 What are the indications for Selective Foetal Reduction?

Selective foetal reduction in monochorionic pregnancy is indicated in cases of
1) Foetal anomaly
2) TRAP sequence
3) TTTS when laser photocoagulation of placental anastomotic vessels is not available or not possible.
Several techniques are available out of which ultrasound guided bipolar cord coagulation and ablation of intra-foetal vessels by laser or radiofrequency are being used more frequently because of their less invasive nature compared to endoscopic procedures.

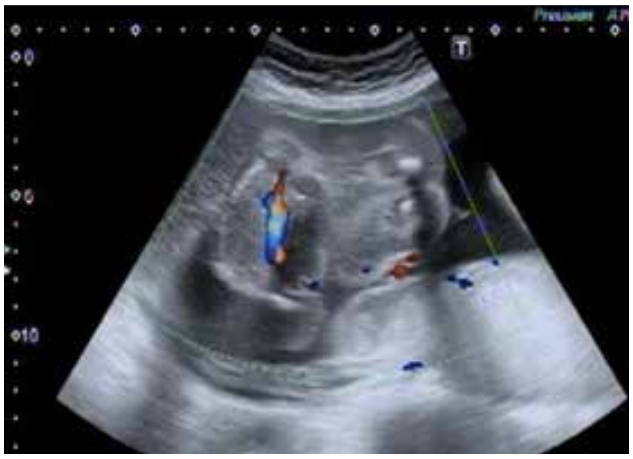
6.2 How is Radiofrequency ablation done?

Radiofrequency ablation of intra-foetal vessels is the most commonly used method in our centre.
In RFA, changes in alternating current at very high frequencies (200 1200 kHz) are generated between the tines of a needle. As the current alternates in various directions between the tines, tissue ions attempt to align with the electrical field and become agitated, generating very high temperatures which lead to tissue coagulation and necrosis.

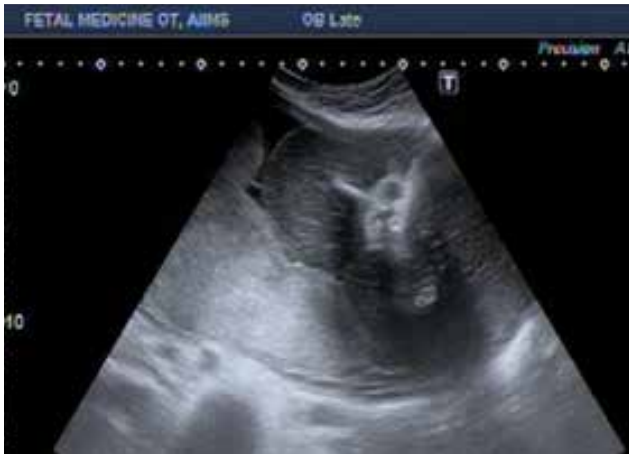
- After informed consent, procedure is done under local anaesthesia by trained foetal medicine specialists.
- Injectable antibiotic and progesterone are given preoperatively.
- Under continuous ultrasound guidance, a 17G RFA needle is introduced transabdominally into the foetal abdomen at the level of umbilical cord insertion while avoiding the placenta wherever possible.
- Radiofrequency energy is applied by the generator

until an average temperature of 100°C is achieved in all three-times for 3 minutes.

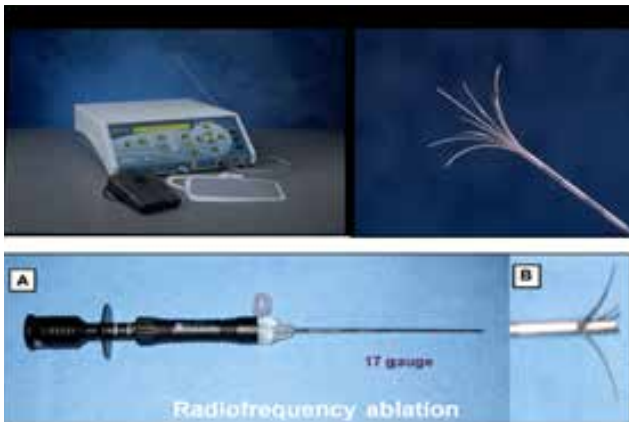
- It can be repeated after a cooling period of 1 minute till cessation of blood flow is demonstrated in the umbilical cord.
- Asystole in the targeted foetus and normal cardiac activity in the other foetus is documented by a repeat ultrasound on the same or next day.
- Post procedure MRI of the surviving foetus is done after three weeks to look for any transfusion related injury that might have occurred.



MCDA with TRAP sequence in one twin



RFA needle at the interstial portion



RFA Equipment

A 2009 review concerning 345 cases of selective feticide in monochorionic pregnancies by Rossi et al. found that cotwin survival rates were highest with RFA (86%) followed by 82% after bipolar cord coagulation, 72% after laser cord coagulation and 70% after cord ligation.

7. Laser for TTTS

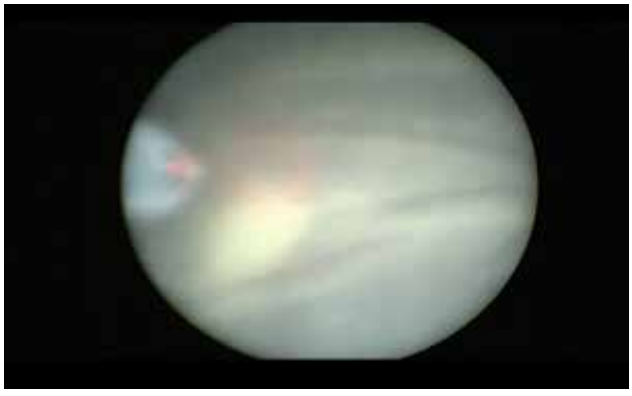
TTTS complicates about 8 10% of MCDA pregnancies. Laser in TTTS has emerged as the intervention of choice as it is the only method which targets the underlying pathology. It involves photocoagulation of vascular anastomoses which cross from one side of placenta to the other so that placenta can be functionally separated into two regions, each supplying one of the twins (dichorionization of monochorionic placenta).

7.1 How is Laser photocoagulation performed?

- The procedure can be done under regional or local anaesthesia.
- A trocar is inserted percutaneously under ultrasound guidance into the recipient sac.

Equipment for Laser

Laser fibre being inserted into the fetoscope



Vessel Coagulation by laser

- Usually, a 0° fetoscope is used for posterior placenta while a 30° fetoscope is used for anterior placenta.
- Photocoagulation is carried out using laser energy while adjusting the delivery watts as required to achieve vessel coagulation. This can be achieved by selective laser ablation of placental anastomoses where all visible inter-twin anastomoses and vessels with uncertain course are coagulated if they cross the equator.
- At the end of the procedure, amnioreduction is performed in the recipient sac.

Complications with laser include PPROM, preterm delivery, abruption, chorioamnionitis, amniotic fluid leakage into maternal peritoneal cavity and single or double foetal loss.

In experienced hands, overall survival rates of 50 70% have been observed with laser treatment for TTTS.

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MULTIPLE PREGNANCY ASSESSMENT

Dr. Vivek Krishnan

Multi-foetal gestations account for nearly 3% of all live births around the world.[1] This incidence is rising, mainly due to delayed childbirth and advanced maternal age at conception and the resultant widespread use of assisted reproduction techniques.[2]

The Hellin's law, which used to describe the incidence of multi-foetal gestations as $1/89n^{-1}$ (where 'n' denotes the order of pregnancy), relates to the incidence of natural multi-foetal gestations and is therefore not applicable, in modern times, to the advent of assisted reproduction techniques. The twin birth rate increased by just under 70% between 1980 (19 per 1000 live births) and 2006 (32 per 1000 live births)[3].

Even though the incidence of multi-fetal gestations is still low vis-a-vis singleton pregnancies, the perinatal morbidity and mortality associated with multi-foetal gestations is disproportionately high.[4-6] There is a higher risk of maternal medical complications like pre-eclampsia and anaemia and still birth. The rates of spontaneous preterm birth or iatrogenic preterm delivery due to maternal or foetal complications (especially with monochorionic twins) contributing to the increased risk of neonatal mortality and long term morbidity is also significantly higher.

Ultrasound plays a crucial role in the assessment and management of twin pregnancies. It is a very important tool in:

1. Dating of the pregnancy
2. Determining chorionicity and amnionicity
3. Labelling the foetuses
4. Screening for aneuploidies and structural anomalies
5. Routine monitoring of twin pregnancy with ultrasound
6. Identifying and managing complications unique to monochorionic twins
7. Foetal reduction/selective termination
8. Screening for preterm birth
9. Screening, diagnosis and management of foetal growth restriction.
10. Managing the co-twin after single foetal demise

1. Dating a multifetal pregnancy

Twin pregnancies should ideally be dated when the crown–rump length (CRL) measurement is between 45 and 84 mm (i.e., 11 + 0 to 13 + 6weeks of gestation). In pregnancies conceived spontaneously, the larger of the CRLs should be used to estimate gestational age. If the woman presents after 14 weeks' gestation, the larger head circumference should be used. Twin pregnancies conceived via *in-vitro* fertilization should be dated using the oocyte retrieval date or the embryonic age from fertilization[7].

2. Determining chorionicity/amnionicity

The determination of chorionicity is of paramount importance as it is the single most important determinant of the outcome of a twin pregnancy. Monochorionic twins have certain unique complications over and above those of twin pregnancy, in general. These are predominantly due to the vascular connections between the two circulations. Besides, chorionicity is also important in prenatal diagnosis, selective feticide, single foetal demise and in multi-foetal pregnancy reduction.

The best time to determine chorionicity by USG is the first trimester of pregnancy, i.e., before 14 weeks.[8] The typical findings become more difficult to elicit and less reliable as pregnancy advances. Sepulveda et al. in 1997 showed in their study on 154 twin pregnancies (101 dichorionic and 53 monochorionic) that while the lambda sign was demonstrable in 100% of dichorionic twins at 10 14 weeks, the corresponding number fell to 98% at 16 weeks and 86% at 20 weeks. In other words, the lambda sign may not be demonstrable in 14% of dichorionic twins at the targeted anomaly scan.

The first trimester ultrasound can assign chorionicity with a sensitivity and specificity for 100% and 99.8%, respectively.[9] The membrane thickness at the site of insertion of the amniotic membrane into the placenta, identifying the T-sign or lambda sign (Fig. 1), and the number of placental masses visualsed using ultrasound are the criteria commonly described to assign chorionicity. It is important to examine the dividing membrane carefully; in dichorionic diamniotic

twin pregnancy, the twins are separated by a thick layer of fused chorionic membranes with two thin amniotic layers, one on each side, giving the appearance of a 'full lambda', compared with only two thin amniotic layers separating the two foetuses in monochorionic diamniotic (MCDA) twin pregnancy (the T-sign). The reliability of the number of placental masses is questionable, as dichorionic placentae are commonly adjacent to each other, appearing as a single mass, and 3% of monochorionic twin pregnancies have two placental masses on ultrasound, the presence of which does not preclude the presence of vascular anastomoses.[10]

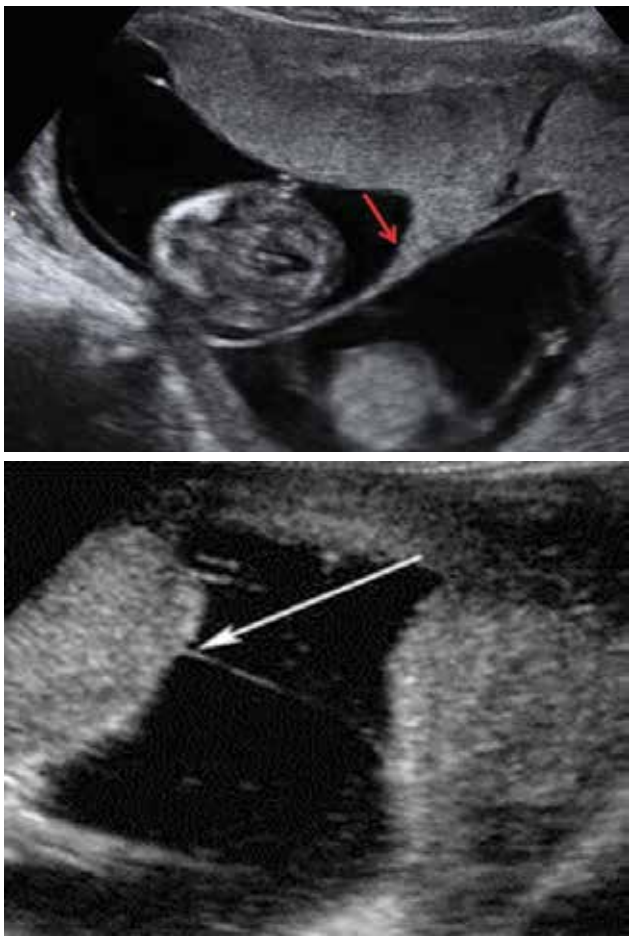


Fig. 1: The lambda and T signs

At the time at which chorionicity is determined, amnionicity (i.e., whether or not the twins share the same amniotic sac) should be determined and documented. All MCMA twin pregnancies should be referred to a tertiary centre with expertise in their management.[2]

3. Labelling of foetuses in a multi-foetal gestation

Labelling/mapping/cataloguing of foetuses refers to assigning an address/name to each of the fetuses using information of ultrasound such as proximity of the gestational sacs to the maternal cervix (with the foetus in the sac closest to the cervix being designated as foetus A or 1). In case of twins, the relative orientation of the foetuses to each other (defined as either lateral (left/right) or vertical (top/bottom) may also be used.11 Correct labelling of twins is needed for consistency in applying and interpreting longitudinal scan and prenatal screening/diagnostic results.

Fig. 2. Labelling of twins: The one on the left shows a longitudinal membrane and on the right a transverse membrane

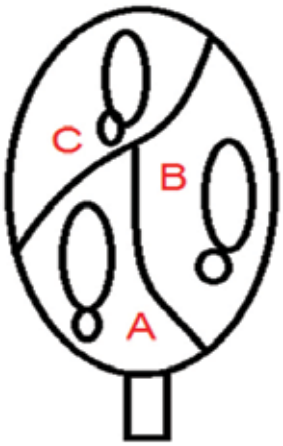


Fig. 3. Labelling of higher order multiples: The foetuses are labelled anti-clockwise

4. Screening for aneuploidies and structural anomalies

In twin pregnancy, screening for trisomy 21 can be performed in the first trimester using the combined test, which includes maternal age, NT measurement and serum ß-hCG and PAPP-A levels. In higher order multiples, the combination of maternal age and the NT recorded between 11 + 0 and 13 + 6weeks of gestation should be used, as biochemical screening becomes unreliable.2 In the case of a vanished twin, if there still is a measurable foetal pole, ß-hCG and PAPP-A measurements are biased and NT alone should be used for risk estimation. The risk of trisomy 21 in monochorionic twin pregnancy is calculated per pregnancy, based on the average risk

of both foetuses (because the twins share the same karyotype), whereas in dichorionic twin pregnancy the risk is calculated per foetus (as around 90% are dizygotic, having different karyotypes).The detection rate (DR) of non-invasive prenatal testing for trisomy 21 may be lower in twins than in singletons, but data is still limited.[7]

Invasive testing for chromosomal or genetic analysis of twins should be carried out by a foetal medicine expert. CVS is preferred in dichorionic twin pregnancy because it can be performed earlier than an amniocentesis. It is important to carefully map the position of the twins within the uterus. During amniocentesisin monochorionic twins, if monochorionicity has been confirmed before 14 weeks' gestation and the foetuses appear concordant for growth and anatomy, it is acceptable to sample only one amniotic sac. Otherwise, both amniotic sacs should be sampled because of the possibility of rare discordant chromosomal anomalies in monochorionic pregnancy[7].

At the first-trimester scan (between 11 + 0 and 13 + 6 weeks' gestation), the foetuses should be assessed for the presence of any major anomalies. Routine second-trimester ultrasound screening for anomalies in twins should be performed by an experienced operator at around 20 (18–22) weeks' gestation. The risk of foetal anomaly is greater in twin compared with singleton pregnancy.[14] In around 1 in 25 dichorionic, 1 in 15 MCDA and 1 in 6 monoamniotic twin pregnancies, there is a major congenital anomaly that typically affects only one twin.[15,16]

5. Routine monitoring of twin pregnancy with ultrasound

Women with an uncomplicated dichorionic twin pregnancy should have a first-trimester scan, a detailed second-trimester scan, and scans every 4 weeks thereafter. Complicated dichorionic twins should be scanned more frequently, depending on the condition and its severity. Uncomplicated monochorionic twins should have a first-trimester scan and be scanned every 2 weeks after 16 weeks in order to detect TTTS and TAPS in a timely manner. Complicated monochorionic twins should be scanned more frequently, depending on the condition and its severity.[7]

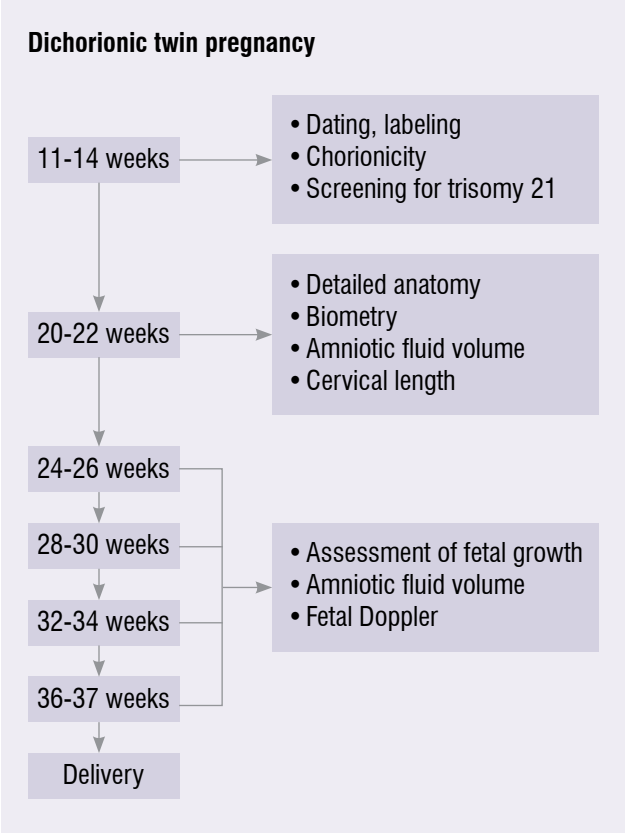


Fig. 4: Ultrasound monitoring pathway in uncomplicated dichorionic twin pregnancy[7]

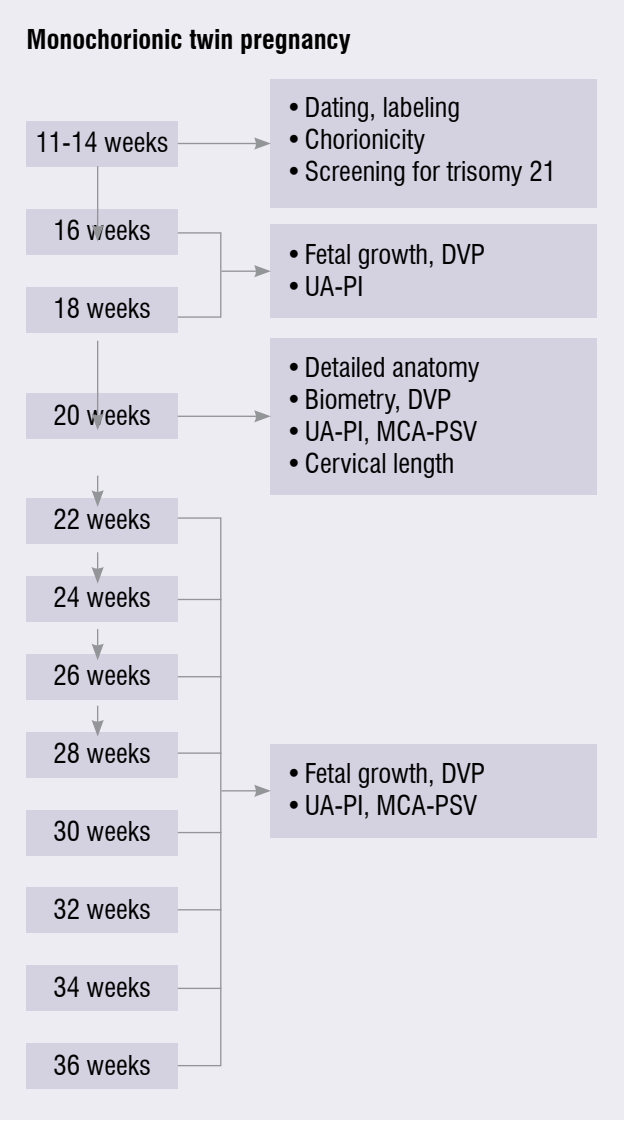


Fig. 5: Ultrasound monitoring pathway in uncomplicated monochorionic twin pregnancy[7]

6. Identification and management of complications unique to monochorionic twins

Complications which occur only in monochorionic twin pregnancy include TTTS, TAPS, TRAP sequence, monoamniotic pregnancy and conjoined twinning. In nearly all monochorionic twins, the placenta contains vascularanastomoses connecting the two foetal circulations. It is the angioarchitecture of these vascular anastomoses that determines the risk profile. Monochorionic twins are at risk of developing TTTS/ TAPS when there is unequal hemodynamic and amniotic fluid balance.[17-20]

In TTTS, there is at least one deep A-V anastomoses with unidirectional flow with or without superficial anastomoses. If superficial anastomoses are present, especially the superficial A-A anastomoses seen in 75% of MC pregnancies, this unidirectional flow is countered to some extent and thereby the risk of developing TTTS is much lesser (15% as opposed to 61% if counter directional flow is absent in the presence of a deep A-V anastomosis). Furthermore, even if TTTS does develop despite the counter, it will be of much less severity. TTTS occurs in 15 25% of MC twins. Severe/clinically significant TTTS occurs in 1% of MC.

In TRAP sequence, an acute difference in arterial pressures between the two twins for some reason, early in the first trimester, disturbs the vascular balance, the bi-directional flow gets abolished and there develops uni-directional flow, in the reverse direction.

Donor-hypo perfusion	Recipient-hyper perfusion
Hypovolemia	Hypervolemia
Anaemia	Polycythemia
↓ RBF; so oliguria/anuria;	↑ RBF; so polyuria
Oligamnios (due to oliguria, RAA activation 2 to hypovolemia)	Polyhydramnios (due to polyuria, ANP secretion secondary to hypervolemia)
Renal failure may occur in serve cases	CCF, HOCM, hydrops in serve cases
IUGR	Hyperbilirubinemia, hypertension
Neurological damage (ischemic)	Neurological damage (ischemic)

Table 1: Summary of changes that occur in the donor and the recipient in TTTS

TAPS or the twin-anaemia-polycythemia sequence is also another form of chronic foeto-foetal transfusion in MC twins, distinct from TTTS. TAPS is characterized by large inter-twin haemoglobin differences in the absence of amniotic fluid discordances. TAPS may occur spontaneously in a minority of monochorionic twins or in TTTS cases after laser treatment. For the development of both TTTS and TAPS, the abnormal anastomoses are the essential anatomical substrate.

The median age at diagnosis of TTTS is 21 29 weeks. The following are certain USS markers that help.

1. A MC gestation invariably has to be the first predictor (diagnosed <10 weeks)
2. Discordance in NT at the 11-13^{+6} weeks scan between the two twins
3. Folding of inter-twin membrane (15-17 weeks)
4. Poor growth of one twin on serial USS
5. Absence of superficial AA anastomosis in Colour Doppler from 14 weeks onwards.

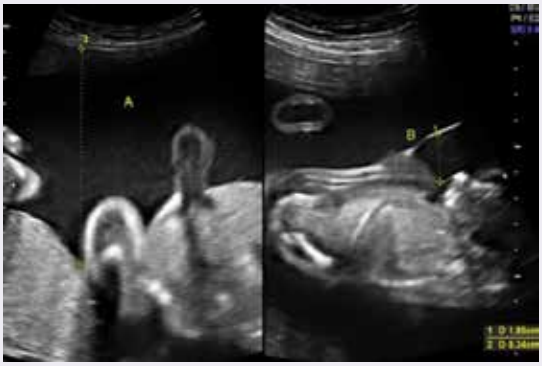
Donor-hypo perfusion	Recipient-hyper perfusion
Oligamnios (SDP <2 cm)	Polyhydramnios (SDP >8 cm)
Non-visible bladder	Over-distended bladder
IUGR	Visceromegaly
–	Cardiac enlargement
'Stuck-twin' appearance (No change in position in different views/planes)	Hydrops (in severe cases)
Abnormal Umb. Artery Doppler - Reduced/absent end diastolic flow	Abnormal venous Dopplers – Reduced or absent flow in Ductus venosus

Table 2: Summary of USS findings in the donor and the recipient in TTTS

Once identified, TTTS is typically staged by the Quintero staging system (Quintero and colleagues, 1999). These are defined as follows:

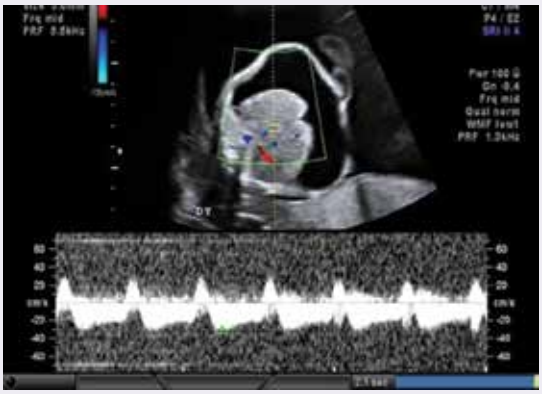
- Stage I: Discordant amniotic fluid volumes as described above, but urine still visible sonographically within the donor twin's bladder; 40% mortality risk.
- Stage II: Criteria of stage I, but urine is not visible within the donor's bladder.
- Stage III: Criteria of stage II and critically abnormal Doppler studies of the umbilical artery, ductus venosus or umbilical vein.
- Stage IV:Ascites or frank hydrops in either twin; (60% mortality risk).
- Stage V: Demise of either foetus.

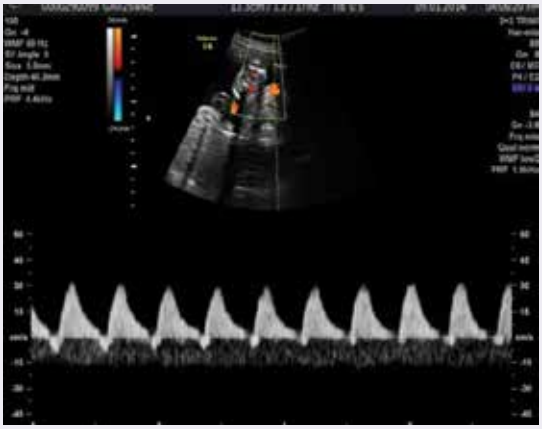
In addition to these criteria, there is now evidence that the cardiac function of the recipient twin correlates with foetal outcome. Thus, many also assess cardiovascular function of TTTS twins with echocardiography. Cardiac function is usually measured by the CHOP score.[21]

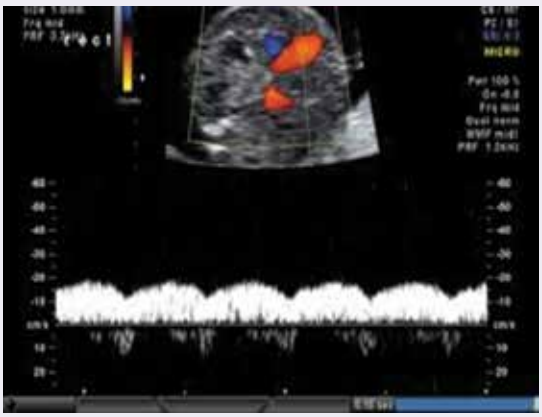


Stage I – Oligo-poly

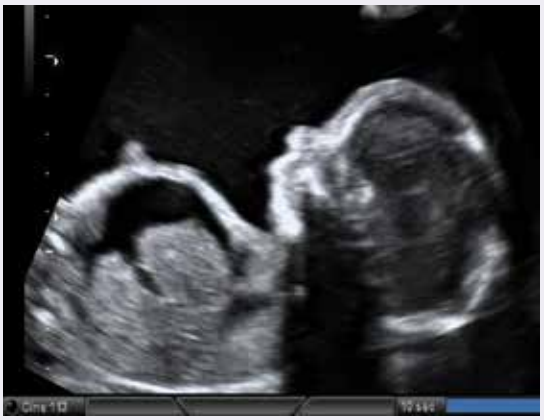
Stage II – Bladder discordance



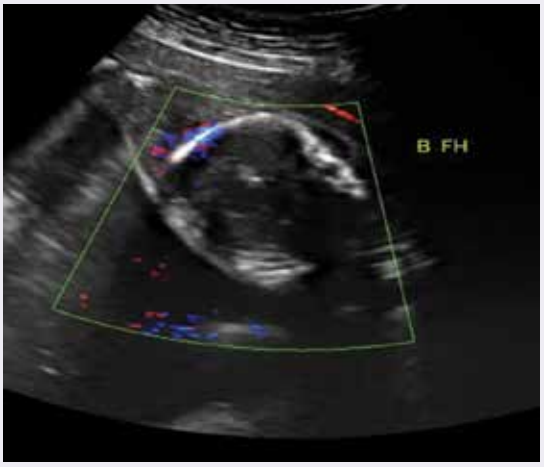




Stage III – Critically abnormal Dopplers (AEDF/REDF in the umbilical artery; reverse flow in the DV; pulsatile flow in the umbilical vein).



Stage IV – Hydrops



Stage V - IUD

Fig. 6. Quintero stages of TTTS

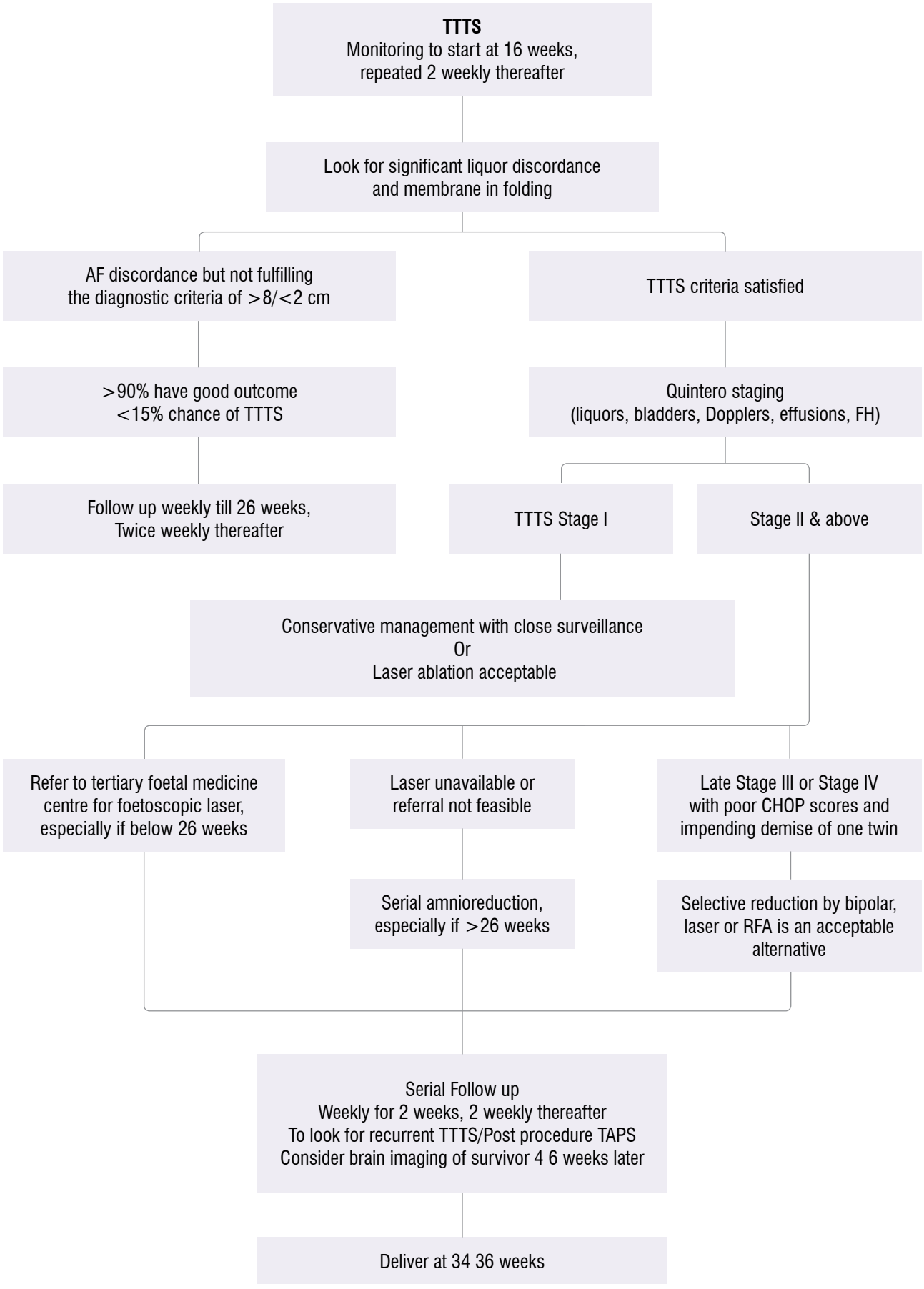


Fig. 7. Management algorithm-TTTS

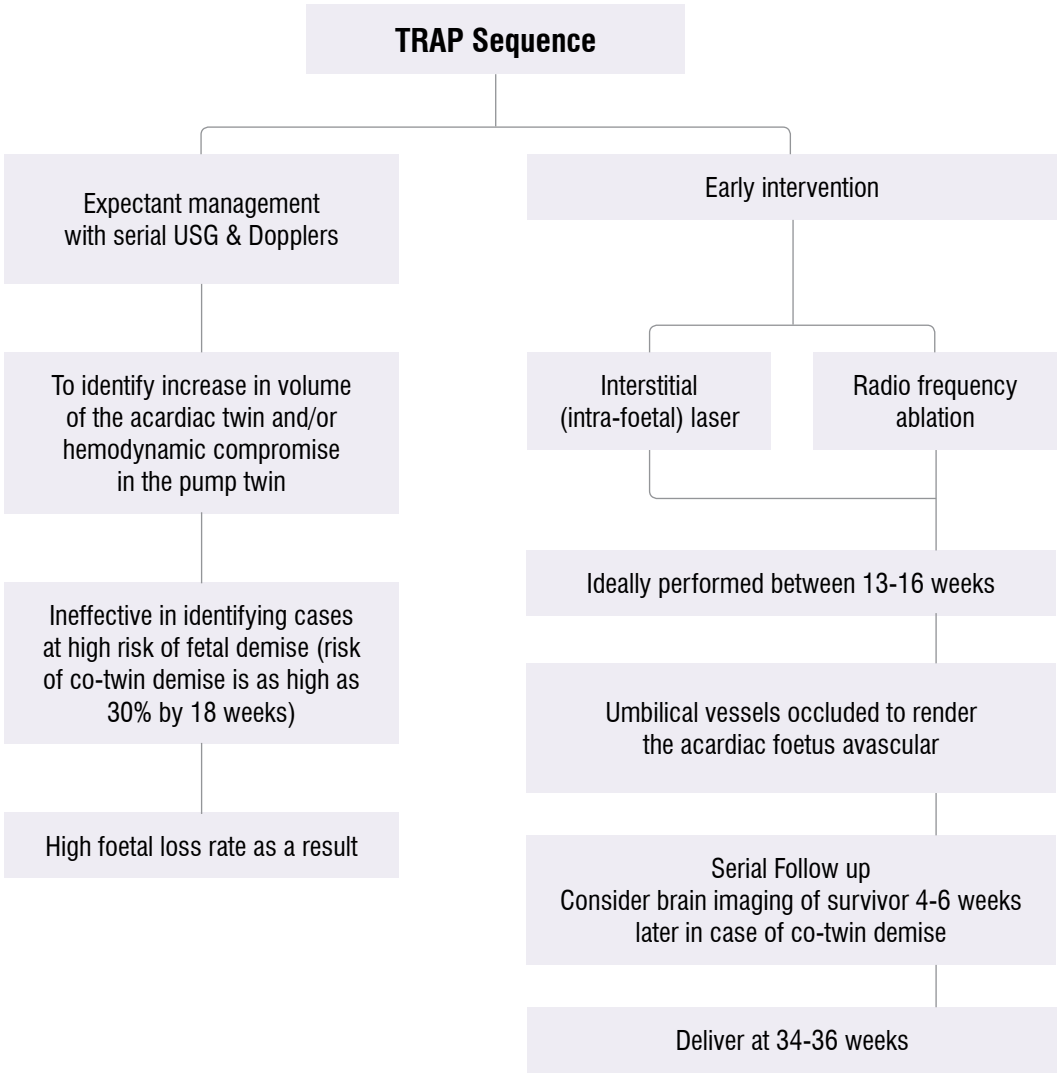


Fig. 8. Management algorithm-TRAP sequence

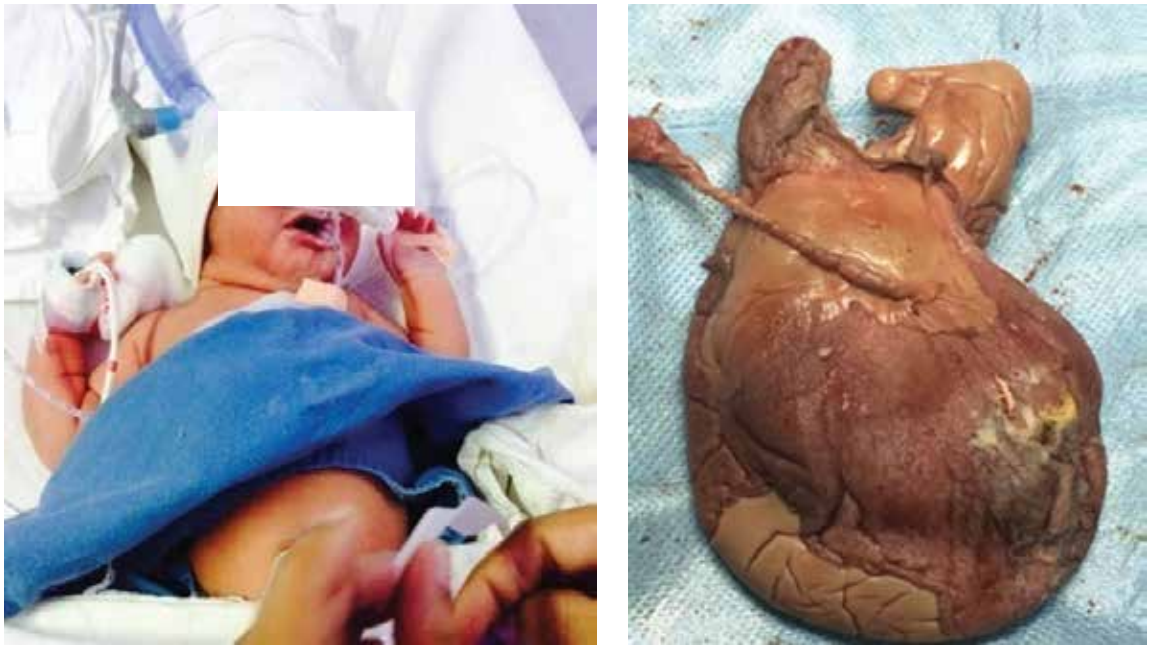


Fig.9. The acardiac mass that was treated with laser (in this case at 25 weeks due to a late referral) along with its healthy co-twin after birth

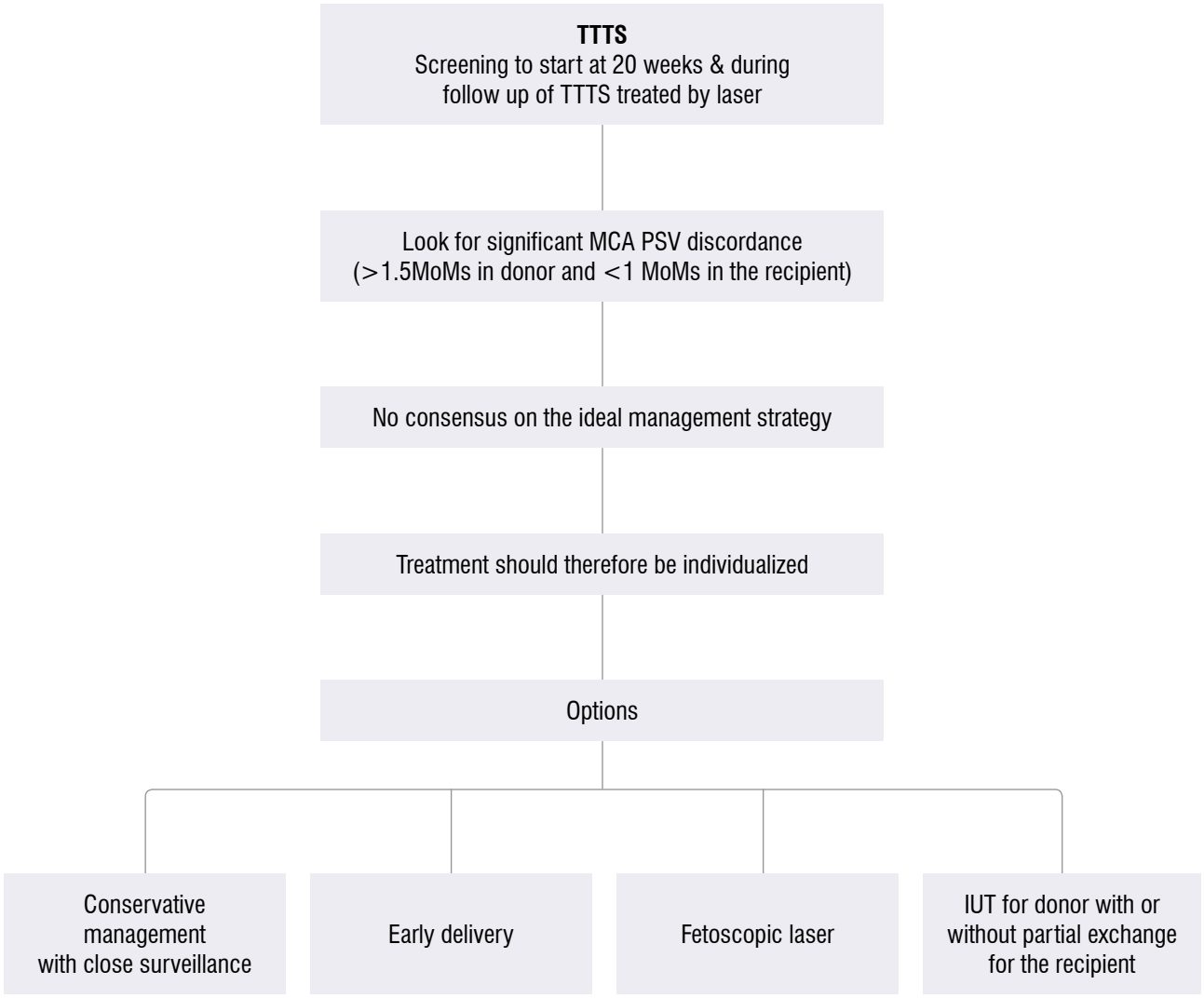


Fig. 10. Management algorithm-TAPS

Monoamniotic twins

Approximately 1% of monozygotic twins are monoamniotic (which makes it a rare entity occurring +1 in every 12500 births).They are the type of twins with the worst obstetric outcome with a perinatal mortality rate as high as 17%. This associated high foetal death rate may result from cord entanglement, congenital anomaly, preterm birth, or twin-twin transfusion syndrome, which is described subsequently. Umbilical cord intertwining, a common cause of death, is estimated to complicate at least half of cases. Once diagnosed, management of monoamniotic twins is somewhat problematic due to the unpredictability of foetal death resulting from cord entanglement and to the lack of an effective means of monitoring for it. Based on current evidence, women with monoamniotic twins are managed with 1 hour of daily foetal heart rate monitoring, either as outpatients or as inpatients, beginning at 26 28 weeks. With initial testing, a course of betamethasone is given to promote pulmonary maturation. If foetal testing remains reassuring, caesarean delivery is performed at 34 36 weeks.

Conjoined twins

They are the rarest forms of twins with an average worldwide incidence of 1 in 50,000 to 1 in 1,00,000.

USS features of conjoined twins
Bifid foetal pole in early pregnancy
Four-vessel umbilical cord
Heads always at the same level
Relative position always constant
Extended spines

Table 3: USS features of conjoined twins

A recent series of 14 cases from a single referral centre reported that, following diagnosis, 20% of parents opted for termination and 10% of foetuses

died *in utero*. Among those opting to continue the pregnancy, survival to discharge was only around 25%, and the majority of these had significant morbidity.

7. Foetal reduction/selective termination

Multi-foetal pregnancy reduction (MFPR) is a procedure used to reduce the number of foetuses in a multiple pregnancy, usually to two. It is known as "selective termination" when it involves a foetus with severe defects or one that is expected to die later in the pregnancy, which would threaten the life of the surviving foetus or foetuses. When a pregnancy involves three or more foetuses (high-order pregnancy) the risks of miscarriage, stillbirth, and lifelong disability increase with each additional foetus.

The goal of MFPR is to increase the chance of a successful, healthy pregnancy. Women electing to reduce a triplet pregnancy to twins have higher gestational ages at delivery, lower rates of gestational diabetes and preterm labour, and spent fewer days in hospital than non-reduced triplet pregnancies.[22] MFPR has also been shown to improve outcomes of patients with quadruplets or higher.[23]

MFPR is usually performed by ultrasound-guided intra-cardiac or intra-funicular injection of potassium chloride or lignocaine.7 Selective feticide in dichorionic twins which are discordant for anomaly is also performed similarly. In case of monochorionic twins/triplets selective feticide has to be by a cord occlusion, intra-foetal laser ablation or radiofrequency ablation (RFA). These procedures are preferably done in the first trimester as termination in the second trimester is associated with a higher risk of miscarriage and preterm birth(7% risk of loss of the entire pregnancy, and 14% risk of delivery before 32 weeks).[24]

8. Screening for preterm birth

Cervical length measurement is the preferred method of screening for preterm birth in twins; 25 mm is the cut-off most commonly used in the second trimester. A cervical length<25 mm at 18–24 weeks' gestation in twin pregnancy is a moderate predictor of preterm birth before 34 weeks, but not before 37 weeks[25,26]. In asymptomatic women, a cervical length ≤20 mm at 20–24 weeks was the most accurate predictor of preterm birth before 32 and before 34 weeks (pooled sensitivities, specificities and positive and negative likelihood ratios were 39% and 29%; 96% and 97%; 10.1 and 9.0; and 0.64 and 0.74, respectively). A cervical length ≤25mm at 20–24 weeks had a pooled positive likelihood ratio of 9.6 for the prediction of preterm birth before 28 weeks[25,26]. The predictive accuracy of cervical length for preterm birth was low in symptomatic women[25,26].

9. Screening, diagnosis and management of foetal growth restriction in twins

sFGR, conventionally, is defined as a condition in which one foetus has EFW<10th centile and the inter-twin EFW discordance is >25%. Nevertheless, a discordance cut-off of 20% seems acceptable to distinguish pregnancies at increased risk of adverse outcome.[7] EFW discordance is calculated by the following formula:

$$\%\ \text{discordance} = \frac{(\text{weight of larger twin} - \text{weight of smaller twin})}{(\text{weight of larger twin})}$$

Once a diagnosis has been made, a cause should be sought[27]. This search should include a detailed anomaly scan and screening for viral infections (cytomegalovirus, rubella and toxoplasmosis). Amniocentesis may also be required to exclude chromosomal abnormalities as a cause of FGR[27]. sFGR in monochorionic twin pregnancy occurs mainly due to unequal sharing of the placental mass and vasculature.[28]

Classification of sFGR in monochorionic twins depends on the pattern of end-diastolic velocity at umbilical artery Doppler. In Type I, the umbilical artery Doppler waveform has positive end-diastolic flow. In Type II, there is absent or reversed end-diastolic flow (AREDF). In Type III, there is a cyclical/intermittent pattern of AREDF. The survival rate in Type-I sFGR is greater than 90% (*in-utero* mortalityrates of up to 4%). Type-II sFGR is associated with a high risk of IUD of the growth-restricted twin and/or extreme preterm delivery with associated risk of neuro-developmental delay if the other twin survives (IUD of either twin in up to 29% and risk of neurological sequelae in upto 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 foetus, which is unpredictable (even in the cases in which ultrasound features have been stable). There is also a high (up to 20%) associated rate of neurological morbidity in the surviving larger twin.[29,30]

In dichorionic pregnancies, sFGR should be followed as in growth-restricted singletons. There is limited evidence to guide the management of monochorionic twins affected by sFGR. Options include: conservative management followed by early delivery; laser ablation; or cord occlusion of the growth-restricted twin (in order to protect the co-twin).[31]

In dichorionic twin pregnancy complicated by sFGR, foetal Doppler should be assessed approximately every 2 weeks, depending on the severity. In monochorionic twin pregnancy complicated by sFGR,

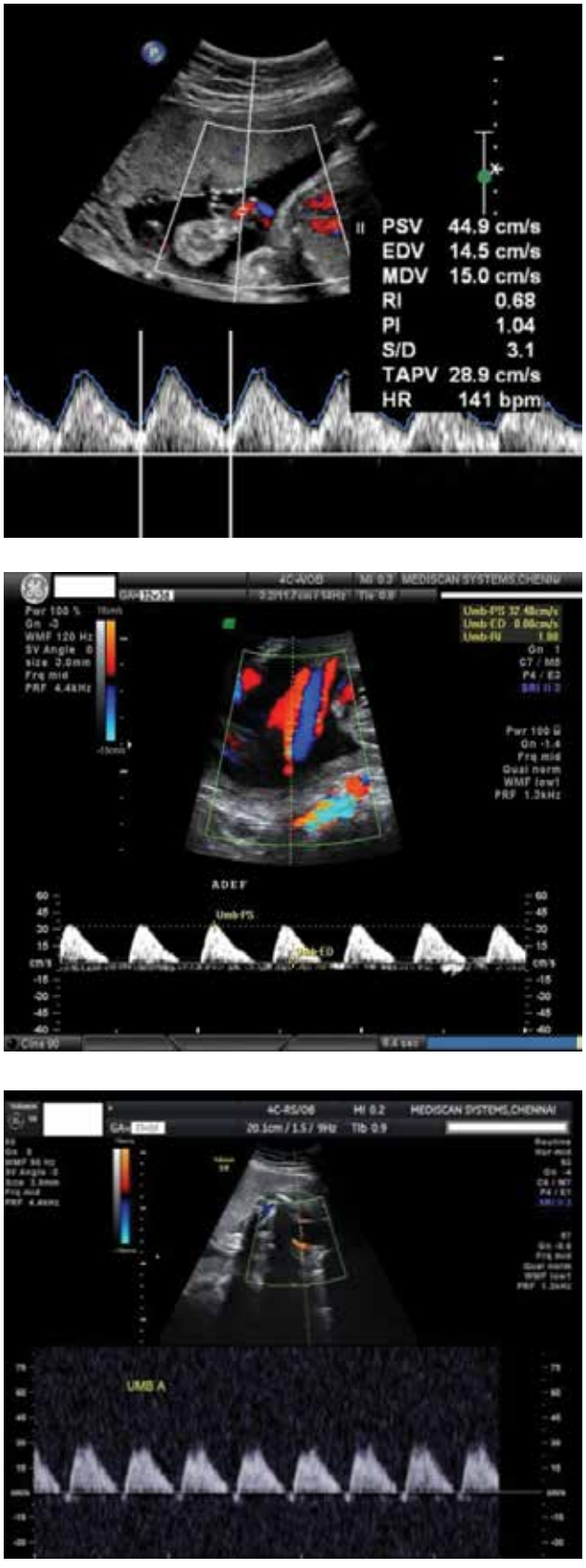


Fig. 11. Classification of selective foetal growth restriction in monochorionic twin pregnancy

fetal Doppler should be assessed, at least weekly. If there is a substantial risk of foetal demise of one co-twin before 26 weeks, selective termination may be considered.[7]

10. Managing the co-twin after single fetal demise

Single foetal demise is seen in upto 5% of twins and 17% of triplets. The cause often remains elusive. Some of the proposed aetiologies include placental insufficiency, abruption, anomalies, TTTS and cord entanglement (MA twins). If the loss is in the first trimester, it is usually inconsequential (vanishing twin). If the loss is in the second or third trimesters, then chorionicity determines the outcome and the management. Dichorionic twins usually pose no problems and can be managed conservatively. Morbidity in the monochorionic twin survivor is almost always due to vascular anastomoses, which first cause the demise of one twin followed by sudden hypotension in the other. Sudden exsanguination of the survivor due to this sudden fall in BP carries a 15% risk of death and 25% risk of neurologic handicap or ischemic multi organ injury like injury to the spleen, kidney, GIT, skin etc.

A recent meta-analysis[32] on the effects on the surviving twin of single foetal death comparing monochorionic to dichorionic twins, reported the rates of co-twin death, preterm delivery, and neurologic morbidity in the surviving foetus as follows:

	Monochorionic	Dichorionic
Co-twin death	15%	3%
Preterm delivery	68%	54%
Neurologic morbidity	26%	2%

Table 4: Effects of single foetal demise on co-twin

In addition, there is also a possibility that the survivor could become anaemic and might need an intra-uterine transfusion.

Management decisions should be based on the cause of death and the risk to the surviving foetus. Pregnancy management is based on the diagnosis and the status of both mother and surviving foetus.

If SFD occurs before 24 weeks of gestation it is worthwhile to consider delivering the mother, if it is a MC twin because the risks to the co-twin far exceeds the possible benefits of continuing the pregnancy. (Most cases of a single foetal death in twin pregnancy involve monochorionic placentation).

If beyond 24 weeks the pregnancy is best terminated

as soon as the survivor attains lung maturity and is capable of extra-uterine survival. Till then serial scans to look for growth, structure and foetal anaemia as well as close ante-partum foetal surveillance is mandatory (NST + BPP). It is pointless to deliver the survivor before attaining lung maturity as whatever hemodynamic changes and its consequences occur will do so immediately.

Later in gestation, the death of one of multiple foetuses could theoretically trigger coagulation defects in the mother. A baseline coagulation profile is therefore indicated.

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MULTI FOETAL PREGNANCY REDUCTION

Dr. Kanchan Mukherjee

Multi-foetal pregnancy reduction (MFPR) is defined as a first trimester or early second trimester procedure for reducing the total number of foetuses in a multi-foetal pregnancy by one or more. These pregnancies may occur through natural conception but fertility treatments have contributed significantly to the increased incidence in recent times. They are not very common but when multi-foetal pregnancies do occur, obstetrician–gynaecologists are obliged to offer the choice of continuing or reducing their multi-foetal pregnancies. Historically, the Dionne quintuplets of Ontariowere seen as a 'miracle' of sorts in the 1930s, but public sentiments were negative in the case of octuplets born in California in 2009. As a result, transfer of more than three embryos lost its popularity in most parts of the world.

History

MFPR started off as a way of trying to save such pregnancies from extreme risks. Aberg et al reported the first foetal reduction in twins back in 1978, with one suffering from Hurler's syndrome. They did the procedure with cardiac puncture and exsanguination by aspiration. In 1980, Beck et al reported a hysterotomy at 22 weeks to eliminate a twin with Down's syndrome and birth of the other twin at term. In the mid-1980s, needles were inserted transabdominally and maneuvered into the foetal thorax. Injection of potassium chloride (KCL) is the most predominant method but mechanical disruption of the foetus, air embolisation and electrocautery have also been discussed. Transcervical aspirations have also been tried but lost their favour in recent times due to higher risk of miscarriage. Currently, virtually all experienced operators perform the procedure by transabdominal insertion of the needle, under ultrasound guidance, into the thorax of the selected foetus.

Why do we need to reduce?

Multiple pregnancies present increased risks with higher mortality rates both for the mothers as well as for the foetuses. Maternal problems may include anaemia, hyperemesis, polyhydramnios, preeclampsia, postpartum haemorrhage, operative delivery etc. However, the biggest problem in a multiple pregnancy is premature delivery.

The recent literature on triplet pregnancies reports delivery to occur at a mean gestation of approximately 32–34 weeks. The typical duration of pregnancy in the case of twins is 36 weeks, in triplets 33 weeks and in quadruplets it is 29 weeks. The length of gestation may be expected to be prolonged to 37 weeks if reduced to a singleton and to 36 weeks if reduced to twins. This reflects the obvious benefits resulting from the use of MFPR.

Foetal problems may range from miscarriage, intrauterine growth restriction, malformations, cord prolapse, respiratory distress syndrome and other prematurity related problems. Decades of data have shown the incidence of prematurity and related sequelae directly correlated with the number of foetuses that have been reduced such that the more the initial number of foetuses, the more the risk of prematurity. (Fig 1).

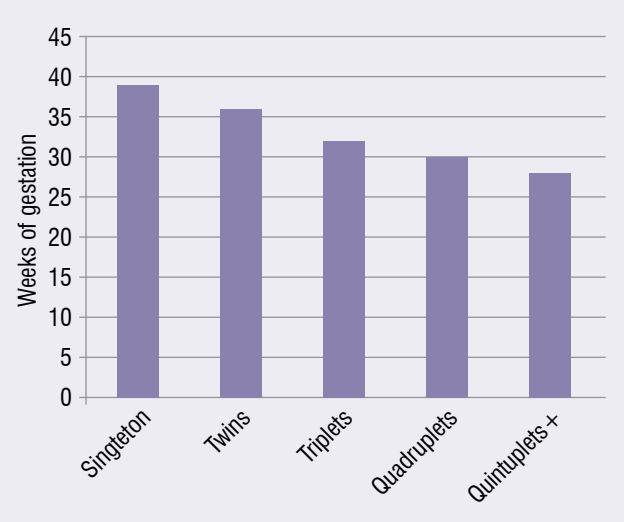

Fig 1: Length of gestation versus number of fetuses

In addition, parental, psychological and socioeconomic issues are also involved more with multiple births. Roughly, the medical costs to parents and society are quadrupled for twins and ten-fold higher for triplets.

There is enough data to suggest that triplets and quadruplets reduced to twins in late first trimester behave essentially in the same manner as if they

started as twins. Both pregnancy loss rate and very early prematurity can be reduced substantially by timely foetal reduction in experienced hands. The author of this article reviewed his own series of 125 sets of TCTA triplets. All cases were done between 10 and 12 weeks of gestation. The miscarriage rate in this study, defined as pregnancy loss before 24 completed weeks, was approximately 3%. The mean gestational age at delivery was 245 days and the mean birth weight of the babies was 2100 gms.

Procedure

The procedure is most commonly done through transabdominal approach with a 20G spinal needle under local anaesthetic. A small amount of 10% KCL is injected in to the foetal thorax and watched up to persistent cardiac asystole. A transcervical approach may be more dangerous due to higher chance of bleeding, chorioamnionitis, subchorionichaematoma and miscarriage.

In general, the procedure is mostly done between the 10th and 12th week, when nuchal translucency and basic foetal anatomy can be reliably assessed. More advanced gestation may be associated with higher rates of miscarriage.

There are mainly two types of foetal reductions. 'Selective' reduction involves dealing with a foetus with identified structural or chromosomal abnormalities. 'Nonselective' reduction is elimination of one or more foetuses for the benefit of others. The three most important criteria for selection are growth restriction, morphological malformation and chromosomal abnormalities, if available. When all foetuses look equally healthy, the most easily accessible foetus is reduced. Utmost attention must be paid to chorionicity.

In a set of uncomplicated trichorionictriamniotic triplets, any foetus may be reduced but for dichorionic triamniotics (DCTA) reducing the one with 'non-sharing' placenta would effectively leave a pair of monochorionic twins. These may subsequently develop problems like twin-twin transfusion syndrome (TTTS). Therefore it is advisable to reduce the "monochorionic pair" in a DCTA situation.

While this is not usually practiced in India, some centres in the world test the foetuses for aneuploidy through chorionic villus sampling before the reduction. This may assist patients in making their decisions about intervention.

Professional's role

A majority of the multi-foetal pregnancies ought to be considered iatrogenic in nature. This may lead to an implicit argument implying "you broke it, you fix it" mentality. Professionals must respect patients' autonomy regarding whether to continue or reduce a multi-foetal pregnancy. They should be allowed to weigh the relative importance of the medical, ethical, religious and socioeconomic factors and determine the best course of action for their situation. Nondirective counselling should be offered which should include discussion of the risks unique to multi-foetal pregnancy as well as the option to continue or reduce the pregnancy. In case of conflicting moral values, the patient must be referred to an appropriate physician.

Counselling should include the potential medical, psychological, economic and social risks specific to multi-foetal pregnancies and to the patient's individual health status. It is the counselling physician's ethical obligation to provide adequate information regarding

diagnosis, prognosis, and alternative choices including the option of "no intervention".

The ethical issues involved in multi-foetal pregnancy reduction are complex. There has also been a shift in the nature of the clinical dialogue between patients and physicians over time, the most obvious change being the questions of mortality to questions of morbidity. Intrinsic value of human life is of prime importance and should be respected by all concerned.

Optimal foetal number to be reduced

The numbers of quadruplets and quintuplets have declined dramatically but the triplets are still plentiful. Most of the TCTA triplets reduced to twins behave in the way similar to those who started off naturally as twins. The serious issue is no longer about whether it is appropriate to offer reduction to triplets but now the debate centres around the question about whether or not it is appropriate to offer foetal reduction routinely for twins. With the changing demographics when women are having pregnancies at more advanced ages, we may face such requests in increasing numbers in the coming days. On one side, this may be justified as a reproductive right but on the other hand, no ethical principle is absolute or immutable.

Legal Issues

MFPR will always be controversial in the context of the abortion debate. However, opinions have never followed the classic "pro-choice/pro-life" conflict. There has been extensive litigation regarding abortion and restrictions imposed on its use, but very little direct legal cases are found involving the legality of MFPR. One needs to keep the expected issues in mind, such as reduction of the wrong foetus in situations with anomalies, alleged failures of informed consent for procedure related risks and for various poor outcomes. It is debatable as to whether we should follow the same statutory paperwork like abortion, which is done to terminate a pregnancy. In contrast, a MFPR is intended to improve the outcome of a pregnancy.

Risk Reduction

Primary prevention strategies to limit multi-foetal pregnancies, especially higher-order multi-foetal pregnancies, can help to minimise the need for multi-foetal pregnancy reduction. All physicians who treat women for infertility should have these policies in place. The risk of higher-order multi-foetal pregnancy may be reduced by limiting the number of embryos transferred or by cancelling a gonadotrophin cycle when the ovarian response suggests a high risk for multi-foetal pregnancy. Single embryo transfer (SET) policy has been adopted by many centres outside India. This has many medical advantages but the economics of IVF in a country like India make it highly unlikely that SET will ever be popular as the pressure remains on the physicians as well as on the patients.

Conclusion

Multi-foetal pregnancies should be prevented whenever possible. When multi-foetal pregnancies do occur, working within the ethical framework will help clinicians counsel and guide patients as they make decisions regarding continuing with, or reducing, their multi-foetal pregnancies. In the hands of trained operators, MFPR is a safe procedure contributing to both maternal and foetal well-being. Any procedure involving death of a foetus is bound to be hotly debated despite the potential of greater good.

Acknowledgement:

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PLANNING FOETAL CARE IN ASSISTED REPRODUCTION

Dr. V. Padmaja

ART pregnancies represent 1.7-4.0% of all births in most developed countries and so form a special group for planning foetal care.

A "good perinatal outcome" among live births after ART is defined as the live birth of a singleton infant born at term (≥37 completed weeks of gestation) and at a normal birth weight (≥2,500 g).

To ensure that we achieve this good outcome, the first visit to the obstetrician should include the following steps:

Trans-vaginal ultrasound

It is the first step in foetal care following assisted reproductive techniques.

- It is used for early confirmation of pregnancy,
- dating of pregnancy,
- looking for multiple pregnancy,
- particularly high order multiple pregnancy,
- rule out heterotropic pregnancy.

Decidualisation of the endometrium is also looked into.

Other than that checking and documentation of co-morbities in the

Adnexa: like ovarian cysts/hyperstimulation of ovaries, uterus: for pathology like fibroids, adenomyosis should be done.

In evaluation of pregnancy

Note should be made of use of medications and hormones, like metformin in a patient without diabetes, bromocriptine, cabergoline, clomiphene citrate, follicle-stimulating hormone, gonadotropin-releasing hormone, human chorionic gonadotropin, human menopausal gonadotropin, letrozole, anastrozole, leuprolide,nafarelin acetate or goserelin acetate.

Previous surgeries: like myomectomy, septal resections, hysteroscopic adhesiolysis for intrauterine adhesions, and ashermans, Bariatric surgery, renal transplant.

Her immunisation to rubella should be confirmed.

Any other medical problems which have impact on foetal growth and development like obesity, hypertension, diabetes mellitus, dyslipidaemia, auto immune disorders, hypothyroidism, polycystic ovary syndrome (PCOS) should be duly noted.

Her LMP and EDD should be noted, Period of gestation according to dates should be written down and note whether the pregnancy is corresponding to dates whould be highlighted.

Prescription of folic acid, luteal phase support medications should be given.

Screening of the patient for gestational diabetes mellitus (GDM) following Diabetes in Pregnancy Study Group in India (DIPSI) guidelines should be done in first visit.

Plan for her pregnancy should be drawn up.

Every visit: should take note of her complaints, her weight gain, her clinical examination, progress of pregnancy and detailed prescription and advice should be given accordingly

The next pregnancy scan should be done between 11 13^{+6} weeks:
This scan is a detailed first trimester genetic scan with uterine artery Doppler which helps in identifying about 55% of significant abnormalities.

Prenatal non-invasive testing, biochemical markers: Compared to its use in spontaneous conceptions in pregnancy following assisted reproductive techniques NIPT is not very reliable due to high frequency of multiple pregnancy, vanishing twins, increased incidence of implantation bleeding,and choriodecidual hemorrhagic.

Reliability of ultrasonography and biophysical parameters is higher with invasive prenatal testing if confirmation is needed.

Next step is between 18-20 weeks, targeted anomaly scan with uterine artery Doppler and localisation of placenta.

In expert hands 88% of significant abnormalities will be identified.

Nearly all the perinatal complications including placenta previa (OR, 2.23, 95% CI 1.79–2.78), placental abruption (OR, 5.06, 95% CI 2.83–9.06), preterm premature rupture of membranes (pPROM) (OR, 3.05, 95% CI 2.48–3.74), placental adherence (OR, 2.37, 95% CI 1.90–2.95), postpartum haemorrhage (OR, 2.72, 95% CI 2.18–3.41), and polyhydramnios (OR, 1.79, 95% CI 1.26–2.53), are more likely to occur after ART in all multiplebirths, as well as in singletons.

High incidence of placental abnormalities in the IVF group may be related to inadequate orientation and or superficial implantation of theblastocyst due to intrauterine embryo transfer. Trophectodermal cells might be more sensitive to preimplantation epigenetic upset than inner cell mass.

Pregnancies after ART are 1.99 times more likely to develop gestational diabetes mellitus (GDM) (95% CI 1.69–2.36),
2.58-times more likely to have gestational hypertension (95% CI 2.11–3.15),
1.49-times more likely to develop preeclampsia (95% CI 1.12–1.98),
and 2.86-times more likely to develop intrahepatic cholestasis of pregnancy (ICP) (95% CI 2.39–3.42) compared with controls.

In singleton gestations, the incidence of GDM, gestational hypertension and ICP is still significantly higher than those of the controls.

Monitoring of growth

This process is done with customised growth charts once in 4 weeks. There is a need for vigilance particularly in multiple pregnancy to check discordant growth, discordant anomalies and discordant viabilities.

ART nulliparous singletons exhibit significantly increased rates of preterm labour (17.1%),
low birth weight (10.3%),
1-minute Apgar≤7 (3.8%) and 5-minute Apgar≤7 (0.7%) compared with spontaneously pregnant nulliparous singletons.

So pregnancies are associated with increased use of antenatal steroids.

There is a need to have protocols to deal with PTL: with inclusion of magnesium sulphate for neuroprotection. Along with provision for in utero transfer to higher centre with NICU facilities if necessary for pre-term delivery.

Screen for GDM every trimester: blood sample 2 hours after 75 g glucose

Inj boosterix in 30 weeks: which is vaccination for dipheria and acelluar pertussis along with tetanus toxoid.

Influenza vaccination at 26 weeks is ideal as it protects the mother against influenza which has increased morbidity and mortality in pregnancy. The passive immunisation conferred to the fetus also protects the newborn.

Monitoring in third trimester

Amniotic fluid index (AFI) and Doppler flow monitoring, along with NST monitoring from 34 weeks till delivery ensures that there is no in utero compromise, picks up early changes of compromise and helps plan delivery

Delivery principles follow obstetric indications.

Conclusion

ART births are strongly associated with poorer maternal and live-birth outcomes. Multiple pregnancies can partly explain this phenomenon.

However, ART nulliparous singletons still exhibit higher risks of pregnancy and perinatal complications compared with spontaneously pregnant nulliparous singletons.

Elective single embryo transfer should be strongly advocated to reduce the obstetrical risks of ART pregnancy.

Since singletons born after the use of ART do worse than those conceived spontaneously, it is suggested that ART process itself is also significantly related to pathologic pregnancy, especially abnormal placental development.

It is suggested that the following measures need to be taken: (1) strict control of indications for ART, (2) promoting SET, (3) improve the safety of manipulation in the ART process, (4) use of better embryo selection techniques, like embryoscope, proteomic and metabolomic studies, endometrial receptive array studies, (5) strengthen antenatal care of ART pregnancies.

Whether these adverse outcomes are attributed to couples subfertility or ART itself need to be investigated further.

Foetal care follows the golden principles of history taking, examination, coming to a diagnosis, being alert and screening for high risk situations, assessing the severity of the situation and planning termination of the pregnancy keeping in mind the final expected result that is a safe mother and a healthy baby.

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BE HAPPY – THE NEW CONCEPT IN FIRST TRIMESTER BIOCHEMICAL SCREENING

Dr. Chinmayee Ratha

Screening for feto-maternal problems in pregnancy by biochemical assessment of maternal serum is a well established concept in Fetal medicine. First trimester serum biochemistry has been traditionally accepted as the "double marker" test that included maternal serum free beta hCG and pregnancy associated plasma protein A (PAPP-A). These two analytes were evaluated as markers for fetal aneuploidies and helped in improving the performance of the fetal aneuploidy screening by enhancing the sensitivity and reducing the false positive rates as compared to screening by the NT scan alone.

The levels of serum PAPP-A have also become recognised as a marker for placental function such that maternal values below 0.4MoM in the first trimester placed the pregnancy at higher risk of pre eclampsia and fetal growth restriction – such screening being improvised by addition of maternal blood pressure data along with uterine artery Doppler studies.

The recently concluded ASPRE trial provided a good predictive model for pre eclampsia by adding placental growth factor (pLGF) to the first trimester screening protocol.

Many prediction models for these problems have been suggested and there is strong evidence to suggest that starting with low dose aspirin at a strength of 150mg/day at bedtime starting around 12 weeks and continued upto 36 weeks in women who are at high risk of developing preeclampsia helps to reduce the incidence of the same. As the etiopathogenesis of pre eclampsia is related to impaired placentation, it is expected that interventions prior to the completion of the natural stages of trophoblastic invasion would be more effective than those initiated later. Thus, the first trimester maternal serum biochemistry occupies an important role in screening for maternal complications in pregnancy at a time period when actual intervention to modify the disease process and reduce the incidence of pre eclampsia was possible.

Maternal serum alpha fetoprotein was one of the first markers to be analysed in maternal blood as a marker for fetal open neural tube defects.Alpha-fetoprotein is a fetal-specific globulin, synthesized by the fetal yolk sac, gastrointestinal tract, and liver. The levels of maternal serum alpha fetoprotein (MSAFP) were low in preganncies associated with trisomy 21 but very high in cases of fetal open neural tube defects although there are many other reasons leading to elevated MSAFP in pregnancy. It is therefore used as a screening test for fetal defects and if elevated, warrants a better fetal imaging evaluation. Traditionally this was done in second trimester but with the advent of high resolution ultrasound for detailed fetal imaging, the role of serum screening for neural tube defects in second trimester was losing its rationality. As a renewed concept a protocol for evaluating levels of maternal serum alphafetoprotein (AFP) in the first trimester has been validated such that high levels corroborate a high risk of open neural tube defects in the fetus. Ultrasound diagnosis of open neural tube defects in first trimester is now possible but requires extremely high levels of skill and high end scan equipment. The diagnosis is much better and definite at 16 weeks of gestation. This maternal serum AFP level test can help in triaging the fetuses who can be referred for high end scans either in the first trimester or early in the second trimester so that the final diagnosis is preponed to a stage where Obstetric decisions can be taken safely even after allowing the couple to understand the implications and seek neonatal/pediatric subspecialty opinions. Post diagnosis work up typically included prolonged counselling sessions with the neonatologist, pediatric neurosurgeons and neurosurgeons. The availability of all sub specialists maynot be a reality in all parts of the country so if a couple want to travel to the nearest city for such consultations it may take them almost a week to arrive at a final reasonable decision regarding continuing the pregnancy. When such problems are diagnosed by the end of 18 weeks or close to 20 weeks (which is the upper limit of allowing termination of pregnancy in our country), we often find ourselves in a frustrating situation as the couple have no time for such extensive workup and decisions are taken in a hurry which is never ideal.

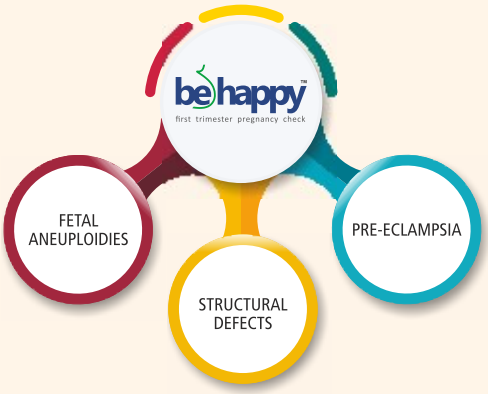
This emerging protocol of doing more markers in the first trimester screening for feto maternal problems is definitely very promising but remembering all these analytes becomes another daunting challenge for the Obstetrician. The constantly changing components of double, triple or quadruple markers makes a simplistic numerical nomenclature rather superfluous. Therefore a new , imaginative nomenclature for the first trimester combined screening has been advocated as the BE HAPPY protocol which is a nemonic for

- **B** – Blood pressure (refers to maternal BP at the time of the test)
- **E** – Extended Clinical history, examination (previous PE, family / medical history, maternal weight)
- **H** – Human Chorionic Gonadotrophin (b-hCG)
- **A** – Alphafetoprotein
- **P** – Placental growth factor (PLGF)
- **P** – Pregnancy associated plasma protein A (PAPP-A)
- **Y** – Your first trimester scan (CRL, FHR, NT, uterine artery Doppler and other markers)

Essentially this summarises the components of a comprehensive feto-maternal screening in first trimester and is easy to remember so that appropriate application can be expected.

ENHANCED FIRST TRIMESTER SCREENING (eFTS) WITH 4 MARKERS

B	E	H	A	P	P	Y
Blood pressure	Extended clinical history	hCGß	Alpha-Fetoprotein	PAPP-A	PIGF	Your First Trimester Scan



Reasons to choose

- ☑ Enhanced performance for Trisomy 21, when combined with ultrasound – 90% DR with 1.4% FPR
- ☑ All the advantages of First Trimester Screening – early reassurance, early intervention
- ☑ Aneuploidy performance of eFTS Biochemistry at par with 2T Quad
- ☑ Identifies risk of pre-term pre-eclampsia
- ☑ Identifies risk of some significant fetal structural abnormalities
- ☑ Multi-centre validation data on Indian population

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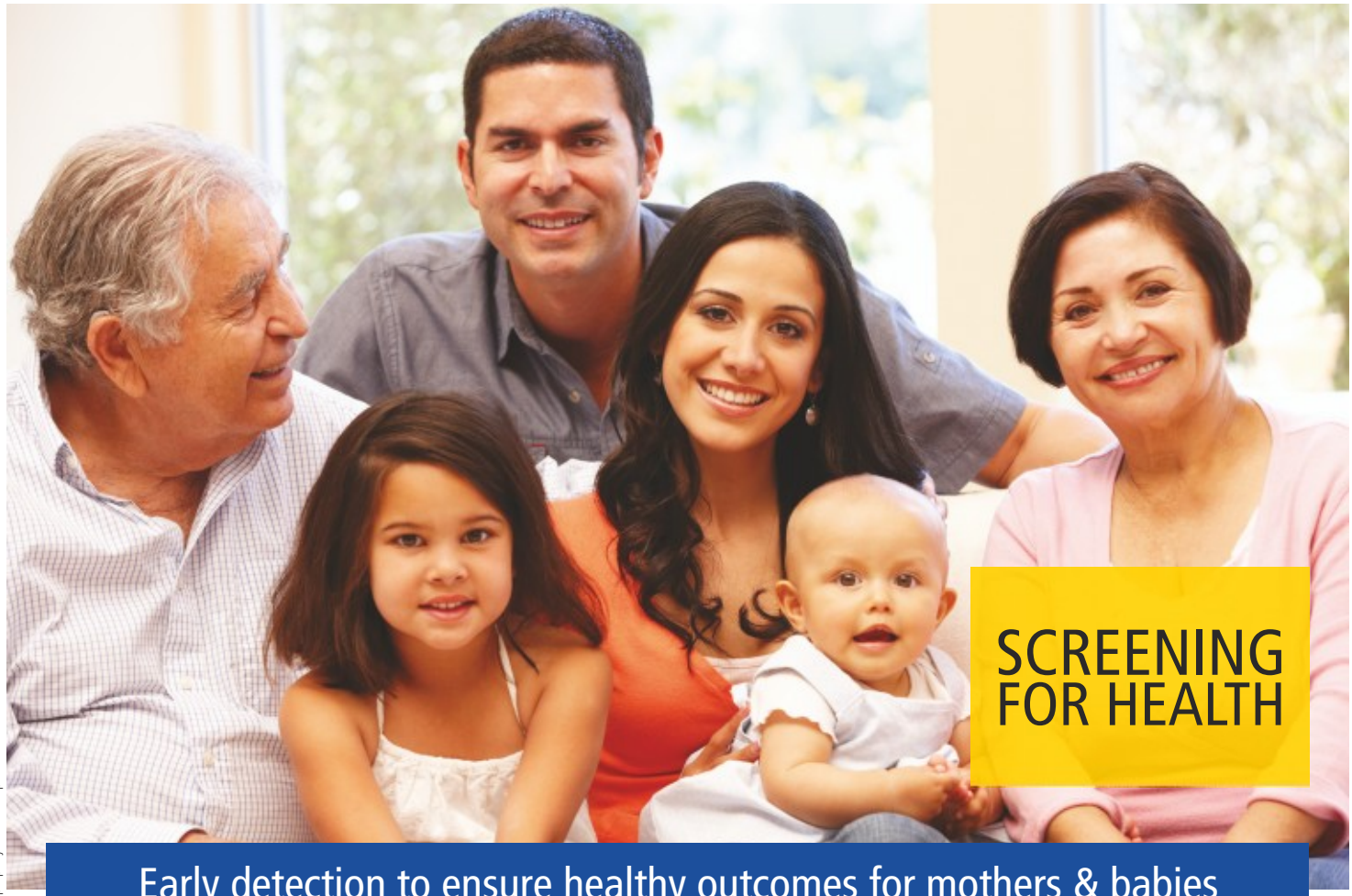

SCREENING FOR HEALTH

Early detection to ensure healthy outcomes for mothers & babies

PRENATAL SCREENING

- Combined First Trimester Screening (hCGß and PAPP-A + NT + Maternal Age)
- Enhanced First Trimester Screening (hCGß, PAPP-A, AFP and PIGF + NT + Maternal Age)
- Pre-eclampsia Screening (PAPP-A, PIGF, UTPI, MAP)
- Second Trimester Screening (hCGß, AFP, uE3 and Inhibin-A)
- NIScreen (cfDNA)
- Second-Tier Tests: Prenatal BoBs™, KaryoLite BoBs™, FISH, Karyotyping

GENETIC TESTS

- Confirmatory Test for Biochemical Screening Tests
- Whole Genome Sequencing
- Whole Exome Sequencing
- Focused Exome Sequencing
- Targeted Disease Panel
- Single Gene Test
- Carrier Testing (launching soon)

NEWBORN SCREENING

Newborn Screening Basic Panels (Screens for 7 disorders):

- CH • CAH • CF • Galactosemia
- G6PD Deficiency • PKU
- Biotinidase Deficiency

Newborn Screening Expanded Panels (Screens for 50+ disorders):

- Fatty Acid Disorders
- Amino Acid Disorders
- Organic Acid Disorders
- Hemoglobinopathies and more...

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