The Mumbai Obstetric & Gynecological Society

MOGS NEWS & VIEWS

NEW VISTAS IN FETAL MEDICINE

Volume 2 - September 2021

The Mumbai Obstetric & Gynaecological Society

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PRESIDENT'S MESSAGE

DR. SARITA BHALERAO
President MOGS 2021-2022
Chairperson, India Representative Committee (West) RCOG
Governing Council Member ICOG

Dear MOGS members,

As the festive season begins, I take this opportunity to wish all my MOGS members Seasons Greetings and Best wishes for the New Year.

I am delighted to bring you the second issue of News and Views for this year. This time, the focus is New Vistas in Fetal Medicine. Dr.Sharad Gogate is a pioneer of Fetal Medicine & I am thankful to Sir for writing the foreward. Dr. Manjiri Khare is a Fetal Medicine Consultant in UK and I happy that she has taken time out of her busy schedule to contribute to this issue. The editors Dr. Reena Wani and Dr. Komal Chavan along with co editors Dr. Tejal Poddar and Dr. Shreedevi Tanksale have worked very hard to bring out this excellent issue.

I cannot believe that 4 months have passed since I was installed on 15/05/2021. These past 4 months have been hectic as well as very enjoyable. In June we had the ENDOART 2.0 conference. I am thankful to Dr.Krishnakumar, President IAGE for collaborating with MOGS. This was a mega event over 2 days. I am thankful to Dr. Rajendra Sankpal, Dr. Sudha Tandon, Dr. Sanket Pisat, Dr.Atul Ganatra, Dr. Ganpat Sawant and Dr.Gaurav Desai for doing an excellent job.

In July, we had the PCO conference in collaboration with The PCO Society. Our conference oration was delivered by Dr. Duru Shah, Founder President of the PCO society. We had International faculty from UK- Dr. Anil Gudi and Dr. Santanu Acharya. Dr. Shashank Joshi was our Guest speaker. Our MOGS members contributed their photos for a unique fitness video called 'Fitness is fun'. My thanks to Dr. Suvarna Khadilkar who was Office bearer in charge along with her entire team of convenors Dr. Sangeeta Agrawal, Dr. Punit Bhojani, Dr. Priya Vora and Dr. Priti Vyas.

Breast feeding week was celebrated by MOGS from 1st to 8th of August. Several hospitals conducted programs for their staff and patients. Dr. Kedar Ganla coordinated a wonderful radio program. Dr. Sudha Tandon and Dr. Rajendra Nagarkatti made a lovely video which is posted on our website. Details of the events are featured in this newsletter.

The HOD program was held in August where many important suggestions were put forwards.

We have been conducting regular webinars, almost 1-2 per week. On 29 August, we did an Oncology webinar with SAFOG where we had faculty from Srilanka & Pakistan. I am grateful to Dr.Shyam Desai for collaborating with MOGS for this wonderful event.

I do hope that we are able to meet up in person in the next few months. At the moment I am planning hybrid events given the unpredictable situation. Last month we were able to have 2 hybrid events where some people were physically present and others were participating remotely. This has the advantage that we can reach out to people who are unable to come plus some of us get a chance to meet and interact physically.

I welcome Dr. Shanthakumari President FOGSI and the entire FOGSI Managing Committee to Mumbai on 25th and 26th September 2021 for the FOGSI Managing Committee meeting.

Our next big conference is **'New Vistas in Fertility'**. This conference will be an E conference, in collaboration with AMOGS. Dr.Nandita Palshetkar, a renowned fertility expert and President AMOGS will deliver the MOGS - Dr. M. Y. Rawal oration. A galaxy of stalwarts will deliberate on the different aspects of Assisted reproduction, Fertility enhancing endoscopic surgery and more. Please block

your dates for 16th and 17th October.

On December 12, 2021 we will have the MOGS Dr. Subhash Penkar Dr. Marie Perreira Oration. This will be delivered by Internationally known Prof Neerja Bhatla, HOD Obstetrics and Gynaecology, AIIMS, New Delhi. She will speak on 'Contemporary Management of Endometrial Cancer'.

Our Dr N.A Purandare programs continue to be very popular .

I would like to thank my Secretary Dr.Suvarna Khadilkar and Treasurer Dr. Shailesh Kore for their valuable help and support. Thank you to all MOGS Office bearers and Managing committee members for their enthusiasm and hard work. Our office staff is back in office with their regular timings. My thanks to all our Pharma supporters. The Onference team is doing a wonderful job of the webinars.

Please send me your feedback and suggestions on saritabhalerao67@gmail.com.

Before I end I take this opportunity to urge my MOGS family to Stay Safe and Stay Healthy in these tumultuous times.

With warm regards

Sarita Bhalerao

Dr. Sarita Bhalerao


FROM THE EDITOR'S DESK


Dr. Reena Wani Dr. Komal Chavan
EDITORS

Dr. Shreedevi Tanksale Dr. Tejal Poddar
CO-EDITORS

"The Child Gives Birth to the Mother"

We being responsible for both patients, thought it was appropriate to focus on the mother-child dyad and challenges to be faced by us obstetricians. It is with great pride that we bring to you the second newsletter with the vision of MOGS President, Dr. Sarita Bhalerao & Team 2021-22, focussing on the theme, **'New Vistas in Fetal Medicine'.** This issue comprises 5 lead articles that cover different aspects of fetal medicine, authored by eminent doctors working in the field.

"Yesterday is History, Tomorrow is a Mystery, Today is a Gift… that's why It's called the Present!"

Speculation about third wave of COVID-19 has continued, but this has become a disease possibly endemic, with challenges for the healthcare systems and health professionals. The inclusion of pregnant and lactating women for Covid vaccination is a step forward but there are unanswered questions. Hence we included this topic too in our issue.

World Breastfeeding Week celebrations were at another level this year with wholehearted participation across the city, and other branches like paediatrics and community medicine. FOGSI with dynamic President Dr. Shanthakumari and our first Lady Secretary General Dr. Madhuri Patel, & MBPC (Mumbai BF Promotion committee) headed by our member Dr. Reena Wani partnered with MOGS for many programs.

This newsletter shares a look into the major programs so far, and offers a glimpse of the upcoming plans. We also focus on what has been achieved by some of our members, and look forward to further inputs from others.

Wishing you and your families good health and safety, and belief that things can only get better!

Editors
Dr. Reena Wani, Dr. Komal Chavan

Co-editors
Dr. Shreedevi Tanksale, Dr. Tejal Poddar

SECRETARY'S MESSAGE

DR. SUVARNA S. KHADILKAR
Secretary, MOGS 2021-2022

- Professor & Head of Dept Obgyn, and Consultant Endocrinologist and Gynecologist, Bombay Hospital Institute of Medical Sciences (MUHS Affiliated), Mumbai
- Deputy Secretary General FOGSI 2021-24
- Secretary, MOGS, 2021-22
- Editor Emeritus, JOGI 2021 onwards

Greetings from MOGS!

We bring you the second issue of the MOGS newsletter, 2021-22 with a special focus on fetal medicine.

The field of fetal medicine is evolving rapidly, and it indeed has a major contribution to modern obstetrics. Advances have happened in both screening and treatment. Screening for fetal anomalies, IUGR, preterm birth pre-eclampsia and fetal health in general. The tests can guide further management, many fetal conditions can now be corrected in utero and such timely preventive interventions do improvise maternal and infant outcomes.

We are extremely thankful to all the authors who are experts in the field of fetal medicine. Dr. Sharad Gogate who is a senior obstetrician having expertise in fetal medicine has given foreword to this beautiful newsletter and I must thank him for the same. Dr. Manjiri Khare, Dr. Vandana Bansal, Dr. Hema Purandare, Dr. Pooja Vazirani have contributed various articles focused on fetal medicine. Dr. Raju Sahetya, Dr. Purnima Satoskar have also shared their expertise in their articles.

Apart from these interesting scientific articles, we have news from MOGS, various reports of programs held. Since we communicated with you last, we have had over 30 programs on the platform of MOGS in collaboration with many of our sister organisations and international organisation.

We have planned many programs and conferences and webinars in coming months and the calendar of upcoming events is included in this newsletter. We also have a section on our members' achievements. We are so proud of many of our members about what they have achieved in their professional lives. MOGS always appreciates good work done by our members.

It was an honour for me to interview our trustee Dr. Shyam Desai and this issue features the same. It will be inspiring and interesting to know how successful careers are built.

I congratulate and appreciate the efforts of the editorial team of Dr. Reena Wani, Dr. Komal Chavan supported by Dr. Shreedevi Tanksale and Dr. Tejal Podar.

We have a special appeal to make to all our members, to promote themselves from life members to patron members to avail of the honour and the benefits with patronizing the society. we have attached the form which you can fill and send along with fees for patron membership.

I sincerely hope that the efforts put in by us are truly helping our members and our members improvise the way they practice. Any suggestions to improvise our work are welcome!

Best wishes on festive times and I hope you have great time with friends and colleagues

Long Live MOGS!!!

Suvarna Khadilkar

Foreword

DR. SHARAD GOGATE
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It is my proud privilege to write this foreword for MOGS issue on foetal medicine. My association with Foetal Medicine and clinical genetics goes way back to 1973-74, when I conducted a KEM-IRR collaborative clinical, Cytogenetic laboratory study of Amniotic fluid culture and cytogenetic studies in second trimester MTP volunteers. We did foetal sex detection by Phenotype, Gonadal histology and cytogenetic studies. It was a totally new idea at that time, which was ridiculed when our paper was presented at an international conference in Mumbai!

From this rather inconspicuous beginning, over last couple of decades, a sub-specialty of "Foetal Medicine, Clinical genetics" has evolved and is now a very sought after specialty. Since then this specialty has rapidly progressed and played a vital role in evaluation and management of birth defects, genetic disorders and their multi-specialty management. Good foetal medicine programs have started in many centres all over the country, providing efficient services in high risk obstetric patients as well.

Recently MCI has added a module on Foetal Medicine for postgraduate courses in Obstetrics, Imaging and Neonatology specialties!

The theme of this issue of "MOGS, News & Views" focuses on new vistas in foetal medicine and genetics, which is the need of this hour!

- **NIPT,** ably covered by Dr Manjiri Khare;
  This is new tool in prenatal screening program, it is imperative for clinicians to know the ground realities of NIPT and not to get carried away by aggressive promotion by companies marketing the NIPT test! We have to follow all PC-PNDT guidelines, make the patient aware about the limitations, sensitivity, specificity and factors affecting the test performance. NIPT is basically still a screening method, though coming close to diagnostic test in it's performance. It is particularly vital to stress need for confirmation of high risk cases identified by NIPT, by invasive procedure of Amniocentesis before advising irreversible step of MTP. Failure to take these precautions can land us in trouble!

- **Cord blood banking :**
  Prof U.K. Sheth, our Pharmacology professor in GSMC, KEM, used to say; any new technique or test has a sigmoidal curve of it's use in practice; with initial rapid rise in clinical use, when everybody climbs the bandwagon. This is followed by sharp downfall, when adverse effects or limitations are seen and then a gradual rise of realistic use, which lasts long. Cord blood banking fits in to this scenario to the last T!! Cord blood banking came with a bang, 3 decades back, with companies promising the moon! Claiming cure for all sorts of disorders with stem cell therapy, offering discounts, EMI as well as aggressive marketing on social media platforms. This resulted in enthusiastic demand from patients and doctors. As the ground realities of stem cell research, limitations and problems of cord blood banking became evident, the enthusiasm waned quickly!

  The main issues affecting it are; 1. As of now, cord blood banking is approved mainly for

autologous use, with limited use in relatives or close contacts. This puts severe restrictions for stem cell use, like the usefulness in blood banking or bone marrow banking, where population at large can use it. 2. Problem of long term storage, successful thawing and use of the stem cells in actual practice. 3. Use of the stem cells in other indications apart from haematological disorders is still not clinically proved and established in long term studies.

These facts should caution us when recommending cord blood banking to our patients.

- **Rh-Iso-immunisation** is ably covered by Dr.Purnima Satoskar;

  It is more than 90 years since, Foetal Hydrops due to Rh Iso-immunisation was recognised. The current efficient management of Rh Iso-immunisation has become a foetal success story ! With availability of efficient prenatal and postnatal prophylaxis of Anti-Rh antibody injection, close monitoring by non-invasive ultrasonography and fairly safe intra-uterine transfusions, managing of Rh Iso-immunised fetuses has become very efficient and safe. Dr. Purnima Satoskar has vast experience of intra-uterine transfusions for Rh Iso-immunisation as well as Non-immune hydrops babies.

  Somehow use of NIPT technology for early detection of Rh status of the foetus in first trimester has not yet become freely available in India, though it is freely available for aneuploidy screening. Early detection of Rh status can confine aggressive screening and monitoring for only Rh positive pregnancies, these can be monitored closely from early second trimester. It also gives option of safe MTP to patient in case of Rh positive pregnancy with very high level of iso-immunisation with rather poor prognosis.

  NIPT for Rh status detection has become a standard practice all over the developed countries, making the clinical management more efficient, cost effective. India is already joining the developed countries club, so must have this useful test available freely at the earliest!

- Turning Pyramid of prenatal care, this unique topic is covered by my close friend Dr Raju Sahetya;

When we were residents in seventies and eighties, it was almost impossible to get volunteers in early second trimester of pregnancy for any study, as most of them used to come to antenatal clinic only after 20-24 weeks! As our understanding of maternal and foetal physiology during the 40 weeks of pregnancy improved, early AN registration and close monitoring to manage various complications of pregnancy was found to be more advantageous. In last 2-3 decades' rapid advances in Ultrasonography, antenatal screening for aneuploidies, PIH, IUGR and cytogenetic and molecular genetic testing have happened. Thus there is a paradigm shift in antenatal care with focus on prevention by pre-conception screening, first trimester antenatal evaluation. The conventional NT scan has become also an early anomaly, growth scan; when combined with serum markers it has become a powerful screening tool for genetic disorders, birth defects, PIH, IUGR/SB etc. This early window can help in starting specific preventive measures in early phase of placental and foetal growth with better results. This certainly helps in reducing maternal and foetal morbidity and mortality. With ready availability of multi-specialty Foetal Medicine clinics, more seamless care is available for high risk pregnancies. This has revolutionized antenatal care!

I am sure this special issue will be very useful for practicing clinicians, post graduate residents.

ENDO ART 2.O REPORT JUNE 2021

MOGS IN ASSOCIATION WITH IAGE organized a two day ENDO ART 2.0 conference on 12th and 13th June 2021. FOGSI, ICOG, RCOG were also the academic partners. Because of COVID pandemic, this was held on a virtual platform. The main theme of the conference was Fertility enhancing Endodoscopy-Laparoscopy, Hysteroscopy and ART. The program ran in 2 halls .

This was organized under the leadership of MOGS President - Dr. Sarita Bhalerao, Secretary - Dr. Suvarna Khadilkar and Treasurer Dr.Shailesh Kore, IAGE President - Dr.S. Krishnakumar, Secretary - Dr. Pandit Palaskar and treasurer Dr. Kalyan Barmade. Dr. Rajendra Sankpal was the office bearer in charge. The conveners of the event were- Dr. Sudha Tandon. Dr. Sanket Pisat, Dr. Atul Ganatra, Dr. Ganpat Sawant and Dr. Gaurav Desai .

The youth council members who worked for the conference were Dr. Ridhi Desai, Dr. Kinjal Shah, Dr. Aditi Tandon, Dr. Amrita Tandon, Dr. Medha, Dr. Zubin Sheriar, Dr. Pranay, Dr. Rajeshree, Dr. Sidra, Dr. Amiti, Dr. Garima Sharma, Dr.Shreya Prabhoo, Dr.Nidhi, Dr.Jiteeka Thakkar, Dr. Parzaan Mistry, Dr. Bhavini and Dr. Mridula

The Scientific program was conducted across two parallel halls, on 12th June, it started with the quick bytes session in which 24 young gynaecologists from across the country presented 10 minute capsules on their work related to topics of endoscopy and ART.

This was followed by a competitive video session where 3 selected free video communications were presented across 3 parallel halls and were judged by 12 eminent judges. This was the first time that free communications were included as part of the main scientific program in the same hall.

The next session was an interesting presentation of "near real surgical experiences" by experts in gynecological endoscopy where surgical videos of 30 minutes duration were presented. This was accompanied by interactive discussion with the faculty and questions by the delegates for getting precise take home messages and surgical tips.

This was followed by panel discussions on Medicolegal issues in endoscopy and ART, and role of vitamin D in women's health. The final session was keynote addresses, delivered by Dr. S. Krishnakumar, President IAGE who spoke on "Endometrioma and sub fertility-current treatment paradigm" and Dr. HD Pai, President elect FOGSI who spoke on "What's new in male factor.

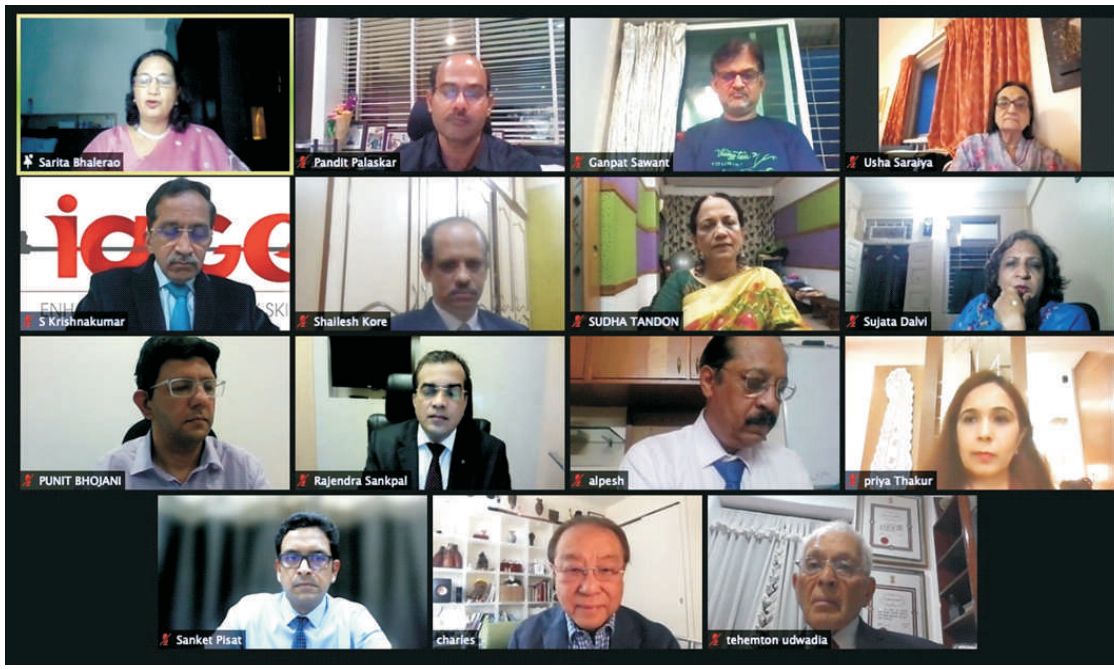
The day concluded with the conference inauguration Dr. Charles Koh from USA graced the occasion as the Chief Guest. Padmashree Dr. Tehemton Udwadia and Dr. Alpesh Gandhi, President FOGSI were the Guests of Honour. Dr. Charles Koh delivered the conference oration, titled "fertility enhancing endoscopic surgery" chaired by Dr. Alpesh Gandhi, Dr.Shailesh Kore and Dr. Rajendra Sankpal.

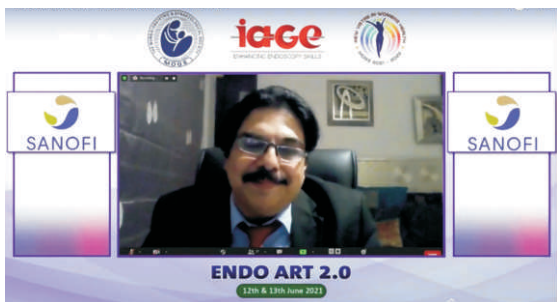
The delegates sat down to unwind themselves with a talent show, which had performances by MOGS members, and a dance performance by the Organising Committee of the Conference.

Day 2 of the conference began with panel discussions in parallel halls on "Safety in Laparoscopy" and "Improving IUI results". The next session had focused lectures on "Modern views in infertility" and "Endoscopy and ART" by stalwarts in the respective fields. This was followed by keynote addresses on topics related to the themes of 'gonadotrophins', endoscopic surgery and 'dilemmas in endoscopy'. This was followed by a special guest lecture on "uterine transplant" by Dr. Shailesh Puntambekar. The late afternoon sessions started with panel discussions on "recurrent pregnancy loss" and "young prolapse'. This was followed by the FOGSI ICOG session, RCOG session and the 'great debates'. The conference concluded with panel discussions on 'tubal factor in infertility' and 'adnexal masses', followed by the valedictory session.

Total registrations were around 3000
Total faculty - 220
Digital support - Onference team

Pharma Support - Torrent, Intas, Ferring, Meyer's, Sun, Emcure, Astra zeneca, Abott and Sanoffi .





REPORT of Dr. Ganatra CME E on Chalenges in management of PCOS – by MOGS in collaboration with PCOS society of India- on 25th July 2021

Dr. Ganatra E-CME on Challenges in management of PCOS – in collaboration with PCOS society of India- on 25 th July 2021 - on a digital platform

This was a unique conference. The theme was PCOS Management. It was a beautiful blend of various faculties from PCOS society and MOGS with a focus on multidisciplinary approach to PCOS.

The scientific program was conceptualized under the able guidance of MOGS President Dr.Sarita Bhalerao and PCOS society Founder and President Dr. Duru Shah along with Secretary Dr. Suvarna Khadilkar, Treasurer Dr.Shailesh Kore Secretary of PCOS society Dr.Piya Balani and Treasurer Dr.Uday Thanawala. Office bearer incharge was Dr.Suvarna Khadilkar, conveners were Dr. Sangeeta Agarwal, Dr. Priti Vyas, Dr. Priya Vora and Dr. Puneet Bhojani.

MOC : Sarita Channawar | Nitu Singh | Kausha Shah | Namrita Sheregar,

Shruti Thar | Shrutika Thakkar | Sidra Khot | Mridula Sarda

The conference had a whooping total of 1800 registerrations.

Inauguration

The Chief Guest was Mrs. Nawaz Modi Singhania a celebrity fitness expert. She gave very good tips and spoke about the importance of diet and fitness both for PCOS patients and everyone in general . She released the videos on MOGS Fitness and Diet video.

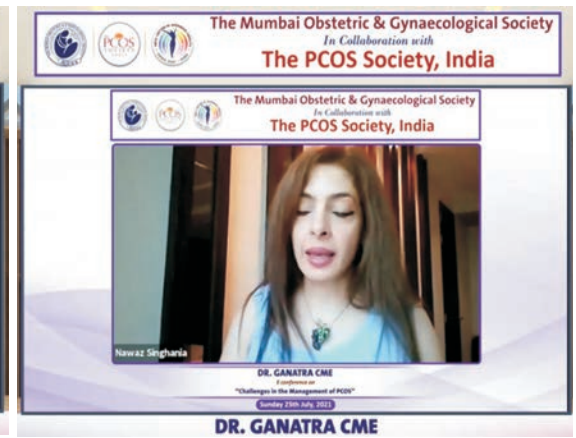
The Fitness Video compiled by MOGS members Dr. Priya Vora, Dr. Amita Tandon, Dr was something unique and displayed how all the gynaecs are so enthusiastic exercisers about exercise. It showed everyone in their own space of fitness – be it Gym or Yoga or Games or walking or running or Cycling or Dancing. The Diet Video was compiled by the PCOS society and was very apt to the fads and helps busting the myths of diets.

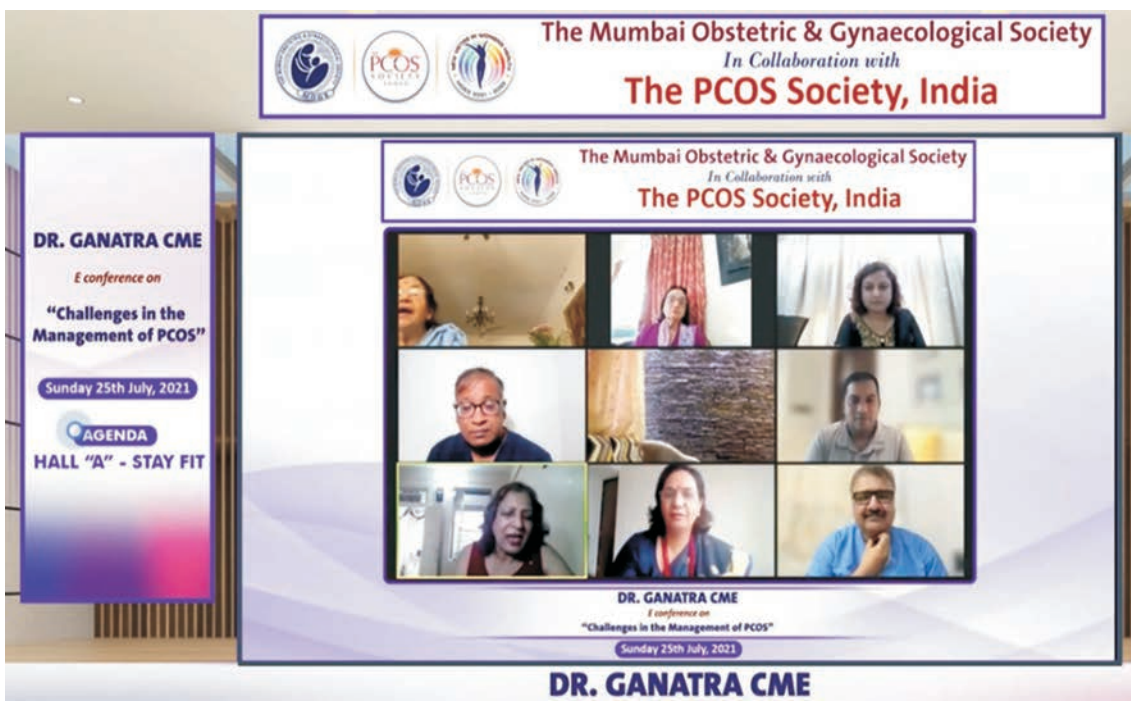
The main highlights of the conference were

1. **Conference oration by Dr Duru Shah -** on Recurrent Implantation failures in PCOS –
2. 6 keynote addresses

3. 3 international faculties, - Dr. Anil Gudi, Dr.Shantanu Acharya.
4. 60 faculties gynaecs and other streams including dietician, bariatric surgeons, endocrinologists, dermatologists etc
5. Fitness tips by Radhika Karle - master Pilate trainer and fitness expert and nutritionist
6. 1 Panel discussion
7. MOGS Quiz, 5 Quick Bytes - short and Crisp bursts-, Short bursts of knowledge
8. At the valedectary function the awards given out to the quiz winners - Dr. Swati Bajpai, Dr. Freni.

The Academic partners were Sun pharma, Emcure, Eris, Torrent pharma Zuventus, Meyer, Abbot, Blisson Pharma The whole event was managed with technical support by onference team.





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Optimising use of Non-Invasive Prenatal screening for aneuploidy in clinical practice

DR. MANJIRI KHARE MD, FRCOG
Consultant Maternal Fetal Medicine, University Hospitals of Leicester
Hon Senior lecturer, University of Leicester
Training Programme Director Subspecialty training programme
University Hospitals of Leicester, UK
Joint Hon RCOG webinar co-convenor

Background to prenatal screening for aneuploidy.

The era of prenatal screening for Downs syndrome involved screening using maternal age alone in 1960's. This has evolved over the next three decades with advances in technology to serum screening in the second trimester using biochemical markers and subsequently using combination of ultrasound, biochemical markers and maternal age for first trimester combined screening in the 1990's (1) (2)The combined test is offered in the first trimester to assess the chance of the baby being affected by Down's syndrome (Trisomy 21), Edwards' syndrome (Trisomy 18) or Patau's syndrome (Trisomy 13) between 10-14 weeks of gestation. The quadruple serum screening test is offered in the second trimester. With the first trimester screening programme the detection rates for Down's syndrome have improved from 60% to 90% with a reduction in false positive rates from 5% to 2%. Women with high-risk results for a cut off 1:150 are offered invasive testing (Chorion villous sampling in the first trimester and amniocentesis after 15 weeks of gestation) as a diagnostic method with risk of miscarriage upto 1%.

With advances in genomic technology cell free fetal (cffDNA) was first detected by Lo et al in 1997 (3). Non-invasive Prenatal testing (NIPT) using cffDNA was first introduced clinically in 2011 in the US and China and since then has been introduced through the commercial sector in these countries as well as in Europe (4). NIPT is now commercially available across the globe.

NIPT involves collecting a maternal blood sample and assessing for cell free fetal DNA in the maternal circulation. This can used as a first line or contingent prenatal screening method for common aneuploidies (Trisomy 21, 18 and 13). The terms Non-invasive prenatal testing (NIPT) and Non-invasive prenatal screening (NIPS) are used interchangeably. NIPT can be offered earlier in pregnancy as screening and is an efficient screening method. It is important to differentiate NIPT from Non-invasive prenatal diagnosis (NIPD). In the context of prenatal screening. NIPT is a good tool although it is not diagnostic.

The main challenges for implementation in clinical practice have been variation in access, high costs, lack of validation before introduction as an effective population screening method, lack of standardised practice for consenting, criteria for offering NIPT and reporting. Although technology has evolved rapidly there is much work to be done in translating this into clinical practice. Differences in availability of NIPT screening and implementation across the globe have made it a challenging task for policy makers, clinicians, scientists, and women to keep pace with the rapid availability of commercial tests mainly in the private sector. This has introduced inequity to access and has cost implications as screening programme. As evidence about the performance of these tests in the general population become clearer, there is likely to be increased uptake of NIPT as a first line screening method. Until this evidence is robust some countries have opted to use the contingent NIPT screening model offering NIPT when the first trimester or second trimester screen has a high risk>1:150 or intermediate risk 1:150 to 1:1000. This model is clinically and economically beneficial. (5)

The UK National screening committee (NSC) recommended using NIPT for aneuploidy screening for Trisomy 21,18 and13 as an evaluative roll out programme in 2016 for singletons and for twins in 2019. (6)The programme has been introduced as an evaluative programme nationally since 1st June

2021 for three years. Sex of the baby is not reported as part of the screening programme. The NHS Fetal Anomaly screening programme (FASP) have a dedicated training resource for NIPT for health care professionals on e-learning for health (e-LfH) http://www.e-lfh.org.uk/programmes/screening

The American college of medical genetics, The International Society for Prenatal Diagnosis (ISPD), The American Society of Human Genetics and The European Society of Human Genetics (ASHG/ESHG) and International Society of Ultrasound in Obstetrics & Gynaecology (ISUOG) have been organisations that have published medical guidelines or position statements to support the use of NIPT as an optimal, screening option for all singleton pregnancies (1,7,8)

NIPT basics :

During pregnancy there is free DNA circulating in the maternal plasma that has its origins from apoptosis of synciotrophoblasts (fetal cfDNA) as well as maternal hematopoietic cells (maternal cfDNA). (9) Although the term cell free fetal DNA suggests this originates from the fetus, the DNA is actually from the placenta. This is present throughout the pregnancy and disappears within hours after delivery.(10)

There are characteristic differences in fragment lengths and patterns of circulating cfDNA between maternal and fetal cfDNA (cffDNA). The fetal fraction derived from the placental-fetal unit can be detected in maternal circulation from five weeks of (11)gestation. By nine weeks of gestation there is adequate amount detectable and there is an increase in the concentration at 0.1% per week between 10 weeks to around 20 weeks and there is a significant increase per week thereafter (1%) until term. (12). The concentration of cell free DNA increases with gestation. Blood tests from the mother would be successful in getting a reliable result if there is a minimum of 3 to 4 percent of free fetal DNA in the sample.

Fetal DNA analysis

Two main methods are currently used - next generation sequencing (NGS) and microarray for assessing NIPT cffDNA is evaluated using massive parallel shotgun sequencing, targeted massive parallel sequencing or single nucleotide polymorphisms (SNP) genotyping using SNP's located on specific chromosomes for screening. (13)

Different methods are used for cfDNA screening. One of the common methods counts cfDNA fragments for the specific chromosome of origin. Second method involves 'shotgun sequencing' where random cfDNA fragments are sequenced but this may need a large number of up to 10 million mapped fragments for a reliable test. Results are usually reported as aneuploidy detected, or no aneuploidy detected or as high or low risk for aneuploidy.

There are limitations of the SNP testing for Donor egg pregnancies, Bone marrow or organ transplant recipients as additional chromosomes are present in the circulating plasma of these mothers. Sequencing method would be the method of choice in these cases.

Benefits of NIPT

- Can be done in the first and second trimester
- High positive predictive value allowing informed decisions regarding further invasive testing
- Offers an option for further testing to women who would have chosen against invasive testing
- Reduces invasive procedure related risks of miscarriage
- Earlier implementation allows couples to make informed choices regarding their plans for the pregnancy.

What NIPT cannot do

- Replace antenatal ultrasound screening
- Screen for neural tube defects
- Early screening for pre-eclampsia
- Does not predict late pregnancy complications
- Screening for single gene disorders

NIPT is not offered on the NHS UK FASP screening programme for following criteria

- Triplet or higher order pregnancies
- Current malignancy
- History of recieving blood transfusion in the last four months
- History of bone marrow or organ transplant
- Immunotherapy in current pregnancy
- Vanished twin pregnancy (an empty second pregnancy sac or a second pregnancy sac containing a non-viable fetus)

- With Downs syndrome or a balanced translocation or mosaicism of Down's syndrome, Edwards syndrome or Patau's syndrome

Also, currently women when a woman receives a lower chance result for T21, T18 or T13 from the combined or quadruple test & women will not be eligible for NHS NIPT screening.

In clinical practice when performing NIPT these are the key steps:

- Education of health care professionals
- Pretest counselling and assessing indication for offering NIPT, rule out contraindications
- Informed consent by trained professionals
- Sending sample to the laboratory with accurate information and history
- Quality control & standardisation in reporting
- Interpretation of the report (Failed, high chance, low chance), fetal fraction, prior risk and posterior risk
- Post test results and counselling: Informing results to the parents and communication using simple language that would help them understand the result
- Discussion of further options, investigation and appropriate follow up

Currently in the UK NIPT is being used as secondary screening test on the NHS screening programme for women that are screen positive high risk following combined screening in the first trimester or serum quadruple screening in the second trimester. The NHS FASP care pathway NIPT screens for T21, T18 and T13 and other chromosomal conditions and baby's sex are not assessed. The options following high chance result include no further testing, NIPT screening or prenatal diagnosis such as chorion villous sampling or amniocentesis. If the woman chooses to have NIPT she has an option to choose for screening for T21,18 and 13 or T21 only or T18 and T13 only. The report will include individual chance results for the conditions tested.

A contingent model is offered for NIPT to improve detection rates and reduce false positive rates. This model (diagram 1) uses a combination of serum screening and cfDNA screening in the general population to give two risk cut offs high risk >1:150 and intermediate risk 1:150 to 1:1000 All those with<1:1000 would be classed as low risk and would not be offered further testing. The intermediate risk group constitute 10-15% of the screened population and are offered NIPT. (14)

Table 1: Screening performance of NIPT for Trisomy21, 18 and 13 in singletons

This can be measured by the detection rate (DR)and false positive (FPR) (15–18)

	Detection rate	False positive rate
Trisomy 21 (Downs syndrome)	99.5%	0.05%
Trisomy 18 (Edwards syndrome)	97.7%	0.04%
Trisomy 13 (Patau's syndrome)	96.1%	0.06%

Results are reported as low chance or high chance or no result, The positive predictive value and negative predictive value require consideration when counselling and implementing national screening programmes as the prevalence of the condition being screened would impact on the predictive values. All high-risk results for NIPT must be confirmed with invasive testing before couples out or if the parents choose non-continuation of pregnancy

Reporting recommendations : Guidance for labs

''The American College of Medical Genetics (ACMG) recommends (11):

- Offering diagnostic testing for a no-call NIPS result due to low fetal fraction if maternal blood for NIPS was drawn at an appropriate gestational age. A repeat blood draw is NOT appropriate.
- Offering aneuploidy screening other than NIPS in cases of significant obesity.
- All laboratories should include a clearly visible fetal fraction on NIPS reports.
- All laboratories should establish & monitor analytical & clinical validity for fetal fraction.
- All laboratories should specify the reason for a no-call when reporting NIPS results.''

As a variety of platforms and protocols are used for NIPT testing, it is important that tests are validated and limitations clearly documented in the report. (19)(Deans et, 2017)

Test failures : Low fetal fraction is a common cause in half the cases with no results. Options following failed test results should be discussed including await events and no further testing, repeat cfDNA testing, ultrasound assessment and diagnostic testing

There are various reasons for a report of 'no call' or 'no result' including samples collected from early pregnancy less than 10 weeks, insufficient plasma volume, higher maternal weight, abnormal fetal karyotype e.g., Trisomy 18 and Triploidy fetuses have lower fetal fractions. The fetal cfDNA is cleared from the maternal circulation very rapidly after birth within hours.

False positive results may be seen with confined placental mosaicism, demised twin, maternal malignancy, transplant recipient, recent history of receiving blood transfusion within 4 weeks, maternal copy number variants

False negative results (defined as fetus actually being affected but the results of testing indicating no chromosomal abnormality) Confined placental mosaicism-Borderline Low fetal fraction,

NIPT in twin pregnancies

The performance of NIPT in twins is more complex to understand than singleton pregnancies. Approximately two-thirds of twins are dizygotic and one third or less are monozygotic in origin. In dizygotic twin pregnancies the maternal circulation has two genotypes from the twins. In monozygotic twins both fetuses are likely to share the same genotype. The fetal fraction in monozygotic pregnancies is higher overall than singletons although the in dizygotic twin pregnancies even though the overall fetal fraction is higher, the contribution from individual fetuses is lower. Chorionicity on scans cannot determine zygosity for dichorionic twins unless both fetuses are of the same sex. All monochorionic twins are monozygous. NIPT can evaluate for zygosity, and this may be of help in management of twins where chorionicity was not able to be reliably established. (20)

A recent meta-analysis by Gil et al (2019) provides evidence that the performance of NIPT for trisomy 21 may be similar to singletons. The pooled weighted detection rate for trisomy 21 was 98.2% (95% CI 83.2-99.8%) for a false positive rate of 0.05% (95% CI 0.01-0.26%) The detection rate for trisomy 18 was 88.9% (95% CI 64.8-97.2%) with a false positive rate of 0.03% (95% CI, 0.00-0.33%). There were only three affected cases with trisomy 13 and two of the three cases (66.7%) were detected by cfDNA test with a false positive rate of 0.19%. (21)The authors concluded that the performance of cfDNA for trisomy 21 is in fact superior to that of combined first trimester screening or second trimester biochemical screening, The performance for trisomy 18 and 13 could not be reliably concluded due to small numbers in the cohort studied.

Other applications for use of the cell free fetal DNA for diagnostic purpose

RHD fetal genotype for Rhesus negative mothers. This is an has revolutionised the management of Rh negative mothers antenatally and has reduced the need for Anti D prophylaxis in women with RhD negative fetus. NIPD >99.8% accurate from 11 weeks gestation

Sex chromosome aneuploidy includes 45X (Turners syndrome), Klinefelter's syndrome (47, XXY), Triple X (47,XXX), Jacobsen syndrome (47,XXY). NIPD for monogenic disorders

Expanded NIPT is available through some commercial laboratories in addition to the common trisomy's for screening Copy Number Variants. Submicrosopic deletions or duplications cannot be detected on routine karyotyping which uses a standard resolution of 5-10 Mb.

Conclusion :

Advances in genomics have offered more choices to women regarding prenatal screening for aneuploidies. Although with using cffDNA there is a higher detection rate for Trisomy 21,18 and 13, it still remains a screening method. Women need to be informed of the possibilities of false positive and false negative results. Appropriate pretest and post-test counselling are important to allow women to make informed choices and decisions about their pregnancies. The advantages of NIPT are that the detection rate is much higher (approximately 99% for T21 and T18, and > 90% for T13) and the false-positive rate is much lower (< 1%), when compared with other screening options. Therefore, it is expected that using this test prior to CVS or amniocentesis will increase the overall detection of fetal aneuploidies, decrease the number of unnecessary invasive

testing procedures performed, and decrease the number of procedure-related pregnancy losses. A positive/high risk result from cell free fetal DNA should (NIPT) should always be confirmed by invasive testing. In some settings, NIPT is offered as the primary screening method for aneuploidies although in countries with national screening programmes this is currently offered as a contingent screening model to reduce the number of invasive testing related miscarriages. NIPT can be offered as a screening method for common aneuploidies in twin pregnancies. There is evolving role for NIPD using cffDNA,

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TURNING PYRAMID OF PRENATAL CARE
The New Normal...

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Introduction

Antenatal care is the most effective preventive strategy for preventing or reducing complications of Pregnancy and Childbirth. Historically pregnancy care was confined to the time of delivery and reserved for the wealthy. Due to high maternal and infant mortality, institutions for provision of prenatal care were started (1, 2). Later, Antenatal Clinics recommending that women should first be seen at 16 weeks, then at 24 and 28 weeks, fortnightly thereafter until 36 weeks and then weekly until delivery (fig. 1) were in practice, these guidelines established in 1929, the pattern of antenatal care that continued for more than 80 years.

The high concentration of visits in the third trimester implies that, firstly, most complications occur at this late stage of pregnancy, secondly, that most adverse outcomes are unpredictable in the first and second trimester and thirdly, that then, there was nothing much to offer, during the first or even the second trimester.

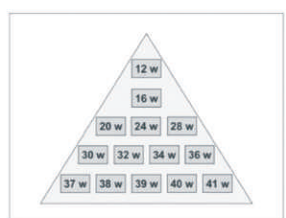

Fig. 1. Pyramid of traditional prenatal care established in 1929. w = Weeks.

In the last 20 years, it has become apparent that an integrated first hospital visit at 11–13 weeks combining data from maternal characteristics and history with findings of biophysical and biochemical tests can define the patient-specific risk for a wide spectrum of pregnancy complications, including fetal abnormalities, miscarriage and stillbirth, preeclampsia, preterm delivery, gestational diabetes, fetal growth restriction & macrosomia.

Early estimation of patient-specific risks for these pregnancy complications would improve pregnancy outcome by shifting prenatal care from a series of routine visits to a more individualized patient- and disease-specific approach both in terms of the schedule and content of such visits.

It is therefore proposed that the traditional pyramid of care should be inverted (Fig. 2)

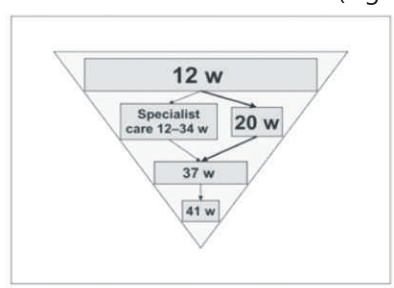

Fig. 2. Proposed new pyramid of prenatal care. w = Weeks.

Evolution in Prenatal Care

Turning the pyramid of Prenatal Care meant to start pregnancy care as soon as pregnancy is confirmed and identify and prevent adverse pregnancy outcome.

The first visit is utilized to unveil the Algorithm of modern pregnancy care by the concerned Obstetrician for healthy pregnancy care (Fig. 3).

Algorithm - Healthy Pregnancy outcome

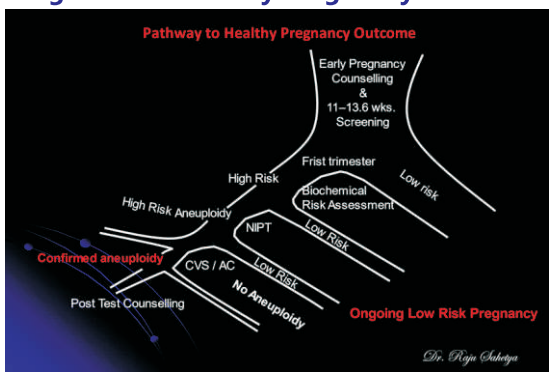

Fig. 3 Diagrammatic illustration

Main emphasis is placed in the first rather than third trimester of pregnancy.

Each visit would have a predefined objective and the findings would generate likelihood ratios that can be used to modify the individual patient- and disease-specific estimated risk.

At 11–13 weeks, the great majority of women would be classified as being at low-risk for pregnancy complications and a small proportion of women would be selected as being at high-risk.

In the low-risk group, medical visits could be substantially reduced. One visit at 18–22 weeks would reevaluate fetal anatomy and growth, reassess risk for as preeclampsia and preterm delivery. Other visit at 37–38 weeks would assess maternal and fetal well-being and determine the best time and method of delivery.

The high-risk group could have close surveillance in 'Specialist Clinics'. Investigations to be performed and the personnel involved in the provision of care would include members of fetal medicine team, namely an obstetrician (a Perinatologist), a Geneticist, an Ultrasonologist and a Neonatologist.

In each of these visits, risk would be reassessed and establish, if to remain in high-risk and for specialist care or become low-risk and for routine prenatal care.

Early Screening for Fetal Aneuploidies

The Combined Test

In the 1990s the emphasis shifted to the first trimester when it was realized that the great majority of fetuses with major aneuploidies can be identified with highest possible detection rate and lowest false positive rate by a combination maternal age, fetal nuchal translucency (NT) thickness, maternal serum-free Beta-hCG and PAPP-A. Screening by this combined test can identify about 90% of fetuses with trisomy 21 and other major aneuploidies with false-positive rate of 5%. Screening for aneuploidy can be further augmented by the addition of other fetal markers, such as Nasal Bone evaluation and blood flow across Tricuspid Valve and Ductus Venosus with combined test.(3)

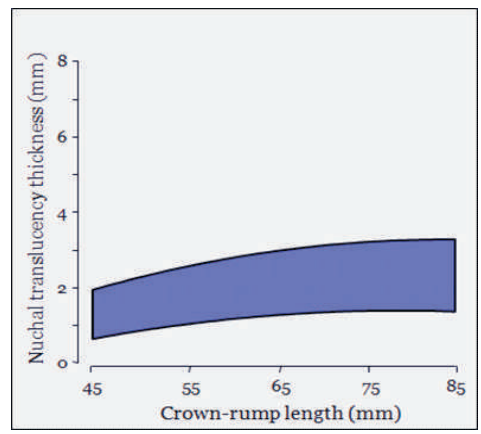

Fig. 4 CRL and NT in mm.

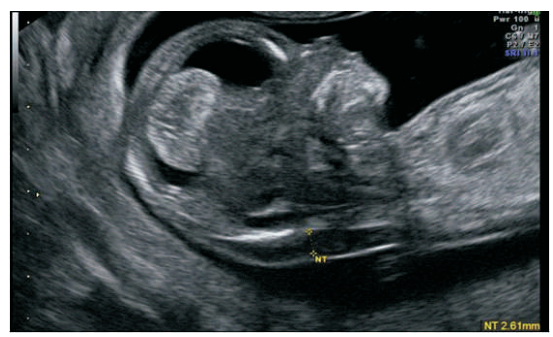

Fig. 5 USG image Mid-Sagital – NT and NB

- NT increases with gestational age (Fig. 4)
- Always interpret with crown rump length (CRL)
- 1.2-2.1 mm at 45 mm
- 1.9-2.7 mm at 85 mm
- Not the old figure of < 3 mm (Fig. 5)

Free Beta-Human Chorionic Gonadotropin (hCG) and pregnancy-associated plasma protein A (PAPP-A) were first used to screen for trisomy 21. Subsequently they were also found to be useful in screening trisomies 18 and 13 and for triploidy. Further expanded to predict pregnancy complications that become apparent only later in pregnancy, such as Preeclampsia (PE) and Severe Intrauterine Growth Restriction (IUGR) (Fig. 6)

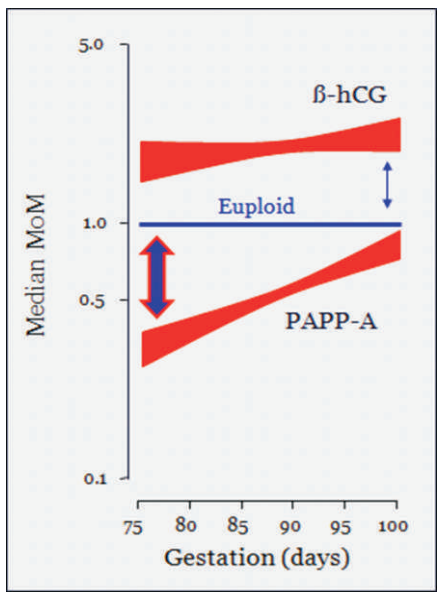

Fig. 6 Beta hCG and PAPP-A with Gestational Age

Timing of Ultrasound and Biochemistry

Perform Biochemical serum markers, Ultrasonography and Counsel In one-stop clinics for assessment of risk (OSCAR), at 12 weeks rather than between 13 to14 weeks.

The ideal gestation for OSCAR is 12 weeks, the aim of the first-trimester scan is not just to screen for trisomy 21 but also to diagnose an increasing number of fetal malformations, the ability to visualize fetal anatomy is better at 12 weeks (4).

First stage : All patients have screening using a combination of maternal age, fetal NT thickness and maternal serum-free Beta-hCG and PAPP-A.

According to the results, they are classified into high- risk, intermediate-risk, and low-risk groups. In the intermediate-risk group

Second-stage : Screening is carried out by one or more sonographic markers, including nasal bone, blood flow in the ductus venosus, and the tricuspid valve. Based on these results, once again re-classified as high-risk or low risk (5), (Fig. 7).

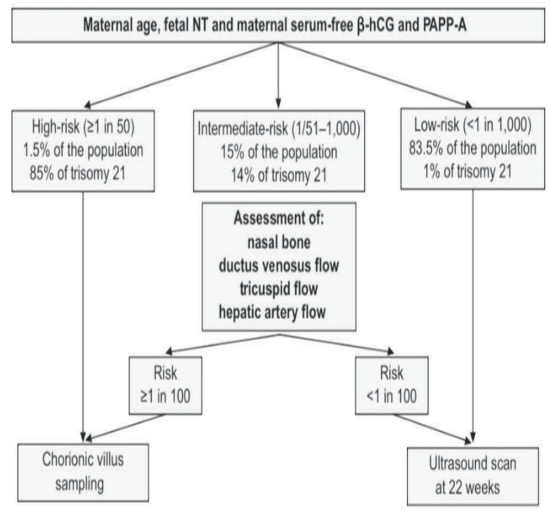

Fig. 7 Two-stage screening for fetal aneuploidies.

Multiple Gestations

Perinatal risk of morbidity and mortality is always increased in multiple gestations. However, the level of risk depends greatly on chorionicity.

In monochorionic and Diamniotic twin pregnancies, a large difference between the NTs measurements of the 2 fetuses or presence of Ductus Venosus blood flow abnormalities may be helpful in identifying pregnancies with an increased risk for twin-to-twin transfusion syndrome.

Early Diagnosis of Fetal Abnormalities

The 11 to 13 weeks' scan essentially a scan for measurement of fetal NT and crown-rump length, Includes a basic checklist.

Overall Scope of Screening

Methods of screening	Detection rate	False-positive rate
Maternal age (MA)	30%	5%
First trimester		
MA+ fetal nuchal translucency (NT)	75-80%	5%
MA+ serum free β-hCG and PAPP -A	60-70%	5%
MA+ NT + free β-hCG and PAPP -A (combined test)	85-95%	5%
Combined test + nasal bone or tricuspid flow or ductus venosus flow	93-96%	2.5%
Second trimester		
MA+ serum AFP, hCG (double test)	55-60%	5%
MA+ serum AFP, free β-hCG (double test)	60-65%	5%
MA+ serum AFP, hCG, μE3 (triple test)	60-65%	5%
MA+ serum AFP, free β-hCG, μE3 (triple test)	65-70%	5%
MA+ serum AFP, hCG, μE3, inhibin A (quadruple test)	65-70%	5%
MA+ serum AFP, free β-hCG, μE3, inhibin A (quadruple test)	70-75%	5%
MA+ NT + PAPP -A (11 -13 weeks) + quadruple test	90-94%	5%

Nicolaides KH. Screening for fetal aneuploidies at 11 to 13 weeks. Prenat Diagn 2011; 31:7 -15.

Fig. 8 Methods of Screening - Detection rate and False-Positive rate

Includes, fetal abnormalities, miscarriage and stillbirth, preeclampsia, preterm delivery, gestational diabetes, fetal growth restriction and macrosomia.

Early estimation of patient-specific risks for these pregnancy complications would improve pregnancy outcome by shifting prenatal care from a series of routine visits to a more individualized patient- and disease-specific approach both in terms of the schedule and content of such visits. Examination of the fetal anatomy with the intention of diagnosing major abnormalities, either lethal or associated with severe handicap.

Fetal Anatomy

Detailed evaluation of fetal anatomy is becoming widely recognized as an integral part of the first trimester ultrasound. A thickened NT > 3.5 mm increases the risk of congenital fetal defects even in the absence of aneuploidy. The overall detection rate of major anomalies, including CHDs, is 84%.

The first group

11 to 13 weeks' scan (Fig.)

Abnormalities which are always detectable body stalk anomaly:

Anencephaly,holoprosencephaly, exomphalos, gastroschisis and megacystis.

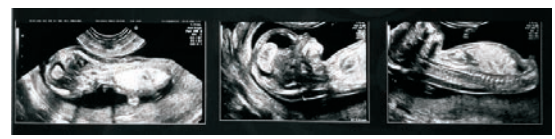

Fig. 9 Transvaginal first trimester fetal anatomy scan

The second group

Abnormalities manifested only during the second or third trimester of pregnancy:

Microcephaly, agenesis of the Corpus Callosum, Semi-lobar Holoprosencephaly, Hypoplasia of the Cerebellum or Vermis, Cystic Adenomatoid malformation or Pulmonary Sequestration, and Bowel obstruction (Fig 10).

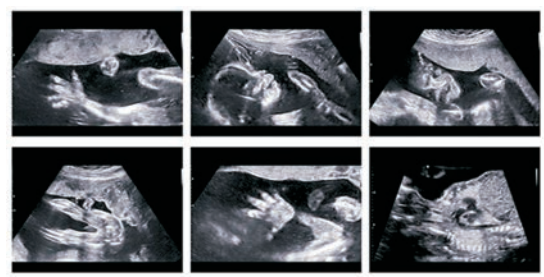

Fig. 10 Transabdominal second trimester anatomy scan

The third group

Includes abnormalities detectable depending on firstly, the objectives set for such a scan and, consequently, depends on, the time allocated for the fetal examination, the

expertise of the sonographer and the quality of the equipment used (Fig. 11).

Additionally, the presence of an easily detectable marker for an underlying abnormality is also important for detection.

A good example of such a marker in the first trimester is high NT, which is found in some fetuses with lethal Skeletal Dysplasias, Diaphragmatic hernia & major Cardiac defects.

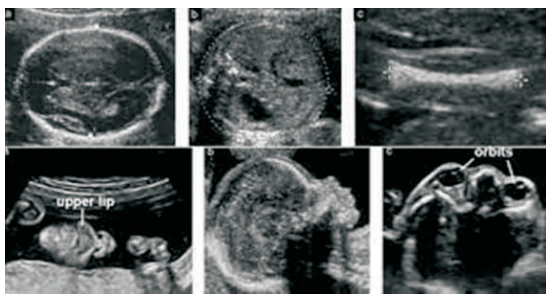

Fig 11 Transabdominal targeted anatomy scan

Major Cardiac Defects

Abnormalities of the heart and great arteries are the most common congenital defects, accounting for about 20% of all stillbirths and 30% of neonatal deaths due to congenital defects. Major cardiac defects are amenable to prenatal diagnosis by specialist fetal echocardiography (6).

The risk of CHDs increases progressively with increasing NT measurement. Doppler evaluation of blood flow across the Tricuspid Valve and Ductus Venosus further improves screening of CHDs.

Early Diagnosis of Fetal Abnormalities

The 11 to 13 weeks' scan evolved over the last 20 years from essentially a scan for measurement of fetal NT and crown-rump length to one which includes a basic checklist for examination of the fetal anatomy with the intention of diagnosing major abnormalities which are either lethal or associated with severe handicap.

Open spina bifida

Displacement of the brain is apparent at 11–13 weeks in the same mid-sagittal view of the fetal face as for measurement of fetal NT and assessment of the nasal bone. In fetuses with open spina bifida, the brain stem diameter is increased, and the diameter of the fourth ventricle-cisterna magna complex is decreased (Fig 12).

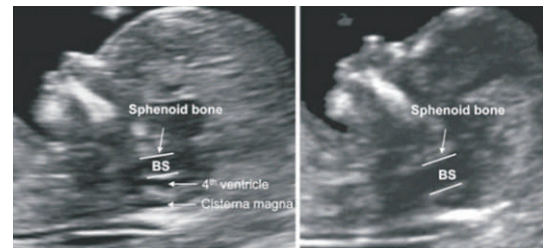

Fig. 12 Midsagittal view of the fetal brain in a normal (left) and a spina bifida (right) fetus at 12 weeks.

Demonstrating the measurement of brain stem (BS) diameter. In open spina bifida, the brain stem diameter is increased (7).

Miscarriage and stillbirth

Early Screening for Miscarriage & Stillbirth

Increased risk for miscarriage and still- birth are associated with certain maternal characteristics, **increasing maternal age and maternal weight, previous miscarriage, or stillbirth.** Also associated with abnormal results of first-trimester screening for aneuploidies, including increased fetal NT thickness, reversed A wave form in the fetal ductus venosus and low maternal serum PAPP-A (8).

Algorithms which combine maternal characteristics and biophysical and biochemical tests at 11–13 weeks **Identify about 35% of pregnancies that miscarry and 25% of stillbirths before and after 34 weeks,** with a false-positive rate of 10%.

Early Screening for Preeclampsia

Algorithms, combine maternal characteristics and biophysical and biochemical tests at 11–13 weeks could potentially identify about 90, 80 and 60% of pregnancies that subsequently develop Early (before 34 weeks), intermediate (34–37 weeks) and late (after 37 weeks) preeclampsia, with a false-positive rate of 5%.(9)

Maternal Characteristics and History

The risk for preeclampsia increases with maternal weight and decreases with height, increased in women conceiving after the use of ovulation induction drugs, Personal or family

history of preeclampsia and Pre-existing chronic hypertension or diabetes mellitus.

Biophysical and Biochemical Markers

The biophysical tests

Uterine artery pulsatility index and mean arterial pressure. Increased uterine artery pulsatility index reflects the underlying mechanism for the development of preeclampsia.

The biochemical tests

These include PAPP-A, placental growth factor, endoglin, activin-A and inhibin-A. As in the case of maternal factors, the differences in biophysical and biochemical markers of impaired placentation between the affected and unaffected pregnancies are in general more pronounced in those developing early preeclampsia compared to intermediate or late disease (8, 9, 10).

Implications of Early Assessment of Patient-Specific Risk

Effective early identification of the high-risk group for subsequent development of preeclampsia potentially improve outcome by directing such patients to specialist clinics for close surveillance.

Gestational Diabetes Mellitus

Algorithms, combining Maternal characteristics and biochemical tests at 11–13 weeks potentially identify about 75% of pregnancies that subsequently develop GDM, with a false-positive rate of 20%.

Maternal Characteristics and History

The risk for the development of GDM increases with maternal age and BMI, increased in women with a family history of diabetes and previous pregnancies complicated by GDM and delivery of macrosomia neonate. Previous pregnancy affected by GDM, the risk of recurrence is very high and such women can be automatically classified as screen positive.

In nulliparous women and in those without a previous history of GDM, screening by a combination of maternal factors and serum adiponectin and sex hormone binding globulin Identify about 65% of pregnancies that subsequently develop GDM, with a false-positive rate of 20% (10).

Diagnosis of Gestational Diabetes at 11–13 Weeks

The desire to diagnose GDM in the first trimester of pregnancy could be achieved by lowering the currently used second-trimester cutoffs in plasma glucose levels both for screening and diagnosis of the condition.

First trimester in screening for GDM the cutoff for the 1-hour plasma glucose level after the oral administration of 50 g of glucose should be 130 rather than 140 mg/dl.

Diabetes in Pregnancy Study Group of India (DIPSI)

Is an evaluation of Plasma Glucose after two hours of ingestion of 75 gram glucose load irrespective of meal timings. When the cutoff is lowered to 130mg/Dl the identification increases to 90%

Implications of Early Assessment of Patient-Specific Risk

To improve pregnancy outcome because appropriate dietary advice and pharmacological interventions. Drugs as metformin, can reduce the incidence of the disease and associated fetal macrosomia.

Small for Gestational Age Fetuses

Small for gestational age (SGA) fetuses with birth weight below the 5th centile for gestational age at delivery are at increased risk of perinatal death and handicap. These risks are substantially reduced in cases of SGA identified prenatally, compared to those detected after birth (11).

Screening for SGA in the absence of preeclampsia by a combination of maternal characteristics and obstetric history with a series of biophysical and biochemical markers at 11–13 weeks could potentially identify about 75% of pregnancies delivering SGA neonates before 37 weeks and 45% of those delivering at term. false positive rate of 10%

Maternal Characteristics and History

The risk for SGA increases with maternal age and decreases with maternal weight and height, Higher in women of African and Asian racial origin, increased in cigarette smokers,

those with a medical history of chronic hypertension, women with a previous SGA neonate and those who had assisted conception.

The estimated detection rate of SGA in the absence of preeclampsia with the use of the algorithm of maternal characteristics and obstetric history is about 35%, with a false-positive rate of 10%.

Biophysical and Biochemical Markers

The risk for SGA is inversely related to fetal NT at 11–13 wks. In pregnancies with SGA in the absence of preeclampsia, there is evidence of impaired placental perfusion and function from the first trimester of pregnancy.

Uterine artery pulsatility index and mean arterial pressure are increased. Placental volume and serum PAPP-A, free-hCG, PLGF, PP13 and ADAM12 are decreased. SGA is a heterogeneous condition

Growth-restricted fetuses are due to impaired placentation, genetic disease, or environmental damage. The impairment in placental function is greater for the subgroup of SGA delivering before 37 weeks than those delivering at or after 37 weeks.

Early biophysical and biochemical markers could be identifying the growth-restricted sub-group amongst the SGA.

Implications of Early Assessment of Patient-Specific Risk for SGA

Could potentially improve pregnancy outcome by directing such patients to specialist clinics Regular monitoring of fetal growth and well-being.

Fetal Macrosomia

Fetal macrosomia is associated with increased risks for the mother during Cesarean section and trauma to the birth canal, for the baby Shoulder dystocia and consequent brachial plexus or facial nerve injuries, fractures of the humerus or clavicle

Maternal Characteristics and History

The risk for macrosomia increases with maternal weight and height and is higher in parous women who had previously delivered a macrosomia infant and/or have a medical history of diabetes mellitus; however, the risk is lower in women of African and South Asian racial origins, in cigarette smokers and in those with a medical history of chronic hypertension.

Biophysical and Biochemical Markers

The risk for macrosomia is directly related to increase fetal NT, maternal serum-free-hCG and PAPP-A, inversely related to serum adiponectin. Likely mechanism underlying the association between low maternal serum adiponectin and neonatal macrosomia is increased insulin resistance and glucose intolerance (12).

Premature Delivery

The risk of spontaneous preterm birth is increased in women with a previous late miscarriage or preterm delivery. It is inversely related to cervical length measured by transvaginal sonography at 20–24 weeks' gestation.

Recent evidence suggests that at 11–13 weeks the cervical length in pregnancies complicated by subsequent spontaneous delivery before 34 weeks is shorter than in those delivering after 34 weeks, the risk for early delivery is inversely related to cervical length.

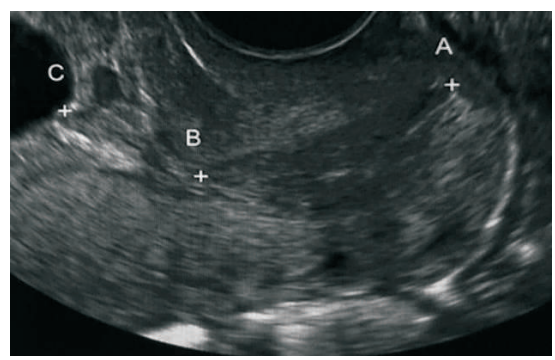

Fig. 13 Transvaginal ultrasound picture illustrating the measurement of the length of the endocervix (A to B) and the isthmus (B to C)

It is important to distinguish between the true cervix, characterized by the presence of the endocervical canal bordered by the endocervical mucosa which is usually of decreased echogenicity compared to the surrounding tissues, and the isthmus (Fig. 13).

The measurement of cervical length at

11–13 weeks will be combined with the algorithm derived from maternal characteristics and obstetric history to provide an effective method for identification of the group at high risk for subsequent early delivery.

Implications of Early Assessment of Patient-Specific Risk.

Effective early identification of the high-risk group for subsequent spontaneous early delivery could potentially improve outcome by directing such patients to specialist clinics for regular monitoring of cervical length.

Stimulating research for identification of potentially useful biomarkers and the investigation of the potential role of earlier intervention with such measures as prophylactic use of progesterone and/or cervical cerclage.

Invasive Prenatal Diagnosis

Aneuploidies are major causes of perinatal death and handicap. Consequently, detection of chromosomal disorders constitutes to frequent indication for invasive prenatal diagnosis. Performed only in pregnancies considered to be at high risk for aneuploidies, irrespective of the age of mother to be and history of affected pregnancy in the past (11), (Fig. 14).

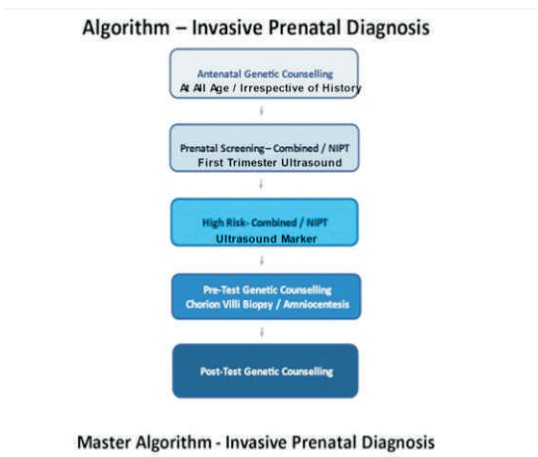

Fig 14 Algorithm – Invasive Prenatal Diagnosis

Pre-Test Counselling

Indication for referral should be reviewed and conclusive result should be possible. The risk should be chromosomal related and not otherwise. Alternative procedures should be kept in mind and counseled about them with the concerned mother to be and her family. One should inform the patient consequences of testing verses no testing. Which means the advantages and disadvantages with regards to the risk to the fetus and the risk for the invasive procedure. Consent is valid only if above guidelines are followed and is truly than an informed written consent.

Procedures which are used to detect genetic disorders during early stages of pregnancy.

Methods of invasive prenatal diagnosis are (11, 12):

(a) Chorionic villus sampling

(b) Amniocentesis

(c) Cordocentesis (Uncommon)

Conclusion:

1. Screening and Diagnosis of fetal anomalies in the first trimester enables women to take an informed decision well in time, keeping in mind the emotional bonding with the fetus and privacy in the matter.
2. cff-DNA is more accurate for detecting high risk for aneuploidy and should be judiciously used.
3. Screening in first trimester for PE, SGA, Risk to Miscarriage and Stillbirth, GDM, Preterm Birth, Macrosomia, gives opportunity to monitor closely and patient risk specific way to treat and prevent pregnancy adverse outcome.
4. Turning the pyramid for prenatal care is the new and established norm.
5. Invasive Prenatal diagnostic test, when screening tests reported high risk, irrespective of age of the mother to be and past history of affected pregnancy outcome.

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Rh incompatibility : Redefining the limits

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Rh isoimmunization is the development of antibodies against the Rh antigens present on the surface of RBCs[1]. Rh is a protein found on the red blood cells. An individual is Rh-positive if their erythrocytes express the Rh D antigen; those without the Rh D antigen as Rh-negative. There is Rh group (C, D, E) and non-Rh group (Kell, MNS, Kidd)

Rh(D) blood type and antibody screen is recommended for all pregnant women at the initial prenatal visit (RCOG)[2]

Pathophysiology of Hemolytic Disease of the Fetus and Newborn (HDFN)

When a Rh-negative gravida is exposed to fetal Rh-positive red blood cells, this may produce antibodies in her blood (alloimmunization).

Rh negative mother when carrying a Rh negative fetus can get sensitized either during the delivery or during any incident causing fetomaternal haemorrhage (FMH).

Primary (Slow) immunological response: IgM antibodies develop in 4 to 9 weeks. IgG antibodies might take 6 weeks to as long as 6 months to develop.

Secondary (Rapid) immunological response- Re-exposure to the antigen lead to a brisk IgG response, usually in days.

IgG anti-D antibodies cross the placenta and coat D-positive fetal red cells, which are then destroyed in the fetal spleen (haemolysis).

- Maternal antibodies enter fetal blood-stream, forming complexes with the Rh positive fetal red cells. These affected RBC get destroyed by the reticuloendothelial system of the fetus by hemolysis.
- Mild to moderate haemolysis leads to increased indirect bilirubin in the amniotic fluid.
- Extensive hemolysis triggers compensatory production of blood cells in liver and spleen (extramedullary haematopoiesis), leading to hepatosplenomegaly.
- Impaired hepatic metabolic function leads to portal venous hypertension and hypoproteinemia both contributing to fetal ascites.
- Umbilical venous hypertension produces placental edema, causing reduced tissue oxygenation (hypoxia), which triggers capillary dilation, activation of renin-angiotensin system, salt and water retention, atrial natriuretic peptide release and increased permeability.
- Cardiac failure ensues with redistribution of body fluid balance at intracellular, intravascular, and interstitial levels leading to hydrops fetalis and fetal death.

ABO incompatibility reduces the risk of isoimmunisation probably because rapid clearance of incompatible red cells reduces the overall exposure to D antigen.

Chance of developing antibodies without Rh prophylaxis is about 16%, with postpartum prophylaxis about 1%. A prophylactic dose of 300 micrograms of anti-D immune globulin can prevent Rh D alloimmunization after exposure to up to 30 mL of Rh D-positive fetal whole blood (or 15 mL of fetal red blood cells.)

Antepartum management of non-sensitized mother

Husband's Blood group and Rh type are determined. If the husband is Rh positive, ideally genotype of the father for Rh-D coding gene should be determined. A homozygous father will inherit Rh-D gene to all his offspring whereas if the father is heterozygous, there is 50 % chance of fetus being Rh-D positive.

RCOG guidelines recommend determining the fetal blood group from circulating cell free fetal DNA in maternal blood. When fetus is Rh-D negative no further testing required. If fetus is Rh-D positive, further follow- up is done.[3]

Consensus guidelines recommend that a routine antenatal antibody screen should be obtained at 28 weeks of gestation before administration of 300 micrograms of anti-D immune globulin.

Post-partum management of non-sensitized mother

Though it increases feto-maternal transfusion, active management of third stage is encouraged due to poor availability of Rh-negative blood in case of postpartum hemorrhage (PPH). Pitocin, Carboprost and misoprostol are preferred as they are associated with less FMH, but methylergometrine should not be withheld in PPH.

Immediate cord clamping done, keeping cord long for neonatal umbilical venous access.

Cord blood should be sent for blood group and Rh, fetal hemoglobin, serum bilirubin, DCT (direct Coomb's test), reticulocyte count.

Determination of amount of feto-maternal hemorrhage (FMH)

In 99.2 -99.3% of women FMH is less than 4 ml. at the time of delivery, so in most of the cases the standard dose of anti D is sufficient.

Large feto-maternal haemorrhage (0.3%) may occur in :

Abdominal trauma during the third trimester

Stillbirths and intrauterine deaths

Traumatic deliveries including Caesarean Section

Manual removal of the placenta

Twin pregnancies (at delivery)

Unexplained hydrops fetalis.

Unexplained fetal death after second trimester

All such cases should be screened for excessive fetal–maternal hemorrhage at the time of the event to determine if additional anti-D immune globulin is required.

Tests to calculate FMH

Kleihauer Betke acid elution test

Flow cytometry

The rosetting technique

Anti D administration

Intramuscular anti D Ig -better to be given in upper part of deltoid. If given in gluteal region, absorption may be delayed.

It should be given as soon as possible after the sensitizing event, preferably within 72 hours post-delivery. If missed it can be administered within 9-10 days, which may provide some protection.

If already sensitized, anti D Ig is ineffective and not indicated.

There are multiple epitopes (configurations) of the D antigen in the population. Monoclonal antibody may not attach to all of them, with resultant sensitization in spite of taking Anti D. Hence, polyclonal Anti D is preferred as it is more effective than monoclonal anti D.

The stillbirths or neonatal death rate due to Rh-D isoimmunization reduced from 120 per 100,000 births in 1971 to 1.3 per 100,000 in 1992 in UK, largely due to widespread use of Anti-D.

Non sensitized with early pregnancy complications: Recommendations

Rh antigen has been identified in the red cell membrane of the fetus as early as 38 days after conception.

Risk of alloimmunization following sponta-neous miscarriage is 1.5-2 % and following induced miscarriage is 4-5 %.

After termination of pregnancy, medical or surgical, Rh-negative women should be given a minimum anti D of 50 mcg during the first 12 weeks and 300 mcg after that.

Complete spontaneous miscarriage before 12 weeks, anti D can be avoided as chance of FMH is negligible.

If incomplete spontaneous miscarriage or any miscarriage after 12 weeks or surgical removal of products of conception, anti D is

recommended.

Anti D should be given to non-sensitized women following ectopic pregnancy

Anti D is not necessary in complete mole but should be given following molar pregnancy evacuation because of the possibility of partial mole.

Threatened miscarriage-anti D should be given if it occurs after 12 weeks. Anti D should be given every 6 weeks till the bleeding stops.

Before 12 weeks, possibility of FMH is very negligible so anti D can be avoided. Though decision is to be taken on case-to-case basis. It is better to give anti D if the woman is approaching 12 weeks, has repeated heavy episodes of bleeding or abdominal pain.

Diagnosis of Alloimmunization

The human anti globulin titer (Indirect Coombs') is performed at the first visit to detect alloimmunization and to determine its degree. An Rh antibody titre of 1:4 is positive. The critical titre for a laboratory is the titre below which no fetal death has been observed, usually between 1:16 and 1:32. When this is reached, further testing with invasive techniques is required.

Anti D levels, if available, are more accurate. Anti-D level of > 4 IU/ml but < 15 IU /ml correlates with a moderate risk of HDFN and an anti-D level of > 15 IU /ml with severe HDFN

Middle Cerebral Artery Doppler

Mari et al[4] proposed that Doppler assessment of the peak velocity in the fetal middle cerebral artery (MCA) could determine accurately whether the human fetus was anemic. A value more than 1.5 multiples of the median (MoM) for gestational age detected all cases of moderate to severe anemia with a false-positive rate of only 12%.

Measurements can be initiated as early as 15 weeks of gestation The general rule is to start monitoring of MCA PSV at least 10 weeks before the gestation of bad outcome in the previous affected pregnancy.

MCA PSV should be repeated at 1 to 2-week intervals. Because the normal peak MCA Doppler velocity increases with advancing gestational age, the value should be plotted on a standardized graph. After 35 weeks of gestation, there appears to be a higher false-positive rate in the detection of fetal anemia.

Invasive Evaluation

- **Indirect :** Spectrophotometry (OD450) using a specimen of amniotic fluid obtained by ultrasound-guided amniocentesis is outdated.
- **Direct :** Fetal blood studies using a sample obtained by cordocentesis.

When to transfuse?

Fetal transfusion should not be undertaken in the absence of hydrops without first confirming that the fetus has significant anemia. A hematocrit below 30% is usually used because it is below the 2.5 percentile for all gestational ages greater than 20 weeks. However, as MCA PSV is very reliable, blood is usually kept ready at the time of cordocentesis to perform IUT at the same sitting. These procedures should be performed preferably by a Fetal Medicine specialist with experience.

How To Transfuse?

Routes

Intraperitoneal

Intravascular by cordocentesis (Preferred)
Intravascular by intrahepatic venous puncture
Intracardiac by fetal cardiocentesis (rare, usually to resuscitate if complications)
Combined intravascular and intraperitoneal (extends interval between transfusions)

How much to transfuse?

For intraperitoneal Bowman's formula is recommended:

Volume = (weeks gestation - 20) × 10 mL

For intravascular required amount of donor blood (Vdonor) is determined by the formula proposed by Rodeck et al.

Vdonor = FPVinitial x (desired Ht- initial Ht)/ Ht donor blood

The initial fetoplacental blood volume (FPVinitial) is based on estimated fetal weight and normal values for fetoplacental blood volume as proposed by Nicolaides et al (Fig I)

A rise in fetal whole-blood viscosity during transfusion can be minimized by restricting the posttransfusion fetal hematocrit to approximately 50–55%. The final target hematocrit in the combined IVT/IPT approach

is usually approximately 40

Pre-Procedure Requirements

Thorough counselling of the parents regarding the procedure, risks and complications involved, follow up, need of repeat procedures and outcome is mandatory.

Written, informed valid consent is taken. Fetal hematocrit confirmed to be <30%

Donor blood

Donor blood : O Rh negative, as fresh as possible, (not more than 5 days old) and compatible with both mother and fetus collected in CPD buffer, NOT SAGM.

Buffy coat poor, washed in saline × 3, irradiated. Final hematocrit 70–80%

Preparation

The procedure should be performed in a sterile room under strict aseptic precautions. Maternal sedation is rarely used. Pancuronium 0.3 mg/kg estimated fetal weight given in fetal buttock for temporary paralysis. The procedure is done under local anaesthesia under continuous ultrasonography guidance through an 18-gauge spinal needle. (Fig II)

At first cordocentesis, c**ord blood is tested for ABO and Rh type, Direct Coombs' test, complete blood count (CBC) and manual reticulocyte count.**

Intraperitoneal transfusion is used when approach to cord is difficult as in cases of obesity, posterior placenta and early gestation or if intravascular transfusion cannot be completed due to complications. (Figures 1 and 2)

Intravascular

Though most fetuses tolerate a hematocrit of 25% or lower without clinically significant sequelae, sudden onset of hydrops can worsen the prognosis markedly.

Hence cut-off point of <30%, which as is below the 2.5th percentile after 20 weeks gestation, has proved a pragmatic threshold.

Repeat Transfusion

MCA Doppler is used both in untreated patients and in planning subsequent transfusions due to changes in circulatory hemodynamics due to adult RBCs.

In nonhydropic fetus, the second transfusion is usually performed 2 to 3 weeks after the first. Subsequently, the fetal hemoglobin in blood decreases at the rate of 0.3 gm % per day.

In a study of 44 MCA PSV values in 15 patients analyzed at Nowrosjee Wadia Maternity Hospital and correlated with Hb level by cordocentesis within 5 days of MCA measurement, 81% of patients with moderate to severe anemia had MCA PSV > 1.2 MOMs. Hence the MCA PSV cut-off is lower in subsequent transfusions.

The rate of decline in hematocrit after transfusion is slower in subsequent procedures compared to between the first and second transfusions.

On ultrasonography, poly/oligohydramnios, splenomegaly, placental thickness >4mm, portal vein diameter >6mm and minimal ascites are warning signs to monitor. Rh antibody titres have limited value after the first transfusion.

To study of impact of MCA PSV as a surveillance method, we analysed trends in management and outcomes at Wadia hospital over a 14-year period[5].

Table I : A comparison of invasive procedures performed before and after the use of MCA PSV by Colour Doppler for surveillance

Study Period	I (1994-1998)	II (1998-2001)
No. of Patients	104	33
Amniocentesis	161	11 (+3 cordocentesis)
Needing IUT	50	29
IUTs	120	77
Procedures/patient	4.7	2.7
Overall survival	52%	79% (p<0.001)

During study period I, out of 104 isoimmunized pts, 161 amniocentesis procedures were performed in 60 patients throughout pregnancy. 50 of these underwent 120 total transfusions. Total procedures per patient were 4.68. During study period II, Colour Doppler ultrasonography was performed periodically to determine MCA PSV. This practically eliminated the need for amniocentesis to determine the timing of intrauterine transfusions. Out of 33 isoimmunized pts needing interventions, 14 patients underwent invasive tests. 29 of these were subjected to 77 total transfusions. Total procedures per patient were 2.7. Overall survival in Study period I was 52% as compared to 79% in study period II.

Severe early sensitisation

The first IUT can be delayed by a few weeks by administering I.V. IgG 0.4g/kg/day for 5 days preferably before 12 weeks. This allows access to the cord for transfusion at 20-22 weeks. Early Intraperitoneal transfusion can be carried out if MCA PSV >1.5 MoM before this period. Plasmapheresis is helpful, but not widely available.

When to deliver?

The timing of delivery in fetuses undergoing serial IUTs has undergone considerable change. During the era of IPT, fetuses affected by hemolytic disease were delivered routinely at 32 weeks' gestation. Hyaline membrane disease and hyperbilirubinemia necessitating neonatal exchange transfusion were frequent complications. The widespread use of IVT during the past decade has led many centers to perform the final procedure at approximately 35 weeks' gestation with delivery planned approximately 3 weeks later. This change in management has virtually eliminated hyaline membrane disease and the need for neonatal exchange transfusions for elevated bilirubin. Once fetal viability is reached, IUTs should be undertaken close to the labor and delivery suite so that an immediate cesarean section can be performed in cases of fetal distress.

However, in patients with technically challenging IUTs, early rescue to NICU is also an option now due to better NICU care.

Hydrops

Because most hydropic fetuses have myocardial dysfunction that prevents them from tolerating the required infusion volume, the target hematocrit after their first transfusion is only 25%. A second transfusion 24 to 48 hours later, can safely bring up the hematocrit to 50%.

Neonatal Top-Up Transfusion for hypo regenerative anemia after IUT

Weekly hematocrit and reticulocyte determinations should be performed for the first 3 months of life in infants with a history of IUT as red cell production may be suppressed. Infants with a hemoglobin of less than 5–6 g/dL should be transfused, even if asymptomatic. Subcutaneous injection of 200 U erythropoietin per kilogram of body weight three times per week, combined with ferrous sulfate and folic acid supplementation markedly decreases the need for postnatal transfusion.

Complications

Acute

Fetal distress during or after the procedure is the most serious complication and may result in fetal death or emergency delivery with the risk of prematurity, neonatal asphyxia or death. Fetal distress can occur after local cord accidents (rupture, spasm, tamponade from a hematoma or excessive bleeding), volume overload, chorioamnionitis, preterm rupture of membranes or preterm labor. Fetal demise after intrauterine treatment may be the result of overload in an already compromised fetal state.

Long-Term Complications

Red blood cell donor transfusions have a minimal but theoretical risk for anaphylactic reactions and transmission of viral diseases. IUT, transplacental puncture in particular, is also associated with the formation of new red cell antibodies. Additional antibodies are formed by small FMH after IUT. The prevalence of additional maternal red cell antibodies is 19–26% and may complicate present and subsequent pregnancies and future transfusions including delayed hemolytic transfusion reactions.

Outcomes : The overall survival rate approaches 96% in nonhydropic fetuses receiving their first transfusion after 28 weeks and about 50% in hydropic fetuses.[6]

Table II- Personal Series 2001-2020:

Number of Intrauterine transfusions in 63 patients =131

	No Hydrops	Mild	Severe	Total
Patient Number	48	6	10	64
Survived	45	5	3	53

No/Mild Hydrops	50/54	93 % survival
Severe Hydrops	3/10	30 % survival

Long-Term follow up after intra-Uterine transfusionS; the LOTUS study of 291 children who underwent IUTs from Leiden University Medical Center revealed a relatively low incidence of neurodevelopmental impairment of 4.8%, severe hydrops being independently associated with neurodevelopmental impairment.[7]

Key Points :

All patients to be screened at first antenatal visit for antibodies

Aggressive prevention of Rh isoimmunization by timely adequate Anti-D

Early referral of alloimmunized women to Fetal Medicine Department for surveillance with Color Doppler & timed intrauterine transfusions

Close liaison of Fetal medicine expert with Neonatologist with excellent NICU care.

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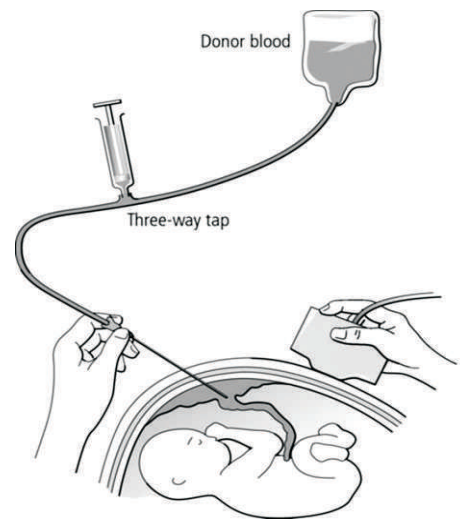

Figure 1: Diagrammatic representation of Intrauterine transfusion (Adapted from Practical Transfusion Medicine 4th Ed. Wiley Blackwell 2013)

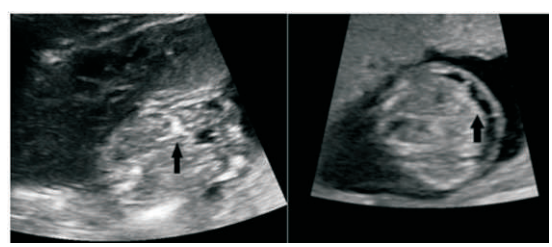

Figure 2: Early Intraperitoneal transfusion. Arrows showing tip of needle in iliac fossa before transfusion and hemoperitoneum after transfusion

Fetal therapy : New Frontiers

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Introduction

In the past, once a disorder was diagnosed prenatally, options available were either termination of pregnancy or continuation till term and have the appropriate pediatric specialist and neonatal care team manage the neonate with the birth defect. However many such abnormalities are progressive in utero and by the time the neonate is delivered, the disorder is either uncorrectable or correctable with residual disease which may compromise quality of life or the fetus may deteriorate to death in utero. With technological advancement in ultrasound we have not only been able to diagnose disorders in utero but also understand the natural history of the disease.

Fetal therapy is defined as any fetal intervention, whether medical or surgical, that attempts to treat a disorder in utero with an aim to improve perinatal outcome. These interventions are aimed at correcting in utero progression of disorder to reduce damage to the fetus and subsequently improve long term outcome. Diseases which are amenable to in utero intervention maybe structural abnormality, cardiac defects or rhythm disorder, fetal metabolic, hematological and hormonal disorders or abnormalities of placental vessels.

Fetal therapy was first attempted by Liley et al. by performing intra-peritoneal transfusion for fetal anemia under X ray control in 1963. Advances in ultrasound technology, MR imaging and improvement in minimal invasive techniques have allowed more successful and less invasive fetal interventions.

Fetal therapy may be categorized into

1. Fetal Medical therapy
2. Fetal Surgery

Routes of fetal interventions maybe

- Noninvasive transplacental route
- Ultrasound guided interventions
- Fetoscopic surgery
- Open fetal surgery

Medical therapy

Transplacental route : Route where maternal administration crosses placenta and treats the fetus. It is a noninvasive intervention.

1. Steroids for lung maturity in fetuses at risk for preterm delivery is the best known pharmacological intervention for preventing hyaline membrane disease and reduce the incidence of intra-ventricular hemorrhage (1).
2. Transplacental transport of folic acid supplementation has a protective effect on neural tube defects.
3. Maternal administration of Intravenous Immunoglobulin (IVIgG) to mothers who is alloimmunised against fetal platelets antigen inherited from father to the fetus.
4. Maternal administration of Magnesium sulfate (Magsulf) in extreme preterm for neuroprotection and reducing risk of cerebral palsy (2).
5. Congenital adrenal hyperplasia: All mothers of fetuses at risk of Congenital adrenal hyperplasia (parents carrier, previous affected fetus) are initiated on 0.25 mg dexamethasone orally as early as 7-9 weeks which transfers to the developing fetus transplacentally. Steroids are continued

through pregnancy only in female fetuses found to be affected on chorionic villus sampling.

6. **Maternal HIV :** Maternal administration of antiretroviral drugs started at 14 weeks of gestation and continued throughout pregnancy, intrapartum period and to the neonate reduces rate of vertical transmission.

7. **Thyroid disorders**
   - Hyperthroidism in the fetus may occur due to transplacental transfer of thyroid stimulating antibodies from a mother with Graves disease to the fetus. This may be diagnosed on ultrasound by the presence of fetal tachycardia, fetal growth restriction and hydrops and confirmed on cordocentesis for TSH values. Maternal administration of higher doses of propylthiouracil or methimazole is used for transplacental treatment of fetal hyperthyroidism in mothers with Grave's disease.

8. **Hypothyroid fetus :** Fetus in utero may becomes hypothyroid in mothers who are thyrotoxic on antithyroid drugs, mothers who have received radioactive radioiodine in pregnancy and euthyroid mother with fetal dysgenesis/ agenesis of thyroid gland. Presence of goiter in the fetus with or without polyhydramnios on ultrasound would initiate an amniocentesis / cordocentesis to evaluate the fetal thyroid status. Increased levels of TSH in the amniotic fluid or cord blood is diagnostic. Intraamniotic instillation of L-Thyroxine (500 mcg) every 2 weeks or 200 mcg weekly may help in regression of goiter, polyhydramnios and normalization of hormonal levels (Figure 1a,b,c).

9. **Fetal arrhythmias**

   a) **Supraventricular tachycardia :** Most fetal arrhythmias (commonly atrial extrasystole) are intermittent and benign in nature. Persistent supraventricular tachycardia may evolve into fetal hydrops and hence must be treated in utero or delivered if pregnancy is close to term.

   Transplacental treatment of fetus with SVT is done by administering digoxin to the mother under supervision of an adult cardiologist. Mother is investigated with ECG, renal function and electrolyte prior to the loading dose as the impact of the drug on the mother should be monitored. Recently sotalol, flecainide and amiodarone are being used as second line treatment when either digoxin is ineffective or when correction is attempted after hydrops develops.

   b) Complete heart block in the fetus is seen in association with maternal autoimmune disease (Systemic lupus erythematosis, Sjogren syndrome) with maternal serum positive for Anti Ro or Anti La antibodies. These antibodies cause fetal myocarditis and damage the conduction fibres leading to dissociation of atrial and ventricular rhythm. Prior to any prenatal intervention, structural cardiac anomalies associated in about 50% of cases like atrioventricular canal defect, ventricular septal defects, transposition of great vessels must be ruled out. Maternal administration of steroids (Dexamethasone 4mg) or beta 2 stimulants transplacentally to the fetus has been reported as effective with variable results (3).

Ultrasound guided medical intervention:

Intrauterine transfusion

Rh incompatibility is a condition that occurs when a woman with Rh-negative blood is exposed to Rh-positive fetal blood cells, leading to the development of Rh antibodies. Fetal RBCs are then hemolysed by these maternal alloantibodies that cross the placenta causing fetal anemia resulting in erytroblastosis fetalis.

Rh negative isoimmunized mother with previously affected fetus or those with Rh antibodies titres above critical levels are monitored noninvasively by middle cerebral artery peak systolic velocity Doppler (MCA PSV) to identify severe anemia prior to development

of hydrops. A cut off value of MCA PSV of 1.5 MOM or evidence of hydrops on ultrasound indicates severe anemia (Hematocrit <30%) requiring intrauterine transfusion. (Figure 2a)

Under ultrasound guidance intrauterine transfusion is done of double packed (Hematocrit of 75-80%) fresh O negative blood, leucodepleted, CMV negative, cross-matched with mother's blood into the intravascular (cord insertion site or hepatic portal vein) or intraperitoneal compartment. Volume of blood to be transfused is calculated depending on the initial fetal hematocrit, donor hematocrit and fetoplacental blood volume.In experienced hands intrauterine transfusion is considered relatively safe with survival rates of about 90% for red cell alloimmunization (4) (Figure 2b).

Intrauterine transfusion may also be used in anemic fetuses secondary to parvo virus infection, large feto-maternal hemorrhage, Twin anemia polycythemia syndrome, intrauterine fetal demise of single fetus in monochorionic twins, placental and fetal tumors like chorioangioma and sacrococcygeal teratoma.

Multifetal pregnancy reduction (MFPR) and selective fetal reduction

With increasing use of assisted reproduction and advanced maternal age, there is a boom of higher order multiple gestation in the past two decades. Triplets or higher order births have increased 400% from 1980 to 1998 (5). Multifetal pregnancy reduction is defined as first or early second trimester procedure for reduction of one or more normal fetuses, to increase the likelihood of survival and reduce morbidity of remaining fetuses.

The risk of preterm delivery for singleton is about 10% and it increases to 80% for triplets(6). Average gestational age at delivery decreases from 35 weeks for twins to 32 weeks for triplets and 29 weeks for quadruplets. Rate of fetal growth restriction reported is 14-25% for twins and increases to 50-60% for triplets and quadruplets (7). MFPR to twins increases gestational age at delivery by 4 weeks and significantly improves maternal and fetal outcome.

Maternal morbidity and mortality increases with presence of each additional fetus and is related to higher rates of gestational diabetes, pregnancy induced hypertension, admission for preterm and premature rupture of membrane, higher operative delivery, postpartum hemorrhage and higher postpartum depression.

The inherent risk of pregnancy loss in MFPR is directly proportional to the higher starting number of fetuses, number of fetuses reduced and finishing fetal numbers. The risk reduces with the experience and expertise of the operator. The average risk of pregnancy loss due to the procedure at <26 weeks is about 4-5% (8,9). The benefit of fetal reduction of triplets and higher order fetuses exceeds the risk involved in the procedure.

Pre-procedure assessment and Counseling

A detailed ultrasound is performed before MFPR to confirm gestational age, determine number of fetuses, labeling them, assessing growth, chorionicity determination, early evaluation for structural defects and screening for aneuploidy by nuchal translucency. It would be beneficial to assess additional soft markers like nasal bone, ductus venosus flow and tricuspid regurgitation in the higher order fetuses planning a reduction as maternal serum screening is not useful for these higher order pregnancies or those with fetal demise. Determining chorionicity is most important before fetal reduction as MFPR with intra-cardiac KCL can only be done in di-chorionic fetuses.

Detailed nondirective counseling is extremely necessary prior to the procedure and the benefits, risks and alternatives should be explained. An informed consent is to be documented.

Choosing the fetus to be reduced

Fetal reduction is done on the fetus that, on initial evaluation, is relatively smaller in size or structurally abnormal or fetus with increased

nuchal translucency. However, if all fetuses are similar in above assessment then the fetus that is easily approachable, fundal and away from the cervix is targeted for reduction (Figure 3a).

Timing

MFPR is an outpatient procedure. The ideal timing for the procedure is between 11 to 13 weeks. The advantage of pregnancy reduction after 11 weeks (crown rump length >45 mm) include

- Most spontaneous fetal loss would have already occurred
- Procedure is technically easier
- Identification of many structural anomalies and aneuploidy screening can be done.
- Risk of procedure loss rate is least

Route

MFPR can be done transabdominal or transvaginal depending on the expertise of the operator. However pregnancy loss rates are higher in transvaginal route than transabdominal (13.3 vs 3.5%) (10). Hence transvaginal route is rarely used unless there is severe maternal obesity or approach to the fetus to be reduced requires it.

Under ultrasound guidance and under aseptic precautions, a 20-22 Gauze spinal needle is inserted into the heart or thorax of the fetus and 0.2-0.5 ml potassium choride (KCL) is injected (Figure 3b).

Risks

- Amniotic fluid leak
- Chorioamnionitis
- Damage of the fetus without death
- Death of rest of the fetuses if chorionicity determination was inappropriate
- Loss of entire pregnancy

Post-procedure

In view of risk for chorioamnionitis a broad spectrum antibiotic is given prior to the procedure and continued for 5 days. Giving progestrone / tocolysis are individual decisions. Patient is advised on restricted activity for few days and to report if fever/ bleeding / leaking / or pain abdomen. Malformation along with cervical length assessment is to be done at 18 weeks followed by routine monitoring for growth and doppler as in any pregnancy.

Reduction in Monochorionic fetuses

In monochorionic twins intracardiac KCL will cross over to the other fetus through vascular communications and cause fetal demise of the co-twin also. In these cases, if indicated, selective cord occlusion, radiofrequency ablation (Figure 4a) or ultrasound guided interstitial laser may be used but carries a higher risk of pregnancy loss.

Selective feticide

This is a term used distinctly for reduction done in a twin fetus for discordant fetal anomaly in an attempt to save atleast one fetus in multiple pregnancy. Selective feticide is indicated in fetuses whose anomaly is nonlethal but with morbidity or if the defect has a potential for affecting the other fetus and the course of pregnancy.

Indications for selective feticide:

- Discordant for Chromosomal aneuploidy
- Discordant for structural anomaly where the outcome of malformed fetus is hopeless
- Severe discordant growth
- Stage 4 TTTS
- TRAP fetus (Figure 4 b)

Fetal Surgery

Principles

Prenatal intervention is justified only if

1. Accurate diagnosis is made
2. Disease is severe enough to warrant risk of intervention
3. The malformation interferes with organ development
4. If alleviated will allow normal development
5. Fetus cannot be safely delivered at that point of time

Three approaches for fetal surgical

intervention:

1. Open fetal surgery
2. Fetoscopic surgery
3. Percutaneous ultrasound guided surgery using shunts

Prerequisite for fetal surgery:

1. **Nondirective counseling :** Although the final goal of fetal intervention is to improve the health of the fetus, any fetal intervention in utero has implications on the mothers health. Hence the women and the family should be informed in detail about the risks and benefits. The informed consent should involve thorough discussion of the options available including fetal intervention, postnatal therapy, palliative nature of the therapy, residual disease and its long term implications and also options of pregnancy termination.
2. Coexisting anomalies and chromosomal abnormalities are ruled out.
3. Prenatal diagnostic procedure is done to determine the functional status of the organ system, which needs treatment.
4. Tertiary level obstetric, anesthetic and neonatal care available.

Conditions amenable to surgery with proven results

- Pleuroamniotic shunt in primary hydrothorax
- Twin to twin transfusion syndrome
- Twin reversed arterial perfusion sequence
- Ovarian cyst aspiration

Conditions amenable to surgery with mixed results

- Vescicoamniotic shunt for obstructive uropathy
- Thoracoamniotic shunt for congenital pulmonary airways malformation (CPAM, initially called CCAM)
- Fetal tracheal occlusion for congenital diaphragmatic hernia
- Surgery for meningomyelocele and sacrococcygeal teratoma

Conditions amenable to surgery with disappointing results

- Ventriculomegaly –Aqueductal stenosis
- Structural cardiac defects – Balloon valvuloplasty/ septoplasty

Open fetal surgery

First attempted in 1960, open fetal surgery involves an initial hysterotomy under general anaesthesia where the fetus is extracted partially without disconnecting from the placenta and undergoes fetal surgery intrapartum. Fetus is then returned back to the amniotic cavity and the uterus with membranes is resutured. Mother has to be under high doses of intravenous tocolysis for the procedure as well as subsequently to tide over the extremely high risk of preterm labour. Subsequently the mother will need a second surgery (LSCS) for delivery of the baby.

Risk involved with open surgery include

- High chances of preterm labour and rupture of membrane
- Bleeding
- Chorioamnionitis
- Pulmonary edema and complications of anesthesia
- Need for LSCS for present and all subsequent pregnancies

Fetoscopic fetal surgery

Open fetal surgery gave way to fetoscopic surgeries as they were relatively less invasive than open fetal surgery. Fetoscopic surgery is done under epidural / local anaesthesia. It requires specialized fetoscopic instruments, atraumatic ports and working fluid media (saline/ ringer). There is no mandatory need for LSCS later as compared to open surgery.

Indications:

1. Fetoscopic tracheal occlusion for treatment of Congenital Diaphramatic Hernia (Fetendo technique):

The aim is to temporarily plug the trachea

using clips or balloon so as to cause obstruction to lung secretion and subsequently cause expansion of lungs pushing the herniated abdominal viscera back into the abdomen.

An ex-utero intrapartum procedure (EXIT) to remove the clips and intubate the trachea is performed at term during LSCS while the partially delivered fetus is still receiving placental supply.

2. Fetoscopic balloon valvuloplasty of critical aortic stenosis in the fetus has been attempted to prevent progression to hypoplastic left heart syndrome with mixed results.
3. 10-15% of all monozygous twins have TTTS where there are unbalanced vascular anastamosis between both the fetuses. Without treatment perinatal mortality reaches 63-80%. Fetoscopic surgery has reemerged as the treatment of choice for twin to twin transfusion syndrome where selective laser photocoagulation of communicating vessels are done (12). Today fetoscopic laser for TTTS is the most common fetal surgical procedure being carried out.
4. Fetoscopic cord occlusion/ ligation of acardiac twin is also a successful surgical modality. Twin reversed arterial perfusion sequence is seen in 1% of monozygous twins and is associated with cardiac failure in the pump twin with perinatal mortality as high as 55%. Radiofrequency ablation or intrafetal interstitial laser in the acardiac fetus under ultrasound guidance using laser fibres inserted via 18 gauze needle has become the treatment of choice as it is simple, safer & more effective (Figure 4a).
5. Fetoscopic fulguration of posterior urethral valves.

Limitations of fetoscopic surgery:

1. Limited depth and field of vision
2. Intra-amniotic bleed may obscure vision
3. Risk of preterm labor and premature rupture of membranes slightly more than USG guided procedures but less than open fetal surgery.
4. Maternal and fetal injury with the trocar
5. Potential teratogenic effect of light and heat.

Percutaneous ultrasound guided fetal shunts:

Ultrasound guided interventional procedures are done under local anaesthesia.

Complication are low as compared to above procedures and include:

- Preterm, premature rupture of membranes
- Fetal injury
- Shunt block or displacement

Indications:

1. **Primary pleural effusion (Chylothorax):** Extrinsic compression on the developing lungs may lead to pulmonary hypoplasia and hydrops. Pleuroamniotic shunt is a double pigtail catheter which is placed under ultrasound guidance with one end of the shunt in the pleural cavity and other end in the amniotic cavity (Figure 5). About 60% survival rates have been achieved in carefully selected cases of primary pleural effusion (13).
2. **Obstructive uropathy :** Severe bilateral obstruction to outflow of urine may cause backpressure changes leading to nonfunctional dysplastic kidneys in utero and pulmonary hypoplasia due to oligohydramnios (Potters syndrome).

   Intervention is justified only if the obstruction is severe, bilateral, causing progressive oligohydramnios and deteriorating renal function on serial ultrasound remote from term. Some amount of residual renal function must be preserved before intervention.

   Renal function is assessed by fetal vescicocentesis where initially urine in the distended fetal bladder is completely aspirated. Subsequent urine sample is analyzed for sodium, chloride and

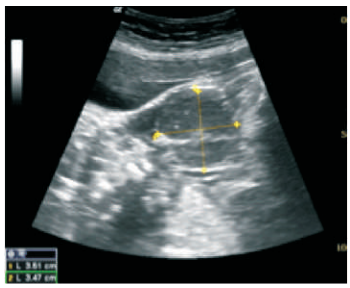

Figure 1a : Thyroid goiter in a thyrotoxic mother on high doses of antithyroid drugs

Figure 1b

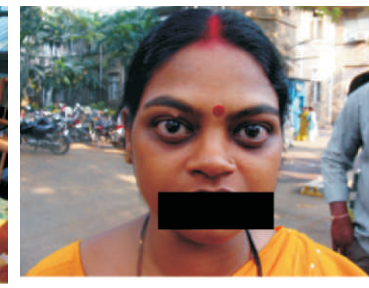

Figure 1c

Mother and neonate with goitre

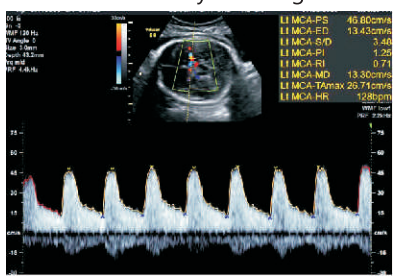

Figure 2a : Middle cerebral artery peak systolic velocity for determining fetal anemia

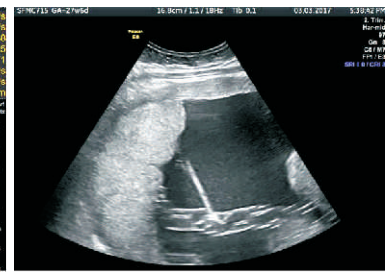

Figure 2b : Intravascular transfusion in the placental cord insertion site

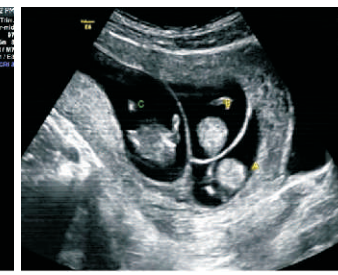

Figure 3a : Assessment of triplets for size, position, labeling, chorioniciy & aneuploidy screen prior to multifetal pregnancy reduction.

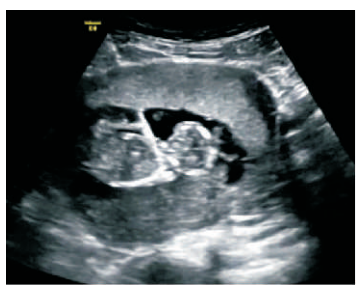

Figure 3b: Fetal instillation of KCL into the heart of the triplet near the fundus. Note the needle traversing the skin, amniotic fluid and thorax of the fetus.

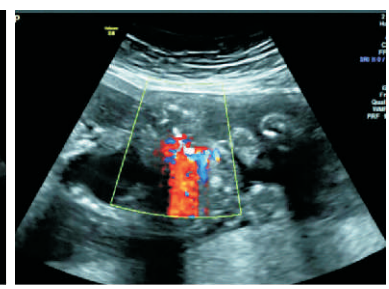

Figure 4a : Monochorionic twin with TRAP undergoing radiofrequency ablation

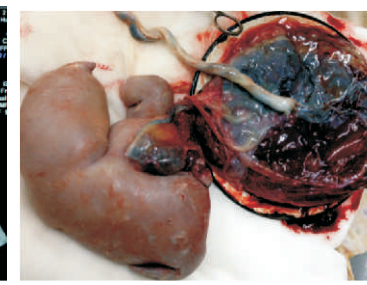

Figure 4 b :
Monochorionic twin with TRAP fetus

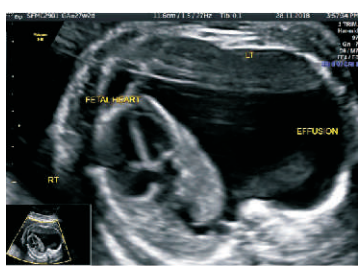

Figure 5 :
Large pleural effusion

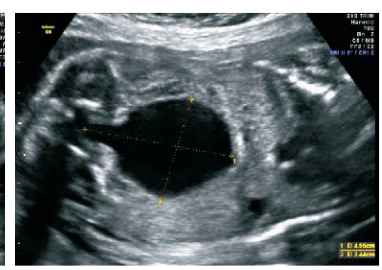

Figure 6a :

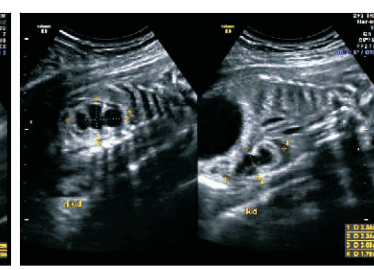

Figure 6b :

Severe obstructive uropathy in a case of posterior urethral valve at 25 weeks requiring vescicoamniotic shunt.