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Enlightening the Path for Next Generation of Gynaecologists

Dedicated Issue:
Fetal Medicine and Therapy

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From the President's Pen

Friends, current issue of AOGD monthly bulletin is devoted to "Fetal Medicine and Therapy". Last twenty five years have witnessed great strides in the field of fetal medicine and fetal therapy. Not only most of the fetal anomalies are diagnosed in early party of pregnancy but also some of the conditions can be managed by intra uterine fetal procedures. With each day we are progressing further till we achieve our goal of diagnosing all aneuplodies, rare familiar and single gene disorders. A team of fetal medicine expert, geneticist and a well trained intervention sonologist are back bone of this super specialty. Finally we resolve to avoid misuse of these advances. Enjoy reading the current issue.

Dr Sunesh Kumar
President, AOGD

From the Secretary's Desk

Dear friends,

Greetings from AOGD Secretariat, AIIMS, New Delhi.

After the previous issue on "Assisted Reproductive Technology", we are happy to bring the current issue on "Fetal Medicine and Therapy". This is an effort to cover day to day practice points in the area of fetal medicine, also including latest advancements in fetal therapy.

We had a number of academic activities including CMEs and workshops under the aegis of AOGD in July, 2019. A CME on 'Tuberculosis and Reproductive health' was organized by safe motherhood committee AOGD at Kasturba Hospital on 3rd July. A CME and workshop on PPH at IMA Hall, Janakpuri was organized by Safe motherhood committee AOGD on 19th July. Another CME on PPH was organized by DGFS and AOGD at Hotel Surya on 23rd July.

Live laparoscopy workshop was conducted under the aegis of Endoscopy Committee, AOGD by PGIMER & RML Hospital on 22nd July, 2019. A Camp was organized on Cancer screening and health by Oncology and rural health committee AOGD at SK Wedding Bells, Dilshad garden.

Quality improvement in health care is the need of the hour. There was a workshop to orient the clinicians towards the methodology for quality improvement to implement the Laqshya labour room guidelines under the quality improvement subcommittee AOGD at LHMC, on 28th July 2019.

The monthly clinical meeting of AOGD was conducted on 26th July at AIIMS, New Delhi and we had an overwhelming response for the same.

We look forward to your presence and support for 41st Annual conference of AOGD on 28th & 29th September, 2019. The last date for early registration is 31st August and for submitting abstracts, it is 15th August, 2019.

Dr Vatsla Dadhwal
Hon. Secretary

Monthly Clinical Meeting

Monthly Clinical Meet will be held at Army Hospital- Research & Referral
on **Friday, 30th August, 2019 from 04:00pm to 05:00pm**.

From the Editor's Desk

Dr J B Sharma
Editor

Dr Reeta Mahey

Dr P Vanamail

Dr Vidushi Kulshreshtha

Co-Editors

Dear friends,

Greetings from the editorial team. With great pleasure, we are presenting this issue on fetal medicine. Fetal medicine is a specialized branch of medicine which is dedicated to unravel the enigmas around the unborn patient and bring a healthy baby in the world by addressing the concerns of fetal growth and development, timely diagnosis of congenital abnormalities, if any; and treatment of these if possible .

A baby is happiness on the way! From conception to delivery, the journey of pregnancy is no short of a grand adventure. Starting from the first page of this great story, complications can occur at any stage. With the advancement in knowledge, screening in first trimester is now an important tool in detection of aneuploidies. Rise in multiple pregnancies due to assisted reproduction, present unique challenges in aneuploidy screening which has been highlighted in this issue. Preterm birth is one of the biggest challenge faced by the obstetrician, but with advances in screening methodology for its prediction, optimal care can be provided.

Handling the Rh iso-immunized fetus has evolved from a seemingly impossible task to a completely preventable condition . Not only that, in this transition from impossible to possible, successful treatment of fetal anemia by intrauterine transfusion is one of the most attractive fetal interventions. Apart from Rh iso-immunization, non-immune hydrops presents as a much greater challenge due to dilemma in approach and management. An algorithm for non-immune hydrops is also highlighted in this issue.

An interesting article on thought provoking images in fetal medicine is also included for the curious learner. We hope you will relish the journal scan and thoroughly enjoy the exciting quiz!

We are immensely grateful to our contributors for the prompt submission of their exceptional articles. We look forward to any suggestions and feedback from you.

Hope you will find this issue enlightening and it will be valuable to you all in your daily clinical practice.

Happy reading to all our readers!

Issue Editors
Dr Vatsla Dadhwal
Dr K Aparna Sharma

Editor
Dr J B Sharma

AOGD Good Clinical Practice Recommendations on Aneuploidy Screening in Pregnancy

Drafted by AOGD Fetal Medicine Sub-Committee (2017-2019)
Published in the year 2017

Advisor: Dr Dipika Deka **Chairperson:** Dr Vatsla Dadhwal
Members: Dr Anita Kaul, Dr Aparna Sharma, Dr Chanchal Singh, Dr Manisha Kumar, Dr Nandita Dimri, Dr Nutan Agarwal, Dr Poonam Tara, Dr Reema Kumar, Dr Rachna Gupta, Dr Sangeeta Gupta, Dr Seema Thakur, Dr Vandana Chadha

These practice recommendations have been drafted after reviewing the currently updated guidelines from American College of Obstetricians and Gynecologists, Society of Obstetricians and Gynecologists of Canada and the Royal College of Obstetricians and Gynecologists. In addition, various large trials and meta-analyses relevant to the PICO (Population Intervention Control and Outcome) questions being studied were reviewed. The guidelines from these standard organizations have been modified to suit the socio-cultural, economical and medico-legal milieu of our country.

The intended users of these guidelines are the general practitioners who should understand the options of screening available in their commonly encountered scenarios. An emphasis has been laid on the decision points and thresholds for referral to a geneticist/ fetal medicine specialist to avoid delay in definitive diagnosis. This document presents a general guide to management and must be integrated into practice keeping in mind the logistics and resources available.

1. Population to be screened

- All pregnant women should be offered screening for aneuploidies after an informed counselling.

2. General Principals of Screening

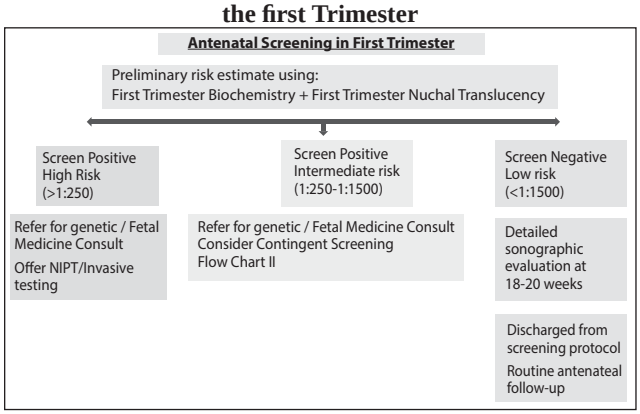
- All pregnant women, regardless of age, should be offered the option of prenatal screening test for the most common clinically significant fetal aneuploidies.
- Informed non-directive counselling is a must before advising the screening test. It includes information about the condition being tested , sensitivity and specificity os screening tests and the need for invasive testing if she is screen positive and the possibility of false negative or a false positive report. Each patient has the right to accept or decline screening test.
- The options for aneuploidy screening are available in both first and second trimester. These are the combined screening test in the first trimester and quadruple test or triple test in the second trimester. Integrated and sequential screening protocols combine the first and second trimester results to give a composite risk. Cell-free DNA testing can be done in all trimesters. Ultrasound can also be used as a screening test in both trimesters.
- In the context of the laws prevalent in our country, the tests should be offered in conjunction with appropriate pre-test and post-test counselling about the feasibility of termination of affected pregnancy only up to 20 weeks in case the couple so wishes.
- At a minimum, any prenatal screen offered should have a detection rate of 75% with no more than a 5% false-positive rate[2]. Therefore, offering maternal age, triple test or only nuchal translucency as standalone tests should be avoided.
- Prenatal aneuploidy screening using age and NT measurement in the first trimester is appropriate for screening in multiple gestations.
- Cost and logistics should be considered while deciding the best modality for screening. Considering the resource differences in various settings, a single screening protocol may not be applicable for all.
- Biochemical tests should be done in accredited labs and the Ultrasounds should be done by sonologists certified to do 11-13^{+6} weeks scan
- For all screening tests, correct dating is important.
- Appropriate post-test counselling must be available. Those with positive screening test are at an increased risk of evaluated aneuploidies and should be offered secondary screening by cffDNA or diagnostic test.
- Those with a negative screening test should be counseled about their lower adjusted risk and

may be discharged from the routine screening protocol. All women should undergo a scan at 18-20 weeks gestation for the detection of structural anomaly.

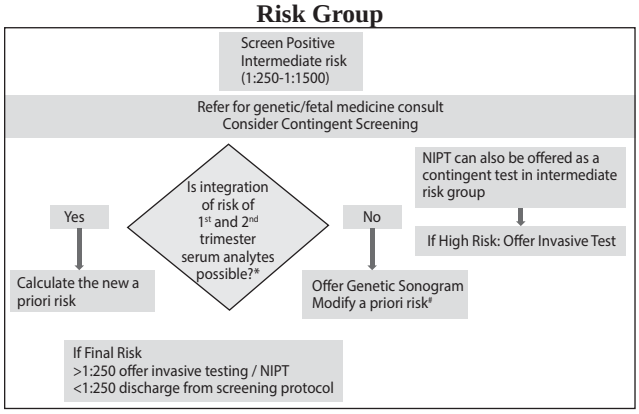
3. Aneuploidy Screening in First Trimester

- A combined screening by Ultrasound markers (Nuchal translucency) and serum biochemistry (PAPP-A and free B-hCG) should preferably be offered if the patient presents in the first trimester. This has a detection rate or 80-85% with a false positive rate of 5%.[2,3]
- Mandatory background information for serum biochemistry should include – ethnicity, maternal age (preferably Date of birth), weight, method of conception, diabetes, smoking, number of fetuses and chorionicity.

Flow Chart I : Desirable Screening Protocol in the first Trimester



Flow Chart II: Contingent Screening in Intermediate Risk Group

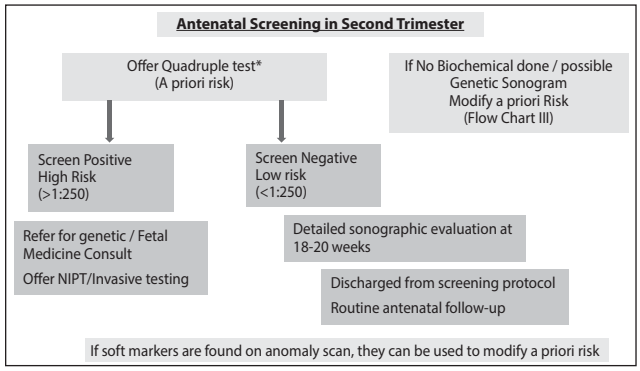


*Combination of first and second trimester biochemical markers needs specialised accredited software and hence, integration is possible only if biochemical markers are analysed both in first and second trimester on the same platform.
See flow chart IV

4. Aneuploidy Screening in Second Trimester

- For pregnant women presenting for first time in second trimester a quadruple test should be offered. Triple test is suboptimal as it has lower detection rate. Both the tests need correct dating and screen for open neural tube defects.
- Women with a low risk on first trimester combined screening test result should be counseled about their lower adjusted risk and should be discharged from the routine screening protocol. They should however undergo a detailed ultrasound at 18-20 weeks, to detect anatomic abnormalities.

Flow Chart III: Screening for women presenting in second trimester



*In situations where quadruple test is not feasible or possible a triple test may be offered with appropriate pre and post test counselling and should be interpreted in conjunction with a genetic sonogram preferably by a fetal medicine expert

5. Combining First and Second Trimester Screening

- Combination of first and second trimester biochemical markers needs specialised software and hence, integration is possible only if biochemical markers are analysed both in first and second trimester on the same platform.
- Integrated and stepwise sequential test protocols improve the detection rates and reduce the false positive rates (Annexure II).
- Contingent screening using cut-off for high risk as 1:250 will only improve the detection rates but will not reduce the false positive rate.
- Doing Quadruple test without integration after low risk first trimester screen, may actually increase false positive rate and hence, should be avoided.
- Genetic sonogram in second trimester can be used to modify first trimester/second trimester screening risk without need for any specialized software.

6. Role of Ultrasound in Aneuploidy Screening in Second Trimester

- All women should be offered a detailed ultrasound at 18-20 weeks, to detect structural abnormalities. "Soft markers" can also be detected at same time

and they can be used to modify a priori risk.

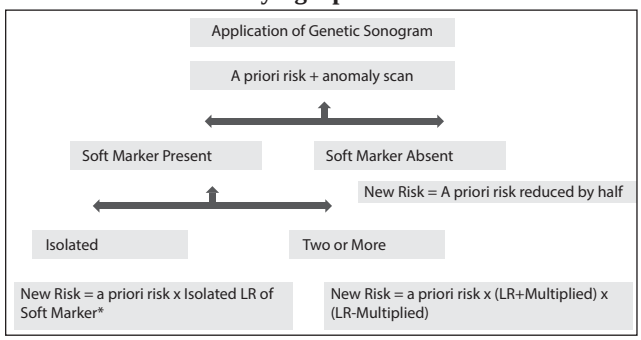
- Scan for soft markers should be done by certified sonologists.

Important pointers to correct interpretation of soft markers:

- Second trimester ultrasound is the least effective method of screening for Down syndrome, with a detection rate of 50-60%, and should not be used in isolation.
- Various soft markers have different associations with Down syndrome, hence the risk with each marker should be considered individually, as shown in the Table below.
- Detection of a soft marker warrants looking for other soft markers and detailed evaluation of fetal anatomy and offering biochemical screen if not done already to calculate a composite risk.
- Some soft markers like increased Nuchal Fold Thickness, ventriculomegaly, Absent Right Subclavian Artery, echogenic bowel and absent nasal bone with high likelihood ratio may warrant an invasive test despite low risk on screening, hence should be referred for counseling to a Geneticist or a Fetal medicine specialist.
- No additional evaluation is required if earlier screen is negative and single soft markers like echogenic intracardiac cardiac focus, choroid plexus cyst are present.
- For women with no previous screening – isolated markers with high positive LR like absent NB, ARSA, ventriculomegaly, increased NFT should be offered invasive testing. If these markers are absent but out of the rest two or more markers are present, invasive test should be offered.
- There is a role for modifying a priori risk in those who have not had any screening or after second trimester screen to reduce invasive procedures (Flow Chart III)

Post scan counselling is again important to make sure that parents understand the results of the genetic sonogram. **The patients should preferably be referred to a Geneticist/ fetal medicine specialist for risk calculation and counseling.**

Flow Chart IV: Algorithm for use of genetic sonogram for modifying a priori risk



* Excel sheet for calculation of LR in presence of multiple marker is available freely and can be downloaded using this link: http://onlinelibrary.wiley.com/store/10.1002/uog.12364/asset/supinfo/uog12364-sup-0002-AppendixS1.xls?v=1&s=2c3d7d64b93d99dd665c355ac0ff687eda3bc708

7. Role of NIPS in Aneuploidy Screening

- Conventional screening methods remain the most appropriate choice for first-line screening for most women in the general obstetric population.
- Certain subgroups of women may be offered NIPS which include:

  Maternal age 35 years or older at delivery,

  Sonographic findings indicating an increased risk of aneuploidy

  History of a prior pregnancy with a trisomy,

  Positive Combined screening tests/ Quadruple test

  Parental balanced Robertsonian translocation involving chromosome 13,18 or 21
- Contingent NIPS can be implemented in routine clinical practice after pretest counselling.
- Cell-free DNA screening has not been validated for women with multiple gestations.
- The cell-free DNA test will screen for 5 common aneuploidies involving chromosomes 13, 18, 21 and sex chromosomes.
- Routine cell-free DNA screening for microdeletion syndromes should not be performed.
- Most appropriate time to offer NIPT in India is after 11-13 $^{+6}$ scan, however test can be done from 9 weeks and any time until delivery.
- An ultrasound for viability, number of fetuses and fetal structural malformations should always be done before sending NIPS. If a fetal structural anomaly or increased NT/NFT is identified on ultrasound examination, diagnostic testing should be offered rather than cell-free DNA screening.
- Minimum fetal fraction for a reliable result is 4%.
- Management decisions, including termination of the pregnancy, should not be based on the results of the cell-free DNA screening alone.

- Women whose results are not reported, indeterminate, or uninterpretable (a "no call" test result) from cell-free DNA screening should receive further genetic counseling and be offered comprehensive ultrasound evaluation and diagnostic testing because of an increased risk of aneuploidy.
- Women with positive NIPS should be offered amniocentesis rather than CVS

8. Aneuploidy Screening in Multifetal Gestation

- Maternal age combined with nuchal translucency may be offered as an acceptable method for aneuploidy screening in twin pregnancies with a DR of 75% with a FPR of 5%.
- First trimester serum screening may be offered for twin pregnancies with slight improvement in performance of screening when combined with age and nuchal translucency
- Chorionicity has definite implications on screening and hence should be reported necessarily. Risk in a dichorionic twins is per fetus while in monochorionic twins the risk is calculated per pregnancy.
- In monochorionic twins a discrepant NT can be an early sign of twin-twin transfusion syndrome .
- For second trimester serum screening in twins, the opinion of a geneticist/fetal medicine expert should be sought as the tests have a low detection rates (50%) with high false positivity(10%)[9]. They should be considered only if first trimester screening was not performed and interpreted with caution in conjunction with a genetic sonogram to keep the invasive testing to a minimum

9. Managing a case of increased nuchal translucency?

- Increased nuchal translucency is an indication for invasive testing to look for chromosomal abnormalities. NIPS should not be offered. If karyotype is normal, further genetic counseling and ultrasonography for fetal structural abnormalities and detailed echocardiography for cardiac abnormalities is also required. Maternal screening for viral infections should be performed (including TORCH, parvo, varicella).

Aneuploidy Screening in Twins

Col Reema Kumar Bhatt
Senior Advisor, Obstetrics and Gynaecology, Army Hospital Research and Referral, New Delhi

Introduction

There has been a noticeable increase in the incidence of multiple pregnancies to about 3.0%[1]. This is attributable not only to increased maternal age but also to the increasing resort to assisted reproductive technologies and ovulation induction as a method of conception. Twin pregnancy poses problems as far as prenatal genetic screening is concerned as compared to singleton pregnancy[2,3].

Inspite of intensive research, prenatal diagnosis still remains a challenge both for the couple and the obstetrician. The complexity begins with deciding the *a priori* risk of Trisomy 21, decision of which screening test to use, which invasive test to employ if screen positive and difficult decisions in IVF conception. The bigger dilemma is the decision to whether or not terminate entire pregnancy; selective reduction; to continue the pregnancy.

Diagnosis of Twins

Randomized trials[4] have shown that 38 percent of twin pregnancies are not diagnosed until after 26 weeks of gestation and 13 percent are not diagnosed until delivery if the routine second trimester USG is missed in the second trimester.

Dating of Twins

Twin pregnancies should ideally be dated when the crown–rump length (CRL) measurement is between 45 mm and 84 mm (i.e. 11+0 to 13+6 weeks of gestation). If the pregnancy is conceived spontaneously, the larger of the two CRLs should be used to estimate gestational age[5]. If the woman presents after 14 weeks gestation, the larger head circumference should be used [6]. When twin pregnancy is the result of in vitro fertilization, accurate determination of gestational age should be made from the date of embryo transfer [44].

Assessment of Chorioamnionicity

It is imperative to highlight that the chorionicity in twins is to be assessed and established in the first trimester by Ultrasonography after 7 weeks with sensitivity ≥98 percent as there is lower but acceptable accuracy (sensitivity ≥90 percent) in the early second trimester Ultrasonography[9,10]. Before 13+6 weeks of gestation the membrane thickness of the amniotic membrane into the placenta at the site of insertion, the T sign or lambda sign and the number of placental masses can be used to determine chorionicity. An ultrasound image demonstrating the chorionicity should be kept in the records for future reference[5]. This is important not only for aneuploidy screening but also for ascertaining the risk of complications due to shared fetoplacental circulation in monochorionic twins, such as twin-twin transfusion syndrome (TTTS) and twin anemia polycythemia sequence (TAPS) [11-12].

Labelling of Twins

It is a good practice to do antenatal twin labelling. Options include: labelling according to their site (left & right or upper & lower); or mapping in the first trimester according to the insertion of their cords relative to the placental edges and membrane insertion. This information should be documented clearly in order to ensure consistent labelling during follow-up scans[5,13]. This becomes even more important in case invasive testing has to be performed later in screen positive patients.

Chorionicity: Not a Surrogate Marker of Zygosity

Another issue that needs adressal is that zygosity is the genetic identity whereas chorionicity is the placentation. When we consider imaging, approximately 80 percent of dichorionic placentas are associated with dizygotic twins and 20 percent are monozygotic. All monochorionic placentas are associated with monozygotic twins, with the rare exceptions in pregnancies conceived by ART. Thus, if the placenta is dichorionic and the fetuses are the same sex, approximately 20 percent will be "identical" twins.[14,15].

Prenatal Screening in Twins

Maternal Age

In a dizygotic pregnancy, maternal age risk for each fetus in twin pregnancy is same as in singletons. Chance that at least one fetus is affected by a chromosomal defect is twice as high as in singleton pregnancies. In monozygotic twins the risk for a chromosomal abnormality affecting both fetuses is same as in singleton pregnancies[16]. However, observed rates of

Down syndrome are lower than expected, possibly due to an increased frequency of early fetal loss[17].

Nuchal Translucency

During the last decade, NT screening has been the election test for first trimester aneuploidy screen. Nuchal translucency distribution does not differ significantly between twins and singletons. The Down syndrome detection rate in multiple pregnancy is similar to that of singletons[18,19].

In monochorionic twins, each fetus has the same risk of being affected with Down syndrome, and the overall risk is the same as in a singleton pregnancy. Thus, the NT measurements are averaged to calculate a single risk estimate for the entire pregnancy, as pregnancy specific risk[20]. Each fetus in a dichorionic twin pregnancy is considered separately, and the risk for each fetus is calculated by using median NT values for singletons [20]. So, it's a fetus specific risk in dichorionics.

Using first trimester NT and maternal age, Sebire and colleagues calculated the DR of 88% for a 7.3% FPR as the specific risk for Down syndrome, for each twin from 448 twin pregnancies. The increased incidence of NT in monochorionic (8.4 %) than dichorionic pregnancy (5.4%) could be a pointer to complications like twin–twin transfusion syndrome (TTTS) [21,22]. Vandecruys et al found that the best screening performance was achieved using the average NT within a monochorionic twin pair compared to highest or lowest NT [23]. Fetal Medicine Foundation, UK recommends an average NT in monochorionic twin pregnancy with 100 % sensitivity for a 4.2 % FPR [24]. Therefore, NT measurement combined with maternal age is an acceptable first trimester screening for prenatal aneuploidy in twins [20,25].

Implications of CRL and NT in Case of Discordance in Twins

We also need to know that in case CRL discordance ≥ 10 % and NT discordance ≥ 20 %, a detailed USG assessment and testing for karyotype abnormalities is required and consultation with fetal medicine specialist is required. The risk of fetal abnormalities was found to be 25% in pregnancies with CRL discordance≥10% compared to 4 % in pregnancies with CRL discordance of < 10 %[5].

Combined Screening (NT + First Trimester Biochemistry)

There is a problem regarding interpretation of biomarkers in twins since both contribute to serum free-beta hCG and PAPP-A. Biochemical marker levels may also be affected by early loss of one or more embroyos and the problem of vanishing twin [26,27]. In case of vanished twin, if there is still measurable fetal pole, NT alone in combination with maternal age should be used for risk estimation because the beta-hCGBand PAPP-A measurements are biased[28]. IVF also affects biochemical marker levels and may be considered when calculating screening results in twins conceived by this method[29]. In the systematic review in 2014 of first trimester combined risk assessment (nuchal translucency and maternal serum biochemical markers) in twin pregnancies, test sensitivity in dichorionic twins was 86 percent (95% CI 73-94) and test sensitivity in monochorionic twins was 87 percent (95% CI 53-98) at FPR of 5 %[30]. First trimester serum screening combined with nuchal translucency may be considered in twin pregnancies. It provides some improvement over the performance of screening by nuchal translucency and maternal age by decreasing the false-positive rate.[20]

Other Sonographic Markers in First Trimester

First-trimester ultrasound screening for chromosomal abnormalities using NT thickness in multiple pregnancies is highly sensitive. However, nasal bone assessment is not only limited in sensitivity but also more challenging in multiple than in singleton pregnancies owing to difficulties in obtaining adequate views of the fetal face[31]. The small advantage in Ductus Venosus is that the FPR decreased from 6.2 to 6%. however, scanning is more challenging and time consuming in twin pregnancies and does not offer any additional advantage[32]

Second Trimester Biochemical Screening

Maternal serum screening in twin pregnancy in second trimester has many unresolved issues. Firstly, serum marker levels in twins are approximately twice those found in singleton pregnancies. But there are wide variations across studies as the number of cases and controls available are much smaller than for singletons[33-39]. Secondly, the interpretation of the markers necessarily relates to the entire pregnancy, while ultrasound markers such as NT are specific to each twin.Spencer et al. evaluated free β-hCG and AFP in 420 twin where the markers were twice as high in the twin pregnancies, the Down syndrome detection rate in twins was 51% at a 5% FPR[39]. Maymon et al[36] found that high false-positive rate in the second trimester serum screening for twins led to an 18.3%

amniocentesis rate in the twin group compared with a 7.5% rate in the singleton group. However, if NT screening is not available or has been missed because of the late diagnosis of a twin pregnancy (after14 weeks), second trimester maternal serum screening may be considered in twins[20].

Integrated Screening

In singleton pregnancies, integrated testing has been proposed to combine the benefits of first and second trimester screening[40]. To date there are no prospective studies of the performance of integrated screening in twins. Wald and Rish have published estimations of the screening performance of integrated testing in twins[41]. Basing their calculations on a number of assumptions, they estimated that for a fixed FPR of 5%, the detection rate would be 93% in monochorionic twins, 78% in dichorionic twins, and 80% overall. The estimated DR of "serum integrated screening" without nuchal translucency is not available. Therefore integrated screening with nuchal translucency plus first and second trimester screening is an option in twin pregnancies. Further, prospective studies are required to validate this[20].

Second Trimester Ultrasound Screening for Aneuploidy

Although the use of the genetic sonogram to detect Down Syndrome in the second trimester has been well studied in singleton pregnancies, there are very few data to estimate the accuracy of this approach in twins[42]. In one study, soft marker discordance was examined in twin sets discordant for Down Syndrome. Nuchal thickness was found to correctly identify 5 of 9 instances of Down Syndrome; the other markers were significantly less efficacious[43]. Currently the data are insufficient to recommend for or against the use of ultrasound soft markers for aneuploidy in twins. Further prospective studies are needed to assess these markers in twins[44].

Non-Invasive Screening Using Cell Free Dna

The use of cfDNA for screening of twin pregnancy is not yet endorsed by ACOG, ACMG or other professional bodies. The amount of cfDNA compared to singleton pregnancy is 35 % higher[45]. This study reported a DR of 95% for Trisomy 21, 85 % for Trisomy 18 and 100% for Trisomy 13[46]. According to, two meta-analyses, the DR for Trisomy 21 was 98.7 % and FPR 0.11 %.[47,48]. The amount of DNA actually contributed by each twin is lower than in singleton pregnancy and maybe quite different for the two fetuses in dizygotic twins. It is impossible to determine which twin is abnormal based on cfDNA analysis alone and the result is reported for the entire pregnancy and invasive testing is required to distinguish which twin is affected[49, 50]. According to two meta-analyses by Gilet al, the DR for Trisomy 21 in twins is 98.7% and FPR is 0.11% which makes it an acceptable screening test in twin pregnancy [51,52]. The most recent metaanalysis reveals that cf DNA testing for Down syndrome in twins is just as effective as in singletons, with a detection rate of 98% and only a 0.05% rate of misdiagnosis[53].

Invasive Screening and its Challenges

Prior to invasive testing or in the context of twins discordant for an abnormality, selective reduction should be discussed and made available to those requesting the procedure after appropriate counselling[20]

Chorionic Villus Sampling

CVS is preferred in dichorionic twin pregnancy. Earlier diagnosis of any aneuploidy is particularly important in twin pregnancy, given the lower risk of selective termination in the first compared with the second trimester (7% risk of loss of the entire pregnancy, and 14% risk of delivery before 32 weeks) [54]. The disadvantage being that in case of CVS in monochorionic pregnancy sample will only be from single placenta so we will may miss rare discordant chromosomal anomalies. When monochorionic twins are discordant for an abnormality, prior to invasive testing, a discussion should take place regarding the complexity of selective termination, should it become necessary[55]. The total loss rate upto 22 weeks is reported at 3.1 % and the total loss upto delivery of about 4.8 % [56,57]. The disadvantage is the risk of Chorionic Villous Sampling error which by current studies is reported to be 2-4 % [58-60].

A meta-analysis showed that the overall pregnancy loss rate following Chorionic Villous Sampling (CVS) in twin pregnancy was 3.8% and following amniocentesis was 3.1 %[5].

Amniocentesis

Amniocentesis is typically performed at or after 15 weeks' gestation[61]. There is much debate about whether single or double sampling is required in monochorionic twins. In view of the multiple case reports of monochorionic twins with discordant karyotypes and the difficulty in assessing monochorionicity at later gestational ages, many advocate sampling of both amniotic sacs[62-64].

It is recommended that, during amniocentesis, both amniotic sacs should be sampled in monochorionic twin pregnancies, unless monochorionicity is confirmed before 14 weeks and the fetuses appear concordant for growth and anatomy[20].

After correcting for as many confounding factors as possible, the most recent studies report an attributable loss rate varying from 0.3% to 2.2%[65,66].

Conclusion

1. Dichorionic pregnancy has a fetus specific risk and monochorionic pregnancy has pregnancy specific risk for aneuploidy.
2. Combined screening is the best method of screening in twin pregnancy.
3. NT scan and age risk is an acceptable method of screening in the absence of serum biochemistry
4. Non invasive prenatal screening is an acceptable method of screening in twins.
5. Second trimester biochemistry has very limited role in aneuploidy screening in twins

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Forthcoming Events

- Next Monthly Clinical Meeting on 30th August, 2019 (4:00-5:00 pm) at Army Hospital- Research & Referral
- DGES Conference with IAGE & AOGD on 31st August & 1st September, 2019 at Hotel Jaypee Sidhartha, New Delhi
- CME on 'Surgical Wounds' on 7th September at GTB by Dr Radhika
- Simm Black Travelling Fellowship Oration on 9th September,2019 organize by AIIMS
- 41st Annual Conference of AOGD, on 28th-29th September, 2019 at Eros Hotel, Nehru Place, New Delhi.
- **Preconference workshops**

  26th September 2019:

  I st Trimester USG - Quality Control – Dr Manisha Kumar (LHMC)
  Urogynaecology – Dr J B Sharma (AIIMS)
  Obstetric Skills – Dr Reva Tripathi (HIMSR)
  Ovulation Induction & IUI – Dr Surveen Ghumman (Max Hospital)

  27th September, 2019:

  Endometriosis (video workshop) – Dr Kuldeep Jain (KJIVF Centre)
  Preventive Oncology – Dr Savita Samsunder (SJH) & Dr Susheela Gupta (Fortis Hospital)
  Endoscopy Live WS – Dr Richa Sharma (GTB Hospital)
  Saving Mothers – Dr Mala Srivastava (SGRH)
  Medico-legal aspects in Obst & Gynae – Dr Asmita (MAMC)

Screening for Preeclampsia

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Screening for Preeclampsia

Preeclampsia is the most enigmatic disease which obste-tricians have known for the longest duration of time and still like the Pandora's box a lot remains to be discovered. It is a major cause of maternal and perinatal morbidity and mortality[1] and the devious part is played by defective placentation. PE can be subdivided into early onset PE with delivery \ 34 weeks' gestation and late onset PE with delivery C 34 weeks. It is the early onset PE which is associated with great amount of neonatal morbidity in terms of prematurity[2]. Therefore with the shift in pyra-mid of antenatal care to first trimester it is logical that as far as screening for preeclampsia is concerned, it becomes imperative to identify early pregnancies at high risk of early onset PE and to undertake necessary measures to decrease the brunt of defective placentation and reduce the prevalence of the disease.

The screening tests for preeclampsia include tests which range from as simple as detailed history taking both obstetric and medical including maternal demographic characteristics, to a very doable test that is measurement of blood pressure of which MAP is validated, to a targeted ultrasound in the form of uterine artery pulsatility index (PI), and biochemical tests like plasma protein-A (PAPP-A) and placental growth factor (PlGF) at 11–13 weeks' gestation which can identify a large number of pregnancies at high-risk for early onset PE[3,4].

Most importantly the need for screening for preeclampsia is important because there exists an evidence based strategy to prevent it. Low-dose aspirin for prophy-lactic use for prevention of preeclampsia has been inves- tigated by a number of researchers. If the treatment is started at an early (\16 week's) gestation there is a sig-nificant reduction in early-onset PE and this is supported by meta-analyses[5,6] and taking this into consideration various national and international agencies currently rec-ommend that women screened to be at high risk of PE should be offered aspirin therapy[7,8]. ''US preventive Services Task Forces Recommendation Statement'' recently recommended of daily low-dose (81 mg/day) aspirin beginning in the late first trimester in high risk cases[9].

This reinforces the need for early identification of high risk women with the objective of implementing targeted interventions for improving perinatal outcome.

Screening by Maternal History

Most of the professional bodies recommend that at the booking visit detailed history should be taken to ascertain her risk of preeclampsia and have issued guidelines for same (Table 1). However, screening strategies using maternal factors and history alone for detection of PE only perform moderately well at best. It has been demonstrated that maternal demographic characteristics, including med-ical and obstetric history are potentially useful in screening for PE only when the various factors are incorporated into a combined algorithm derived by multivariate analysis[10].

There is another risk model called competing risk model where it is assumed that all women would develop preeclampsia if the placenta malfunctions before delivery.

This approach, is based on a survival time model, which assumes that if the pregnancy was to continue indefinitely, all women would develop PE and whether they do so or not before a specified gestational age depends on a competition between delivery before or after development of PE[3].

Table 1: Maternal risk factors for preeclampsia

National Institute for Health and Care Excellence[7] High-risk factors (one)
Hypertensive disease during a previous pregnancy Chronic kidney disease
Autoimmune disease such as systemic lupus erythematosis or antiphospholipid syndrome
Type 1 or type 2 diabetes
Chronic hypertension
Moderate-risk factors (more than one)
First pregnancy
Age 40 years or older
Pregnancy interval of more than 10 years BMI of 35 kg/m^2 or more at first visit Family history of PE Multiple pregnancy
World Health Organization[8]
Risk factors
Previous PE
Diabetes
Chronic hypertension
Renal disease
Autoimmune disease
Multiple pregnancy

Estimated DR of PE requiring delivery before 34, 37 and 42 week's gestation in screening by maternal factors are about 36, 33 and 29% respectively at FPR of 5%, and 51, 43 and 40% respectively at FPR of 10% [10]. Inspite of such low detection rates most of the professional bodies including American College of Obstetricians and Gynecologists rec-ommends taking a detailed medical history only to assess a patient's risks for developing preeclampsia[11].

Screening by Maternal Biophysical Markers

Blood Pressure

Women who subsequently develop PE have higher systolic blood pressure and MAP before the onset of clinical dis-ease. MAP is calculated by dividing the sum of the systolic and twice the diastolic blood pressure by three and is thus easily measurable.

The correct method of BP is that MAP should be measured by validated automated devices with women in sitting position with back supported and legs uncrossed that two measure-ments should be taken from each arm simultaneously with each arm supported at the level of the heart and that the average of the four measurements should be used[12].

Measurement of Blood pressure is very doable in every set up and if MAP is taken in first trimester along with maternal characteristics the detection rate of preeclampsia goes upto 74% for early preeclampsia, 63% for interme-diate preeclampsia and 49% for late preeclampsia with a false positive rate of 10%. If we measure MAP in both first and second trimester we have a detection rate of 84% for early preeclampsia, 66% for intermediate and 53% for late preeclampsia with a false positive rate of 10%[13].

Uterine Artery Dopplers

The spiral arteries undergo a transformation to low resis-tance vessels by trophoblastic invasion and increases blood flow in the placental bed in pregnancy[15]. If this mech-anism fails it leads to defective placentation[15,16]. As predictors of preeclampsia average PI of both uterine arteries was taken at 22–24 weeks. It has a good negative predictive value which is better than positive predictive value and was considered better predictor for early onset severe PE however interventions have shown no statisti-cally significant benefit at this stage to prevent preeclampsia and there was a definite need to get better as far as the screening performance of uterine artery for preeclampsia was concerned, so there came the need to measure uterine artery Doppler in first trimester as surro-gate marker of defective placentation and this also supports the inversion of pyramid of antenatal care where emphasis is shifting to first trimester screening. The uterine artery PI MoM is significantly increased at 11–13 week's gestation in women who subsequently develop PE.

Gestational age at screening, maternal weight, racial origin and history of pre-existing diabetes mellitus, affect the first-trimester uterine artery PI and therefore it should be it should be expressed as MoM after adjustment for these factors. The addition of uterine artery PI to maternal factors improves the DR from 36 to 59% and 33 to 40% at FPR of 5% and from 51 to 75% and 43 to 55% at FPR of 10% for PE requiring delivery before 34 and 37 week's gestation[4].

However even though detection rate of preeclampsia goes up with measurement of uterine artery Doppler, a reliable measurement of uterine artery PI is infact operator depen-dant. A sagittal section of the uterus should be obtained by using transabdominal ultrasonography and the cervical canal and internal cervical os needs to be identified. Color flow mapping is used to identify each uterine artery along the side of the cervix and uterus at the level of the internal os. Pulsed wave Doppler is then used with the sampling gate set at 2 mm to cover the whole vessel and care should be taken to ensure that the angle of insolation is less than 30L. When three similar consecutive waveforms are obtained the PI is measured and the mean PI of the left and right arteries is calculated to ensure the accurate artery is not being sampled instead of the uterine artery[17]. It is important to ensure that the peak systolic velocity is greater than 60 cm/s.

Screening by Maternal Biochemical Markers

A plethora of biochemical markers have been investigated for the prediction of PE which includes PLGF, PAPP A, Inhibin-A and Activin-A, PP13, Disintegrin and Metalloprotease 12(ADAM12), Cystatin C, Pentraxin 3, P-Selectin, Fetal Hemoglobin. These markers are thought to be representative of reduced placental perfusion leading to placental ischemia-related damage with the release of inflammatory factors and abnormal oxidative stress[16,18]. Maternal serum PAPP-A and PlGF are two biochemical markers that have stood the test of time and evidence as useful markers not only for aneuploidy screening but also for predicting preeclampsia[19]. Preg-nancy-associated plasma protein-A is a syncytiotrophoblast— derived metalloproteinase, which enhances the mitogenic

function of the insulin-like growth factors by cleaving the complex formed between such growth factors and their binding proteins[20]. PAPP-A plays an important role in placental growth and development, therefore low serum PAPP-A is associated with a higher incidence of PE. Placental growth factor is a glycosylated dimeric glycoprotein, which is a member of the vascular endothelial growth factor sub-family. PlGF is proangiogenic and has been speculated to play a role in normal pregnancy, and decrease in its level has been implicated in development of PE[21,22]. These reduced levels of serum PlGF are evident from both the first- and second-trimesters of pregnancy[23, 24].

In biochemical testing, the serum metabolite concentration is then expressed in a multiple of the expected median (MoM) of the normal [25] because both PAPP-A and PlGF have shown to be affected by gestational age at screening, maternal weight, racial origin, cigarette smok-ing, conception by IVF, nulliparity and pre-existing dia-betes mellitus. In addition, serum PlGF is also affected by maternal age [26]. The addition of maternal serum PAPP-A and PlGF to maternal factors improves the DR from 36 to 60% and 33 to 43%, at FPR of 5%, and from 51 to 74% and 43 to 56%, at FPR of 10%, for PE requiring delivery before 34 and 37 weeks' gestation[14].

Screening by Maternal Biochemical and Biophysical Markers

Effective screening for PE can also be achieved by a combination of maternal factors, biochemical and bio-physical markers. If MOM values of biochemical markers serum PAPP-A and PlGF, MAP and uterine artery PI in pregnancies with PE, are added to the maternal character-istics all four markers together increase the risk assessment of preeclampsia. Estimated DR of PE requiring delivery before 34, 37 and 42 weeks' gestation in screening by maternal factors with biochemical and biophysical markers are 93, 61 and 38%, respectively, at FPR of 5%, and 96, 77 and 54%, respectively, at FPR of 10%[14]. Here comes the role of intervening by giving aspirin before 16 weeks to prevent preeclampsia[27–29].

Screening in Third Trimester

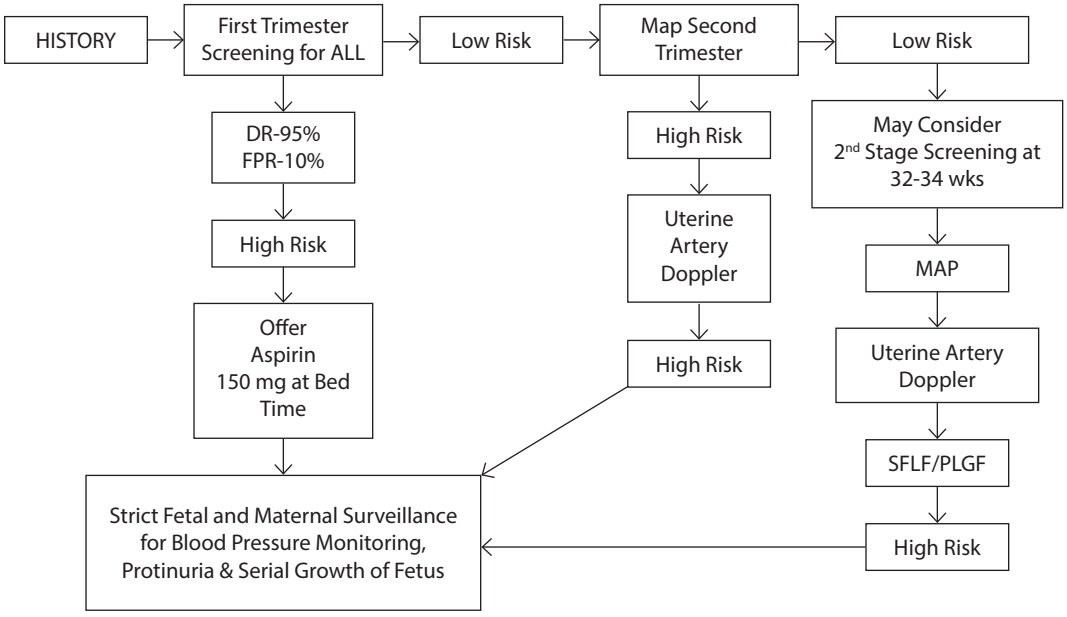
For early onset PE the first-trimester of pregnancy gives us an opportunity to do a good screening. However, late onset PE still remains a challenge. Nicolaides and his team therefore proposes screening at 11–13 weeks, which mainly aims at early onset PE prediction and here comes the role of aspirin in the dose of 150 mg at bed time which if started before 16 weeks substantially decreases the incidence of early onset preeclampsia[5,36]. The second stage screening at 30–33 weeks, is required for predicting preeclampsia that aims at intensive close monitoring of these pregnancies by blood pressure measurements, proteinuria and intensive fetal moni-toring for growth restriction and warrants delivery at or after 34 weeks[30]. This particular combines maternal character-istics and history, biochemical and biophysical markers at 30–33 week's gestation to estimate the risk of developing PE requiring delivery within selected intervals from the time of screening. They have used MAP, UTPI, PLGF (pro angio-genic), and SFLT (antiangiogenic) at 30–34 week's gestation to examine the potential improvement in performance of screening by maternal factors along with the addition of each biomarker and combinations of biomarkers. In pregnancies that developed PE, the values of MAP, UTPI, and SFLT were increased and PLGF was decreased. For all biomarkers the deviation from normal was greater for preterm-PE than term-PE and therefore, the performance of screening was inversely related to the gestational age at which delivery become nec-essary for maternal and/or fetal indications. Combined screening by maternal factors, MAP, UTPI, PLGF, and SFLT predicted 98% of preterm-PE and 49% of term-PE, at a false-positive rate of 5% [31]. The main aim of third trimester screening is to identify the subgroup that will develop severe PE requiring delivery within the subsequent 1–4 weeks. In such high-risk pregnancies measurement of serum PlGF or soluble fms-like tyrosine kinase-1 (sFlt-1) to PlGF ratio are highly accurate in identifying the target group[32,33]. In pregnancies complicated by PE, compared with normal preg-nancies, serum PlGF MoM is decreased, and sFlt-1 MoM is increased. Researchers are now talking about screening as late as 35–37 weeks to predict preeclampsia[34].

Screening in Second Trimester

The main value of the 22 weeks assessment is to identify first the high-risk group for development of early PE that would then require close monitoring for development of high blood pressure and proteinuria at 24–32 weeks and second the high-risk group for preterm PE that would require reassessment at around 32 weeks and on the basis of such assessment stratification into a high-risk group in need of close monitoring at 32–36 weeks and a low-risk group that would be reassessed at 36 weeks. In pregnancies that developed PE the values of MAP, UTPI, and SFLT were increased and PLGF was decreased. For all

biomarkers the deviation from normal was greater for early than for late PE and therefore the performance of screening was inversely related to the gestational age at which delivery became necessary for maternal and/or fetal indi-cations. Screening by maternal factors predicted 52, 47, and 37% of PE at \ 32, \ 37, and 37 week's gestation respectively at a false-positive rate of 10%. The respective values for combined screening with maternal factors and MAP, UTPI, and PLGF were 99, 85, and 46%. The per-formance was not improved by the addition of SFLT. Therefore performance of screening for PE by maternal factors and biomarkers in the middle trimester is superior to taking a medical history[35]. Performance of screening for PE by this method is by far superior to those recom-mended by ACOG [11] or NICE[7] where screening performance of preeclampsia is very poor.

Algorithm We Can Follow for Preeclampsia Screening



Summary

1. We should follow universal screening for all pregnancies in the first trimester because it has a detection rate of 95% with a false positive rate of 10%. This method of screening is far superior to screening by history alone as recommended by ACOG and NICE.
2. This early screening gives a window of opportunity to offer aspirin which as per the Combined Multimarker Screening and Randomized Patient Treatment with Aspirin for Evidence-Based Preeclampsia Prevention (ASPRE) trial has demonstrated that aspirin at 150 mg/day given at night to high-risk women at 11–13 weeks till 36 weeks reduces the risks of PE at \ 32 and \ 37 week's gestation by 80 and 60% respectively. There was no reduction in the risk of PE at [37 week's gestation[36].
3. There is role of second stage screening for preeclamp-sia at 30–33 weeks for early detection of those who are likely to develop preeclampsia in the next 4 weeks, which would enable us to increase fetal and maternal surveillance.

Conclusion

Preeclampsia continues to remain the most dreaded obstetric complication of pregnancy. Effective first trime-ster screening at 11–13 weeks gestation in which bio-physical and biochemical markers when combined with maternal characteristics for predicting early onset PE is now achievable with a DR of about 95% and a FPR of 10%. The motive remains to identify those cases that would potentially benefit from prophylactic pharmacolog-ical interventions to improve placentation. It is foreseen that a similar integrated screening at 30–33 weeks in future will emerge as a protocol for effective prediction of preg-nancy complications that develop during the third-trime-ster. This would help to tailor make the monitoring and content of subsequent visits for selection of the best time for delivery. Prospective studies are underway to confirm the predictive abilities of the biomarkers identified both for early and late onset PE as well as for other related obstetric complications.

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Role of Ultrasound in Prediction and Management of Preterm Labour

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Introduction

Preterm birth, defined as a baby born alive before 37 weeks continues to be a major contributor to perinatal morbidity and mortality. Complications related to prematurity are the leading cause of death amongst children under 5 years of age.[1] As per the World Health Organisation (WHO) factsheet, India tops the list of countries with the greatest number of preterm births.[2] Several risk factors are implicated as being causative of preterm labour and considering the etiologic heterogeneity, a single strategy to screen and/or prevent this pathology seems elusive. However, research over the last 2 decades has conclusively proven that a short cervix in mid-trimester is a strong predictor of preterm labour in both low and high risk women.[3-5] This chapter aims at reviewing the current evidence on role of ultrasound in prediction and management of spontaneous preterm labour.

Rationale behind assessment of cervical length

The cervix plays a unique role in pregnancy - it remains closed and 'holds' the pregnancy till term and then becomes soft, gets effaced and then fully dilates during the process of birth. Thus, it only makes sense that a decreasing cervical length should increase the risk of spontaneous preterm labour. Most published literature defines a cervical length less than 25 mm at 16-24 weeks as the threshold to identify women at risk of preterm delivery (sensitivity 37.3%, specificity 92.2% and a negative predictive value of 97.4%[6]).

Technique of measuring cervical length by ultrasound

Transvaginal ultrasound (TVS) is the gold standard for assessing cervical length. It is highly sensitive, measures the total cervical length and has less than 10% interobserver variability. Transabdominal assessment is not only suboptimal for getting an acceptable image, it also overestimates the cervical length because of the full bladder that is needed to visualise the cervix abdominally.

However, adherence to the correct technique of assessing the cervix transvaginally is essential for accurate and reproducible measurements. It should be assessed empty bladder. The pregnant woman is asked to empty her bladder and lie down in the dorsal position. The TVS probe covered with a probe cover or a condom is introduced into the anterior fornix. The cervix is imaged in the midsagittal plane with magnification such that it fills up at least 75% of the screen. The bladder tip should be visible. Both the internal as well external os should be clearly seen. Care should be taken to avoid undue pressure as it might give an erroneously elongated measurement. The cervical length is measured along the endocervical canal with a straight caliper (Figure 1A). In case of a curved cervix, 2 or more linear measurements should be taken and then added rather than tracing the cervical length. Three measurements should be taken and the shortest should be reported. Mild suprapubic or fundal pressure should be applied to look for funnelling (Figure 1B).

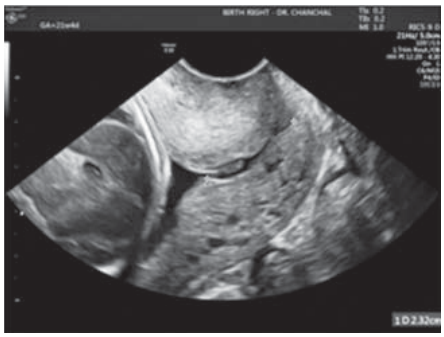


Figure 1 [A]: TVS for measurement of cervical length. Cervix is short at 23 mm though internal os appears closed.

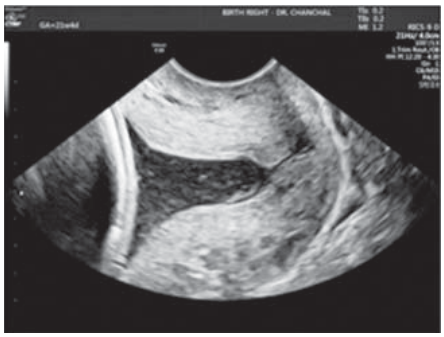


Figure 1 [B]: Funneling on application of fundal pressure in the same patient.

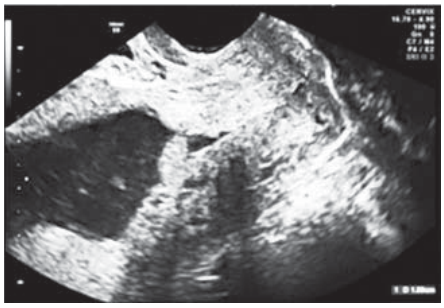
The correct technique is described and can be accessed online at the Fetal Medicine Foundation (https://fetalmedicine.org/education/cervical-assessment) as

well as the Perinatal Quality Foundation websites (CLEAR - Cervical Length Education and Review programme, https://clear.perinatalquality.org). Both foundations offer voluntary image reviews and cervical length ultrasound certifications and can be made use of by sonologists interested in improving and standardising the quality of their imaging.

Additional ultrasound features apart from length of the cervix

Funnelling ('opening up of the internal os') in the absence of a short cervix is not reported to be a predictor of preterm birth. So, it may be reported but should not alter management nor does it call for repeat measurements.[7]

Sometimes echogenic material in the amniotic fluid is seen near the internal os on TVS – this debris labelled as '*sludge'* is an inflammatory exudate consisting of fibrinous material, white blood cells and bacteria.[8] Presence of sludge in conjunction with a short cervix increases the risk of preterm birth above the risk conferred by a short cervix alone.[9] However, it does not call for routine antibiotic treatment when seen.



Prevention of preterm birth in women with short cervix

As mentioned above, there are several publications implicating a short cervix as a major predictor for preterm birth in both high and low risk women.[3-5] Natural progesterone has been proven to reduce the risk of preterm birth in women with a short cervix by almost 50%.[10-13] Women with history of previous preterm birth at less than 34 weeks and a short cervix may benefit from cerclage. There is no role of cerclage in low risk women with an incidental finding of a short cervix. Women with progressive shortening despite natural vaginal progesterone may be candidates for cerclage though as per current evidence vaginal progesterone is equally effective as cerclage.

Considering that there is both an effective screening method as well as an effective 'intervention' for screen positive women, it has been suggested that universal cervical screening may be a cost-effective measure and should be adopted in places where facilities are available.[14] Training and accreditation are essential before this can be adopted as a universal screening modality. An Indian study also found routine cervical length screening useful in predicting early preterm birth; however, they did not find any utility in either progesterone or cerclage in these women.[15] However the numbers were too small to draw any definite conclusion.

Role of ultrasound in management of preterm labour

Short cervix in women presenting with symptoms suggestive of preterm labour can help in triaging women who need admission, in utero transfer, tocolysis and antenatal steroid cover – all of which are known to improve outcomes in premature babies. The WHO recommendations on interventions to improve preterm birth outcomes lists all these interventions – however the difficulty is in identifying women who will actually go into labour or deliver prematurely. Thus ultrasonographic assessment of cervical length can be used to identify women who will benefit from these measures. Adding fetal fibronectin to cervical assessment is reported to have a high negative predictive value (97.6% for delivery within 7 days of testing).[16]

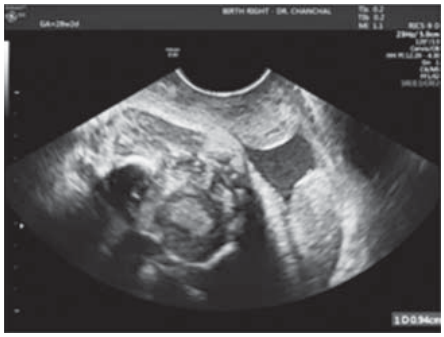


Figure 4: 31-year-old Primi gravida with 28 weeks singleton pregnancy presented to the emergency with lower abdominal discomfort. Speculum examination was not informative because of obesity (BMI 42 kg/m2) as well as patient discomfort. TVS (performed with aseptic precautions) showed an open cervix. These findings warrant admission and antenatal steroid cover.

Conclusions

An appropriately performed transvaginal ultrasound in asymptomatic women at 16 to 24 weeks can identify a subset of women at risk of preterm birth who can benefit from interventions known to prevent preterm birth (vaginal natural progesterone, cerclage).

Assessment of cervical length in women presenting with symptoms suggestive of preterm labour can triage women who do not need admission and/or antenatal steroids with a high negative predictive value.

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Management of RH-Negative Pregnancy

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The advent of routine antenatal and postnatal Anti D prophylaxis has resulted in a substantial decrease in Rh isoimmunization in developed world. Sadly, in developing nations like ours, we still come across Rh iso-immunized pregnancies with bad obstetric history, multiple fetal and neonatal losses. Lack of adequate number and quality of antenatal checkups, lack of availability of free Anti D prophylaxis in government setups, non-affordability of patients and very importantly, lack of awareness on part of obstetricians continues to increase the number of iso-immunized pregnancies in our country.

This article deals with management of Rh negative pregnancy in very practical and simple terms.

First Pregnancy of a Patient with Rh (-) Blood group

When we come across an antenatal patient with a Rh Negative Blood group, first step should involve checking blood group of the husband/partner. If the husband's blood group is negative, there is no risk of iso-immunization and patient can be followed up like any other low risk pregnancy. If the husband's blood group is positive, mother's antibody screen using the Indirect Coombs test (ICT) titre should be done as soon as possible. If ICT is negative, and it's a low risk pregnancy, ICT can be repeated at 28 weeks[1] and if still negative the patient should be administered routine antenatal anti D prophylaxis in a dosage of 300 microgram intramuscularly[1] to prevent sensitization in the third trimester and peripartum period. After receiving the Anti D prophylaxis at 28 weeks, patient's ICT titres may become positive upto 4 times [upto 1:4]. However titers more than this reflect sensitization.

After delivery, baby's blood group should be checked. If negative, no need for any further intervention. If baby's blood group is positive, mother should be given another shot of anti D injection.

In an ideal scenario, dose of Anti D should be calculated using the Kleir Bethke test that can quantify the amount of feto maternal hemorrhage if it has occurred. Four ml of fetal blood (1 ml of Fetal RBC) is neutralized by 300 micrograms of Anti D. If it is not possible to quantify the exact amount of feto-maternal hemorrhage, a dose of 300 micrograms is recommended for all patients.[1]

Management of a Rh iso-immunized Pregnancy

These patients warrant referral to fetal medicine centers well experienced in management of such high risk pregnancies.

Rh negative antenatal patients with Rh positive husbands/partners who test positive for ICT, should have their ICT titers measured. A critical ICT titer is defined as a titer at which there is a risk of development of fetal anemia and hydrops in the fetus. It is usually taken as a titre of 1:16 to 1:32.

In women with prior history of an affected neonate (requiring exchange transfusion or phototherapy), or intrauterine fetal death, hydrops or history of previous intrauterine fetal blood transfusion, getting the ICT titers may not be necessary as it would anyways be more than the critical titer.

In every Rh isoimmunized pregnancy, there might be two possibilities. The fetus may either be Rh Negative or Rh Positive. If the fetus is Rh negative, this can be managed like a low risk pregnancy. Only if the fetus is Rh Positive, would there be a chance of fetal anemia thus requiring antenatal surveillance [stringent follow-ups with middle cerebral artery doppler peak systolic velocities (MCA PSV)]

For an Rh negative women with an Rh positive husband, we should determine zygosity of the husband's blood group. If he is homozygous positive, 100 % of the fetuses will be positive. So all such pregnancies need to be followed up with MCA PSV. If father is heterozygous positive, then 50 percent of fetuses will be Rh positive. So in this scenario, we need to look for blood group of the fetus. This can be done either by amniocentesis or by cell free fetal DNA technique (as is being commonly done in USA and European countries). Fetal RHD status is looked for by evaluation of cfDNA sequences in maternal plasma using a reverse transcriptase PCR.[2] Only if the fetal blood group is positive, will this requires fetal surveillance.

However in low resource set ups like ours, if facility for checking zygosity of husband's blood is unavailable, then we follow all Rh isoimmunized pregnancies that have achieved critical ICT titer with ultrasound for

MCA PSV. If the critical titers have not been reached, such patients need a repeat ICT titer every 2 weeks. Women who test ICT positive should not be given Anti D prophylaxis in pregnancy or post partum. For women with previously affected pregnancies/ neonates, MCA PSV monitoring should be done from 18 week period of gestation.

Detection of Fetal Anemia

Traditionally, fetal anemia was looked for by doing amniocentesis and then measuring the amount of bilirubin in the amniotic fluid by spectro-photometery at Δ450. This was an indirect method of looking for fetal anemia as bilirubin is a by-product of hemolysis. Levels of bilirubin were then plotted on graphs (Liley's/Queenan's) and if they were in high risk zones, cordocentesis was done to determine fetal hematocrit and intrauterine fetal blood transfusion would be done accordingly. If the bilirubin levels fell in the low risk zones, amniocentesis was repeated at 2 weekly intervals.

However, after years of research and understanding that MCA PSV doppler correlates well with fetal anemia, this non invasive technique has almost entirely replaced the traditional invasive method of looking for fetal anemia in almost all fetal medicine centers world wide. This works on the principle that with anemia, hematocrit of fetal blood and thus viscosity decreases, which in turn leads to increased velocity of blood in the fetal arteries. Fetal Middle Cerebral Artery has been studied well and it has been found to be 88% sensitive and 82% specific for detection of fetal anemia[3], with a false positive rate of 12%. Beyond 35 weeks, the false positivity increases so values many not be very reliable.[4]. The use of Doppler for management of such patients avoids an invasive amniocentesis in about 50% of patients.[5]

Measurement of Middle Cerebral Artery – Peak Systolic Velocity (MCA-PSV)

Technically, Circle of Willis is visualized at a transverse section of the fetal head just above anterior wing of sphenoid bone at level of base of skull. Middle cerebral artery is identified originating from the internal carotid artery. Ideally the artery closer to the maternal abdomen should be chosen to measure the peak systolic velocity. Angle of insonation should be kept as close to 0 degrees as possible. [Figure1, Figure 2]. Peak systolic velocities (PSV) are measured in cm /sec and depicted in multiple of median (MOM) for that period of gestation POG [Figure 3] [3].

- Peak systolic velocity of value of less than/equal to 1 MOM depicts there is no fetal anemia
- MCA PSV between 1-1.29 MOM depicts mild anemia
- MCA PSV between 1.29-1.5 MOM depicts moderate anemia
- MCA PSV value of more than ≥1.5 MOM depicts severe anemia

Patients with MCA PSV values less than 1.5 MOM require regular follow-up with doppler and delivery should be planned around 37-38+6 weeks period of gestation.[1,6]

Intrauterine Fetal Blood Transfusion (IUT) Procedure

Indications for IUT

MCA PSV ≥ 1.5 MOM, hydrops and Δ 450 values in the high risk zones of Liley's/Queenan's curve are indications for cordo-centesis followed by intrauterine fetal blood transfusion. Fetuses with MCA PSV values < 1.5MOM are followed up weekly or twice weekly with doppler MCA PSV.

Blood Preparation Required for IUT

RBC's used for fetal blood transfusion are O negative, cross matched with the maternal blood. The blood is doubly centrifuged to attain a hematocrit of 75-85%, irradiated to reduce graft versus host reaction and leukocyte depleted to reduce risk of cyto -megalo virus (CMV) infection. Blood should have been freshly donated (<7 days old) to prevent decrease in 2-3 diphospho glycerate levels and thus allow for maximum availability of oxygen to fetus.[7]

Volume of blood to be transfused is calculated by the Mandelbrot formula[8].

Volume of blood to be transfused (ml) = ([Final hematocrit - Initial hematocrit)/ Transfused blood hematocrit] x fetoplacental volume.

Fetoplacental volume (ml) = 1.046 + fetal weight(g) x 0.14

Intrauterine Fetal Blood Transfusion (IUT): Procedure

Sites for IUT:

Intravascular (fetal umbilical vein), intrahepatic and intraperitoneal (in the fetal abdominal cavity) are the sites for intrauterine blood transfusion. The most preferred one being intravascular route. Intraperitoneal

site may be chosen in very small fetuses (around 18 - 20weeks) since performing a cordo-centesis would be extremely challenging at this stage as the cord would be very thin making the procedure very difficult.

Procedure is performed under ultrasound guidance taking full aseptic precautions.

Requirements for IUT are shown in Figure 4. Blood is preloaded in 10 cc syringes. Using a 20 G spinal needle, vascular access is gained in the fetal umbilical vein at site of placental cord insertion [Figure 5]. This may be difficult if the placenta is posterior and it may then be required to choose a free loop of the umbilical cord however this is technically much more challenging.

A muscle relaxant (vecuronium: dose 0.1mg/kg estimated fetal weight) may be used paralyze the baby and this may be injected intravascularly at the start of the transfusion immediately after obtaining the pre transfusion fetal blood sample or it may be given as an intramuscular injection in the fetal thigh before gaining vascular access. Blood is pushed slowly using a triway connector. Following the transfusion, the post transfusion, sample is obtained to measure the post transfusion fetal hematocrit.

Ideally, at the start of IUT, after cordocentesis, pre transfusion sample of fetus should be obtained, hematocrit should be measured immediately and amount of blood to be transfused should be calculated using the Mandlebrot formula as discussed. If facilities for immediate calculation of fetal hematocrit is not possible, then for the first transfusion, initial hematocrit is assumed to be 30%. Final hematocrit is kept at 50-55%. For fetus with hydrops, the initial hematocrit is assumed to be 20%. In such cases the volume to be transfused is to be decided keeping in mind not to raise the final hematocrit to 4 times the initial value, because that might result in volume overload and further worsening the cardiac failure of the hydropic fetus. A second transfusion is usually done after 48 hours.

MCA PSV may be used to guide the initial transfusion. But after two transfusions, the sensitivity of doppler measurements decreases and transfusion is usually decided by the rate of fall of fetal hematocrit calculated from the past two transfusion values.

Termination of pregnancy is usually planned around 35 weeks of period of gestation. However, in expert hands and only at the most experienced fetal medicine centers, last transfusion may even be given upto 34-35 weeks.[9]

Management of the Neonate

At birth, baby's cord blood hematocrit and bilirubin is looked for. If hematocrit is less than 30% or serum bilirubin is more than 5gm% exchange transfusion is required. Multiple fetal blood transfusions may entirely replace the fetal blood with transfused donor red blood cells and thus may suppress erythropoiesis in the neonates. These passively acquired maternal antibodies in the fetal circulation can persist for upto 3-6 months thus these babies are at risk of developing anemia and might need subsequent top up transfusions and require to be on follow up.

Management of Pregnancy with Anemia before 20 weeks Period of Gestation

For rare cases with severe alloimmunization with hydrops or severe anemia before 20 weeks, intraperitoneal transfusions may be performed. Plasma exchange and intravenous immunoglobulin administration Iv IG may also be an option in women that slows down the degree of hemolysis in such fetuses that may help in delaying the first transfusion to a period of gestation in which intravascular transfusions may be possible.[10]

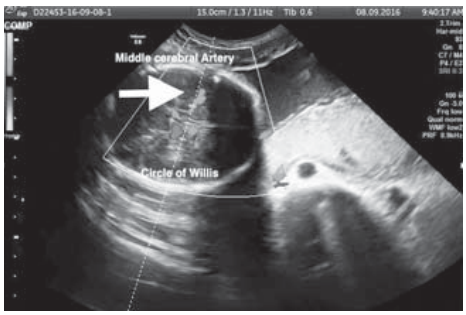

Figure 1: Circle of Willis is visualized at a transverse section of the fetal head just above anterior wing of sphenoid bone at level of base of skull. Middle cerebral artery is identified originating from the internal carotid artery. Angle of insonation should be kept as close to 0 degrees as possible.

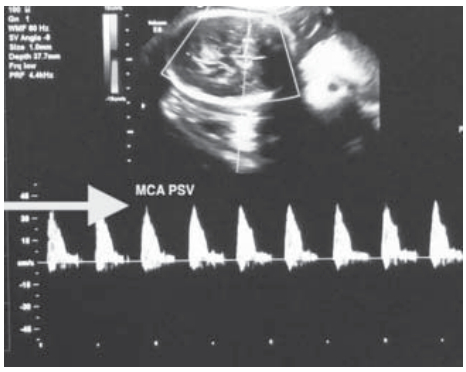

Figure 2: Doppler measurement of Middle Cerebral Artery Peak Systolic Velocity (MCA-PSV)

Week of Gestation	Multiples of the Median			
	1.00 (Median)	1.29	1.5	1.55
	cm/sec			
18	23.2	29.9	34.8	36.0
20	25.5	32.8	38.2	39.5
22	27.9	36.0	41.9	43.3
24	30.7	39.5	46.0	47.5
26	33.6	43.3	50.4	52.1
28	36.9	47.6	55.4	57.2
30	40.5	52.2	60.7	62.8
32	44.4	57.3	66.6	68.9
34	48.7	62.9	73.1	75.6
36	53.5	69.0	80.2	82.9
38	58.7	75.7	88.0	91.0
40	64.4	83.0	96.6	99.8

Figure 3: Expected MCA PSV as a function of gestational age: adapted from Mari et al [3]

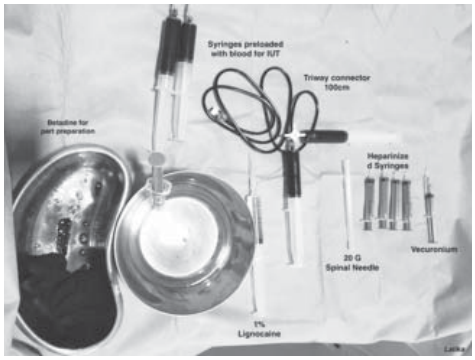

Figure 4: Requirements for preforming an Intrauterine blood transfusion

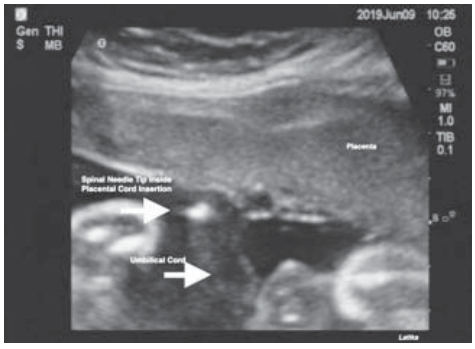

Figure 5: Image of intrauterine blood transfusion showing tip of spinal needle inside the cord insertion

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SIMMS BLACK TRAVELLING FELLOWSHIP

Date: 9th September 2019, Monday
Venue: Maulana Azad Medical College, Delhi

Topics: "Preterm Birth Prevention: What Works and What Doesn't"
"Early onset IUGR: Management Dilemmas"

Speaker: Professor Zarko
Coordinator: Dr Nirmala Agarwal
Dr Asmita Rathore
Dr Sangeeta Gupta
Dr Arbinder Dang

Date: 8th September 2019, Sunday
Venue: Varanasi

Coordinator: Dr Nirmala Agarwal
Dr Uma Pandey

Registration free but Mandatory
Contact Mr. Asif +919560069925 / 9716801190

RCOG UK MRCOG Part III Revision Course

(Franchised)

Sunday 15th & Monday 16th September 2019
(Total 2 Days)

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(First Come First Serve basis)

Course Fee Rs. 45000

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Civil Lines, Delhi 110054

RCOG UK MRCOG Part II Revision Course

(Franchised)

Friday 3rd, Saturday 4th & Sunday 5th January 2020
(Total 3 Days)

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(First Come First Serve basis)

Course Fee Rs. 35000

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18 Sham Nath Marg
Civil Lines, Delhi 110054

SECRETARIAT

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Administrative Assistant, Mr Asif Muniri +919560069925 / 9716801190
Tel No – 91-11-23981260, 23994401-10 Ext 314; Email- rcognz2017@gmail.com
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Events Held

- CME on "different aspects of ANC" on 11th June, 2019 organized under the aegis of Safe Motherhood Committee AOGD at Guru Gobind Singh Govt. Hospital.

- CME on PPH on 13th June, 2019 organised under the aegis of Safe Motherhood Committee AOGD by West Delhi Gynae Forum at Hotel Surya, Rajouri Garden.

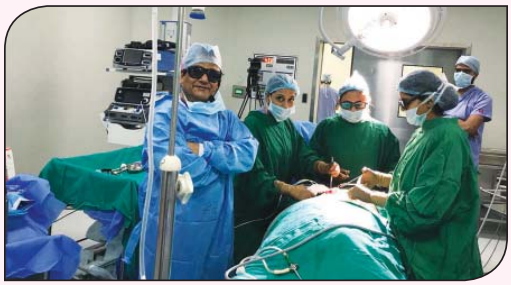
- Orientation Programme on "PPH and eclampsia" on 18th June, 2019 organised under aegis of Safe Motherhood Committee AOGD by DDU Hospital.

- CME on 'Tuberculosis and Reproductive Health' on 3rd July, 2019 organized by Safe Motherhood Committee AOGD at Kasturba Hospital.

- CME and workshop on 'PPH' on 19th July, 2019 organized by Safe Motherhood Committee AOGD at IMA Hall, Janak Puri

- CME on PPH on 23rd July, 2019 organized by DGFS and Safe Motherhood Committee AOGD at Hotel Surya.

- 3D Live Workshop on Laparoscopy on 12th June, 2019 organized under the Aegis of Endoscopy Committee – AOGD at Manipal Hospital, Dwarka.



- Live Laparoscopy workshop on 22nd July, 2019 was organised under the aegis of Endoscopy Committee AOGD by PGIMER & Dr. Ram Manohal Lohia Hospital, Delhi.

- Cancer Screening and Health Camp on 16th July, 2019 organized by Oncology & Rural Health Committees AOGD at SK Wedding Bells, Dilshad Garden, Delhi.

- Monthly Clinical Meeting on 26th July, 2019 at AIIMS Hospital, New Delhi.

41th Annual Conference of AOGD 2019

Organised by: **Department of Obstetrics and Gynaecology AIIMS, New Delhi**

Theme: Enlightening the path for the Next Generation

Date: **28th - 29th September 2019**
Venue: **Eros Hotel, Nehru Place, New Delhi**

Pre-Conference Workshops

26th September 2019

Ist Trimester USG - Quality Control
Dr Manisha Kumar (LHMC)

Urogynaecology
Dr J B Sharma (AIIMS)

Ovulation Induction and IUI
Dr Surveen Ghumman (Max Hospital)

Preventive Oncology
Dr Savita Samsunder (SJH)
& Dr Susheela Gupta (Fortis Hospital)

27th September 2019

Endometriosis (video workshop)
Dr Kuldeep Jain (KJIVF Centre)

Obstetric Skills
Dr Reva Tripathi (HIMSR)

Endoscopy
Dr Richa Sharma (GTB Hospital)

Saving Mothers
Dr Mala Srivastava (SGRH)

Medico-legal aspects in Obs & Gynae
Dr Asmita (MAMC)

Theme Topics for Invited Abstracts

Abstract Submission till 31st August, 2019

High Risk Pregnancy & Fetal Medicine

Cutting Edge Technology in Obstetrics and Gynaecology

Preventive Oncology

Miscellaneous

Early Bird Registration till 31st August, 2019

For more details visit AOGD website www.aogd.org
For Online registration https://tinyurl.com/y39uqljd

41th Annual Conference of AOGD 2019

Date: **28th - 29th September 2019**
Venue: **Eros Hotel, Nehru Place, New Delhi**

Tentative Scientific Program

28.9.2019 (Hall 1)	28.09.2019, (Hall 2)	29.09.2019, (Hall 1)	29.09.2019, (Hall 2)
Recurrent pregnancy Loss	Reproductive Endocrinology and Infertility	Assessment of Critically ill Women – Obstetric Triage	Gynaecological Oncology
Stage Based Management of FGR	Premature ovarian insufficiency	Surviving Sepsis Campaign	ERAS
Managing Rh Negative Pregnancy	Fibroids and Fertility	Maternal Collapse: Case scenarios	HIPEC in Ovarian Cancer: Standard of Care or Experimental Approach
Hyperglycemia in Pregnancy : Case based Management	Panel: PCOS and Fertility - Can we improve outcome	Defining Normal and Abnormal Labor	Current Indications of Menopausal Hormone Therapy in Cancer Survivors
Role of USG in Multiple Gestations	Hirsuitism: Case based Management	Optimising Labor and Birthing Positions and RMC	Panel on Management of Gynaecological Cancers in Younger Women
Establishing Services for caring of Multiple Pregnancies	Obesity and Fertility	Interpreting CTG	Controversies in Gynaecological Oncology: MIS in Carcinoma Cervix
Screening in Twins	Fertility Preservation-For Whom-when	QUIZ on General Gynaecology	Drills and Role Plays Eclampsia Shoulder dystocia
Approach to Common Fetal Anomalies: Panel	Ethics in Medical Practice	Basic Life Support Maternal CPR	Safe Abortion Practices
Urogynaecology	Documentation and Communication Role Plays: Building a better doctor and patient relationship	The robot in Gynecology	Slogan Competition
OAB: Evaluation	Scar ectopic	Advances in Fetal Therapy	Consortium on Safe Abortion Panel Discussion
OAB: Management	Reducing Caesarean Section Rates	Sentinal Lymph Node Biopsy	Video Session
Panel: Current Diagnosis and Management of SUI	Morbidly Adherant Placenta: Diagnosis and management	Time Lapse Imaging in ART: Where do we stand	Staging Laparotomy in Carcinoma Cervix
Debates	Medical Management of Fibroids	Recent advances: Guidelines	Lap Cerclage
NIPT vs Invasive testing	Fluid management in Hysteroscopy	PE : What's new	Difficult TLH
To Freeze or not to Freeze	Panel : Case Based Approach to AUB	Preterm Labor	Repair of 3rd Degree Perineal-Tear
Mesh or Mess	Ethics and Medicolegal issues Breaking bad news	Anticoagulation in Pregnancy	Adenomyomectomy
Induction at 39 weeks	Examining a Rape Victim	Thyroid	
		Amenorrhea	
		Anemia in Pregnany	

41st Annual Conference of Association of Obstetricians and Gynecologists of Delhi

28th - 29th September, 2019

Venue: **Eros Hotel, Nehru Place, New Delhi**

REGISTRATION FORM

Full Name ..... Qualification ..... Institution .....

Speciality .....

Category: (Tick any) Delegate ( ) PG Student ( ) Faculty ( )

Department ..... Designation .....

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Mobile No. ..... Landline No. ..... E-Mail .....

AOGD Membership No.....

ACCOMPANYING PERSON'S Details

Name ..... Age .....

THEME TOPICS FOR ABSTRACT SUBMISSION

1. High Risk Pregnancy & Fetal Medicine ( )
2. Cutting Edge technology in Obstetrics and Gynaecology ( )
3. Preventive Oncology ( )
4. Miscellaneous ( )

Guidelines for abstract submission on aogd.org

Last date for Abstract Submission for Free Communication and Poster: 15th August 2019

Preconference workshops (Tick any one)

26th September 2019

1. Ist Trimester USG - Quality Control ( )
2. Urogynaecology ( )
3. Ovulation induction and IUI ( )
4. Preventive Oncology ( )

27th September 2019

5. Endometriosis (video workshop) ( )
6. Obstetric skills ( )
7. Endoscopy ( )
8. Saving mothers ( )
9. Medico-legal aspects in Obs & Gynae ( )

Registration Fees: (inclusive of 18% GST)

	Conference		Workshop	
Registration Category	**Upto 31st Aug. '19**	**Spot Registration**	**Upto to 31st Aug. '19**	**Spot Registration**
AOGD Member	Rs. 6000	Rs. 7000	Rs. 1500	Rs. 2000
PG Student	Rs. 4000	Rs. 4500	Rs. 1000	Rs. 1500
Non- AOGD Member	Rs. 6500	Rs. 7500	Rs. 1500	Rs. 2000
Accompanying Person	Rs. 5000	Rs. 5500		

All DD/Cheque payable at New Delhi & should be made in favour of **"Association of Obstetricians and Gynaecologists of Delhi"**

- ❖ Write your Name and Contact No. at the back of DD/Cheque
- ❖ Registration for the conference is mandatory in order to register for the pre conference workshops.

AOGDIANS above the age of 70 years are exempted from registration fees. Kindly submit copy of your Aadhar Card.

PAYMENT DETAILS

Please find enclosed herewith DD/Cheque No. ..... Dated .....

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REGISTRATION GUIDELINES

1. Conference registration is mandatory for registration for the pre conference workshops.
2. AOGDIANS above the age of 70 years are exempted from registration fees, please submit copy of your Aadhar card as age proof along with the duly filled registration form.
3. Post Graduates to attach a certificate from HOD and also should be an annual member of the AOGD in order to attend and present a paper.
4. Conference registration includes delegate kit, lunch & tea on 28th - 29th September 2019, participation in scientific session & exhibitions. No guarantee of delegate kit for spot registration.

CANCELLATION & REFUND POLICY

1. All cancellation should be made in writing and sent to AOGD secretariat.
2. All cancellation received before 15th August 2019 will be entitled for 75% refund of the amount paid.
3. All cancellation received between 15th August 2019 to 2nd September 2019 will be entitled for only 25% refund of the amount paid.
4. No refund for cancellation made after 2nd September 2019.
5. The refund process will begin only 30 days after the completion of the conference.

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41st Annual Conference of Association of Obstetricians and Gynecologists of Delhi

28th - 29th September 2019, Eros Hotel, Nehru Place, New Delhi

Pre-conference Workshops: 26th-27th September, 2019

ABSTRACT SUBMISSION FORM

Presenting Author's Name: ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

Post Graduate Resident: Yes ☐ NO ☐

Qualifications: MD ☐ MS ☐ DGO ☐ DNB ☐ Fellowship ☐

AOGD Member: Yes ☐ No ☐ Registration no ☐☐☐☐☐☐☐☐☐☐

Designation: .....

Institute Name: .....

Type of Presentation ☐ Oral ☐ Poster

Address: .....

Phone: ☐☐☐☐☐☐☐☐☐☐

E-Mail: .....

Theme Topics for Abstract Submission (tick one)

1) High Risk Pregnancy & Fetal Medicine ☐ 2) Cutting Edge technology in Obstetrics and Gynaecology ☐

3) Preventive Oncology ☐ 4) Miscellaneous ☐

ABSTRACT : (Copy & Paste abstract here as / per instructions below)

Note:

1) Only members of AOGD are entitled for paper & poster presentation (Proof of membership should be enclosed)
2) Registration is Mandatory for Abstract Submission
3) Abstract to be sent by email at **aogdabstract2019@gmail.com** with the Pre-registration details for the conference.
4) Last Date for Abstract Submission 15th August 2019

Free Papers & Poster Submission

Theme Topics for Abstract Submission

1) High Risk Pregnancy & Fetal Medicine 2) Cutting Edge technology in Obstetrics and Gynaecology 3) Preventive Oncology 4) Miscellaneous

Please send Abstract Submission Form to **AOGD Secretariat, Room No. 3080, Department of Obstetrics and Gynaecology Teaching Block, IIIrd Floor, All India Institute of Medical Sciences, Ansari Nagar, New Delhi-110029**

Last date for accepting free paper and poster abstract is 15th August, 2019.

Competition Papers

- Candidates should be less than 30 years of age. Place of study should not be mentioned anywhere in the paper.
- Three hard copies of the competition paper & a soft copy of the competition paper along with structured abstract should be sent to AOGD Secretariat, Room No. 3080 at Department of Obstetrics and Gynecology Teaching Block, IIIrd Floor, All India Institute of Medical Sciences, Ansari Nagar, New Delhi-110029
- Last date for submission of competition paper is 15th August, 2019.

Notes: Papers/ Posters will not be considered without registration payment.

Instructions for Abstract Submission

Please follow these instructions carefully:

1. The abstract must be in English with not more than 250 words (excluding title, author and Institutional affiliations). It must be typed within the frame in the Abstract Form (using Times New Roman with font size 12). Please use MS Word 2007/2010 formats only. Text should be in black only.
2. Title must be in capital letters. It should be short and concise.
3. The name of authors should follow immediately under the title in one line. Type initials and family name of authors in BLOCK letters and underline the presenter's name. DO NOT include degrees or professional designations. The name of institution, city and country should be in lower case, following immediately after the authors, on a different line.
4. Leave one line between the title/ authors/ institution block and the body of the abstract.
5. Abstracts should be structured under following headings.
   - Objectives
   - Methods
   - Results
   - Conclusions
6. It is not desirable to simply state: like "The results will be discussed"
7. Use of standard abbreviations is desirable. Please write special or unusual abbreviation in brackets after the full word, the first time it appears. Use numerals to indicate numbers, except to begin sentences.
8. Do not include graphs and references in the abstract.
9. Use single-line vertical spacing and leave one line between paragraphs.
10. Hard Copy in triplicate of abstract along with copy of registration receipt should be sent by the post at AOGD Secretariat, Room No. 3080, Department of Obstetrics and Gynecology, Teaching Block, IIIrd Floor, All India Institute of Medical Sciences, Ansari Nagar, New Delhi-110029
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    In e-mail correspondence, please mentions 'Abstract' in the subject line. Abstracts will be reviewed and rated by scientific committee prior to final decision on acceptance.

    Decision for acceptance as oral presentation or poster presentation rests with the Scientific Committee.
16. For case report submission, the words "case report" should be included in the title. Headings are not required in abstracts for case reports
17. **DATES TO REMEMBER**

    Last Date of Submission 15th August 2019

Non Immune Hydrops

Jaya Chawla
Associate Professor, RML Hospital, New Delhi

Hydrops fetalis is the collection of fluid in the extra vascular compartments of the foetus in utero. By definition, fluid should accumulate in two or more cavities or potential spaces. These could manifest as, pericardial or pleural effusion, ascites and generalized skin thickness greater than 5 mm.[1]

Non immune hydrops (NIH) is an array of disorders that remains after exclusion of immune mediated hydrops.

Fetus as patient is more susceptible than adults to develop hydrops.[2] (Table 1)

Table 1: Factors making the fetus more susceptible to hydrops than adults

1. Capillary permeability in the fetus is much higher than adults
2. In the fetus the interstitum is much more compliant causing a pressure gradient towards it.
3. Rise in central venous pressure needed to halt lymphatic drainage is less in fetus compared to adults

Table 2: Causes of Non Immune Hydrops

1. Cardiovascular causes
   - Anatomical
     - Cardiac tumors e.g rhabdomyosarcomas
     - Myocarditis
     - Cardiomyopathy
     - In association with aneuploidy
     - Heterotaxy
   - Functional:
     - Bradyarrhythmias/ congenital heart block
     - Tachyarrhythmias: SVT/ Atrial flutter
2. Chromosomal abnormalities:
   - Turner's syndrome
   - Trisomy: 21/18/13
   - Triploidy
3. Abnormalities of lymphatic drainage:
   - Lymphatic Dysplasia,
   - Lymphangiomas
   - Lymphangiectasia
4. Intrathoracic masses:
   - CPAM
   - Congenital diaphragmatic hernia
   - Congenital high airway obstruction syndrome
5. Abdominal tumors:
6. Neurological
   - Myotonic Dystrophy,
   - Arthrogryposis
   - Fetal Akinesia Deformation Sequence
7. Gastro intestinal causes:
   - Midgut Volvulus
   - Jejunal atresia
   - Meconium peritonitis
   - Hepatic Diseases
     - Cirrhosis,
     - Biliary Atresia,
     - Polycystic Disease of Liver
     - Cholestasis
8. Hematologic causes
   - Anemia:
     - ICH
   - Feto maternal haemorrhage
     - Hemoglobinopathy
     - Enzymopathy
     - Parvovirus infection
   - Leukemias:
     - Intrauterine Infections
     - Myeloproliferative Disorders
     - Infiltrative Disorders
9. Skeletal dysplasia:
   - Osteogenesis Imperfecta,
   - Osteochondrosis
   - Osteopetrosis,
   - Thanatophoric Dysplasia,
   - Asphyxiating Thoracic Dysplasia
10. Intrauterine infections:
    - TORCH
    - Listeria
    - Parvovirus
    - Syphilis
    - Echovirus
    - Adenovirus
11. Inborn Error of Metabolism:
    - Mucopolysaccharidoses,
    - Gaucher Disease
    - G6PD Deficiency
    - Niemann-Pick Disease
12. Tumors:
    - Sacrococcygeal teratomas
13. Placenta & cord abnormality
    - Chorioangioma of placenta
    - Monochorionic multifetal gestation
    - Angiomyxoma of cord,
    - Aneurysm of Umbilical Artery,
    - Thrombosis / Torsion of Umbilical Vein

Conventionally, hydrops fetalis has been categorised on the basis of the system affected.

1. **Cardiovascular**

   Cardiovascular disorders, both anatomical and functional, can cause hydrops. In reviews by

Bellini et al these disorders have consistently accounted for more than 20% cases.[3-5] The underlying pathophysiology causing hydrops is heart failure with concomitant fluid overload. Impaired venous return from the placenta to the heart results in placentomegaly and hypoxic injury. *Cardiac tumors* can cause hydrops by means of mass effect, impaired cardiac function, or raised intrathoracic pressure. *Fetal myocarditis* secondary to autoimmune disorders or intrauterine infections affects myocardial contractility. *Cardiomyopath*y due to congenital infections, maternal insulin dependent diabetes, tachyarrythmias or high output conditions such as fetal anemia or AV malformations, can result in similar insult. The prognosis for foetuses with hydrops due to structural cardiac causes is extremely poor, with mortality rates touching 100% in some series. Cardiac compromise can also prove to be the common pathway for development of hydrops in aneuploidies and intrathoracic masses. Among disorders of rhythm, tachyarrhythmias are the most common treatable causes of hydrops. Brady arrhythmias are less likely to be a cause, yet congenital heart blocks merit a mention. More than two third of cases are secondary to maternal autoimmune disease. When associated with structural disease, this set has a particularly dismal prognosis.

2. **Abnormalities of lymphatic drainage** may lead to hydrops. Examples include lymphatic dysplasia, lymphangiomas and lymphangiectasia. Cystic hygromas represent the most frequently encountered aberrations of lymphatic system with a prevalence of 1 in 8000 live births. They are differentiated from nuchal edema by the presence of a nuchal ligament/ septations. Most commonly found in the neck, but also encountered in thorax and abdomen, they cause hydrops by mass effect leading to aberrations in the flow of lymph as well as venous return.[6] More than half the cases are associated with aneuplodies, the most common being Turner's syndrome followed by Trisomy 21. Less frequently encountered are Edward's and Patau's syndrome and triploidy and tetraploidy.[7] More recently, the application of microarray to evaluation of cystic hygromas is reported to increase the yield of diagnosis by nearly 5-10%, in cases where karyotype is found to be normal. The most frequent findings in CMA are deletions and duplications at 22q11 locus.[8] More importantly, cystic hygromas are frequently associated with malformations of the cardiac and skeletal systems besides, congenital diaphragmatic hernia (CDH), arthrogryposis and pes equinovarus which can contribute to hydrops.[9]
3. **Anomalies of the thorax**, such as, CDH and congenital pulmonary airway malformations (CPAM) are likely to cause hydrops by mass effect of the space occupying lesion. This impedes lymphatic as well as venous return, causes mediastinal shift, and compresses the heart. The size and site of the lesion also has prognostic implications. Congenital high airway obstruction, a relatively rare cause of hydrops, causes massive pulmonary distension leading to compression of vena cava, thereby jeopardising venous return.[10]
4. **Neurological impairment** can be attributed to etiologies such as intracranial haemorrhage, hemangiomas, or genetic syndromes causing impaired mobility in the fetus. The mechanism of development of NIH in each of these varies. In ICH, it is fetal anemia, in hemangiomas, high output cardiac failure and in hypomotility syndromes (e.g Myotonic dystrophy, arthrogryposis and fetal akinesia deformation sequence) impaired respiratory movements raise CVP and capillary hydrostatic pressure.[11,12]
5. **Gastrointestinal malformations**, can lead to hydrops secondary to reduced colloid oncotic pressure due to infarction and necrosis. Tumors or malformations of the GIT such as midgut volvulus, may lead to hydrops via mass effect similar to thoracic lesions. Hepatic diseases such as, cirrhosis, biliary atresia, polycystic disease of liver and cholestasis lead to hypoproteinemia and hydrops.[13] Arteriovenous shunting leading to high output cardiac failure is the mechanism by which hepatic hemangiomas cause hydrops.
6. **Urinary abnormalities** have been relatively infrequent causes of hydrops. Rupture of bladder or the collecting system has been reported leading to urinary ascitis, simulating NIH. Congenital nephrotic syndrome, an entity indicated by abnormally high levels of alfa feto protein in the maternal serum can cause hydrops due to hypoproteinemia. The fetal prognosis is guarded as these babies are likely to develop renal failure in early years of life.[14]
7. **Hematologic causes:**

   Hydrops secondary to anemia can develop in the setting of haemorrhage, hemolysis and decreased

or aberrant production of red blood cells. While the former can be due to ICH, or hemolysis as in hemoglobinopathy, enzymopathy associated with RBCs, or hemangiomas, the latter can be a presentation of intrauterine infections (e.g parvovirus), myeloproliferative disorders (which may be secondary to Down's syndrome) or infiltrative disorders (such as congenital leukemias)[15]

8. **Causes of the placenta, cord and membranes** can be a set of heterogenous entities ranging from chorioangioma of the placenta [16]causing high output cardiac failure to cord abnormalities in the form of angiomyxoma of the cord, aneurysm of the umbilical artery, thrombosis or torsion of the umbilical vein.

   Pathologies of the cord such as aneurysms, umbilical vein torsion, thrombosis, true knots etc. eventually translate into reduced placental perfusion, causing impairment of myocardial contractility and heart failure in more advanced cases.[17]

   Shared placenta in case of monochorionic multiple gestations, in 10-20% cases leads to vascular anastomosis where the arterial supply comes from the circulation of one twin but the venous drainage of the anastomosis communicates with the circulation of the other twin leading to net flow of blood from the donor to the recipient. NIH can complicate both foetuses in case of twin to twin transfusion syndrome.[18]

9. **Intrauterine infections** can cause fluid accumulation in serous cavities in about 5-10% cases. The pathways could be myelosuppression, hepatic dysfunction or edematous vascular endothelium. Direct infiltration of the cardiac musculature, leading to myocarditis can also be a pathway.

   Major infections that affect the foetus include, TORCH group, Parvo virus, Respiratory syncytial virus, Varicella, Coxasackie virus, adenovirus, syphilis, Listeria etc. (TORCHES-CLAP)

   Parvovoirus is the most common intrauterine infection associated with hydrops fetalis accounting for a third of cases. Destruction of erythroid precursors causes severe anaemia. The foetal infliction is more serious prior to 20 weeks of gestation. In later periods of gestation, in utero transfusion to tide over the aplastic crisis, can improve perinatal outcome; and is currently recommended by the SMFM.[19]

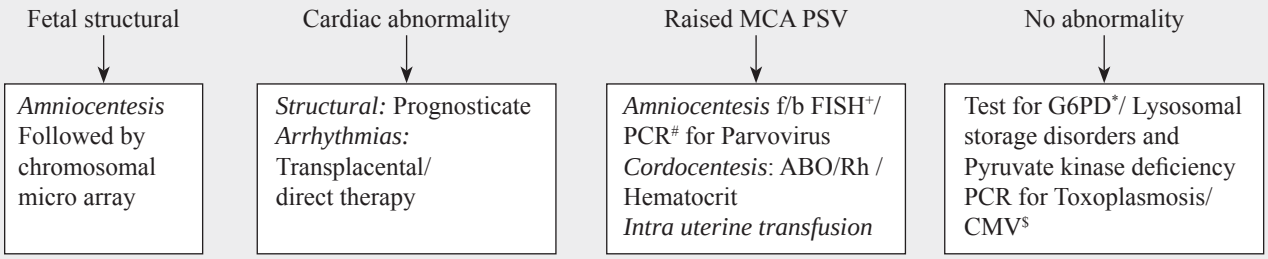
10. **Numerous genetic syndromes and inborn errors of metabolism** (IEM) also lead to this condition. These cases are more likely to be associated with *recurrent* NIHF. Neu lexova, multiple pterigium syndrome, Noonan's syndrome, yellow nail syndrome are some of the genetic disorders the possibility of which merits a CMA analysis of NIHF. IEM are yet another group of disorders, most commonly inherited in an autosomal recessive pattern. These cause hydrops by way of accumulation of metabolic substrates in tissues.

    While the diagnostic criteria for hydrops are well defined, finding the underlying cause may be quite intriguing. Figure 1 provides a simplified algorithm for this disorder

It is important to evaluate the mother, for conditions known to be associated with foetal hydrops such as mirror syndrome. In this condition the accumulation of fluid in the serous cavities of the mother reflects the collection in the foetus leading to maternal oedema, hypertension, proteinuria, pulmonary oedema and in some cases, foetal demise in utero.

Figure 1: Algorithm for work up of non-immune hydrops:

1. Maternal history: Age/ Ethnicity/ Consanguinity/ Infections/ Family history / Drug history/ Radiation exposure
2. CBC: Genetic evaluation for alpha thalassemia if Mean Corpuscular Volume < 80 femtolitres
3. Blood group/ HIV/ VDRL/ Kleihauer Betke test/ liquid chromatography/ Indirect Coomb's test/ TORCH serology
4. Detailed obstetric scan for malformations/ soft markers/ biometry/ AFI estimation/ fetal echocardiogram/ Evaluation of placenta



Footnotes: + Fluorescent in situ hybridization #: Polymerase chain reaction *: Glucose 6 phosphate deficiency
$: Cytomegalovirus

Management options for NIHF are as varied as the underlying pathology and need to be customized to the clinical presentation. Fetal cardiac arrythmias can be managed using transplacental therapy, or in some cases direct in utero therapy to the foetus, in case the pregnancy is remote from term. Intensive cardiac monitoring of the mother is imperative and a multidisciplinary team ensures a better outcome. The choice of drugs is according to the type of tachyarrythmia. Overall, Flecainide and Sotalol have been found to be better than Digoxin in the control of fetal tachyarrhythmias in the presence of fetal hydrops. Detailed description of drug therapy for this condition is beyond the scope of this review.[21]

Cases of foetal bradyarrhythmia, such as first and second degree heart blocks may be offered transplacental steroid therapy with dexamethasone to prevent inflammatory damage to the fetal cardiac conduction tissue. Such a therapy is however investigational and should be started bearing in mind the adverse effects on the mother as well as foetus secondary to derangements of glucose homeostasis and fetal growth restriction.[22]

Fetal anemia due to Parvovirus B19 or other causes is amenable to management using intrauterine transfusion to tide over the aplastic crisis.[23]

CPAM (especially those with an isolated large cyst), respond well to needle drainage. Recurrent cases may be offered the option of a thoracoamniotic shunt. The microcystic CPAMs can be managed with maternal administration of single course of steroids. [24]

Vascular anastomosis of multifetal gesation can be addressed with laser ablation of the communicating vessels.[25]

Pathologies such as amniotic bands, chorioangioma of the placenta, bronchopulmonary sequestrations and sacrococcygeal teratomas can be managed using laser ablation of the feeding vessels.

Massive pleural effusions that pose a threat of pulmonary collapse can be managed using thoracoamniotic shunts or pleurodesis, if initial attempts at thoracocentesis fail to check recurrences.[26]

Transplacental therapy for maternal infections such as Toxoplasmosis and HIV is now, standard medical practice.

From diagnosing foetal hydrops, to understanding the pathophysiology, the aim of foetal medicine is now, primarily, offering management that can salvage these babies. However, many of these may not be salvageable. Counselling *would be* parents regarding the outcome of these conceptions is hence, of considerable significance.

Proportion of live births has varied from 12.9% to 89.4% in various series. The perinatal mortality rate, however, varied from 37% to 61.9%.[27-29]

That survival depends primarily on the underlying etiology, is to state the obvious. Thoracic malformations such as bronchopulmonary sequestrations, by far, carry the best prognosis whereas, cases with chromosomal abnormalities and inborn errors of metabolism, generally do not have a favourable outcome. In a series of 42 cases of NIH, Yeom et al have concluded that the number of sites of fluid collection, out of four, was the best prognostic determinant.[28]

Nassr in his experience of 142 cases found that presence of ascitis was independently associated with higher neonatal mortality reflecting more advanced pathology.[29] In 2010, Randenberg concluded that foetuses with cardiac arrhythmias and those with congenital malformations of lymphatics were likely to have a better prognosis; and those with a chromosomal anomaly, a genetic syndrome or haematological basis were expected to have a more guarded outcome.[30]

To conclude, the etiology remains elusive in 40% cases despite extensive pre as well as post natal evaluation. Therapy is customized to the underlying etiology and only symptomatic management of idiopathic cases has not yielded very encouraging results. Systematic research on outcome based analysis of NIH, shall bridge the gaps in our understanding of this fascinating disorder.

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Images in Fetal Medicine

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Isolated Large Bilateral Choroid Plexus Cyst Associated with Trisomy 18

Case:

A 20 year lady at 18 week period of gestation (POG) was referred to fetal medicine clinic in view of ultrasound (USG) finding of lobulated irregular bilateral choroid plexus cysts measuring 16 x 11 mm in right lateral ventricle and 18 x 9 mm in left lateral ventricle as depicted in the above picture. She had no prior combined first trimester screen or second trimester biochemical screening. A repeat level II USG at our institution confirmed the finding of large bilateral choroid plexus cyst with no other structural anomaly or soft markers (Figure 1). She opted for amniocentesis after genetic counselling. Quantitative Fluorescence-Polymerase Chain Reaction report of amniotic fluid was suggestive of Trisomy 18. She underwent termination of pregnancy in view of the genetic report.

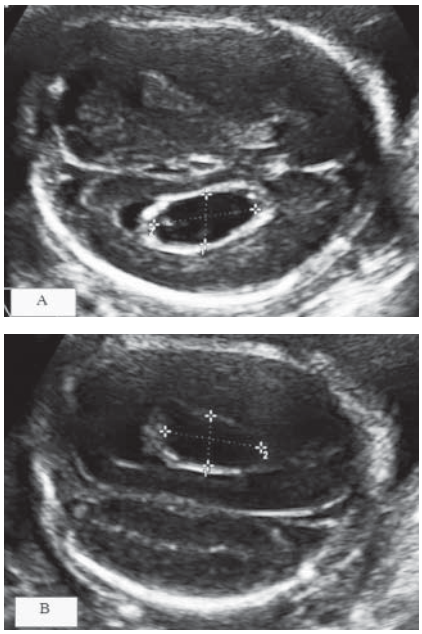

Figure 1: Ultrasound images of the fetal brain (axial plane) show presence of large choroid plexus cysts measuring 16.2×7.9 mm in the right lateral ventricle **(A)** and 14.4×7.4 mm in the left lateral ventricle **(B)**.

Discussion:

Choroid plexus cysts (CPCs) are noted in approximately 1-2% of fetuses upon second-trimester ultrasound examinations and are rarely symptomatic. They appear as sonolucent spaces measuring 2-3 mm in diameter in the echogenic choroid plexus of lateral ventricles of brain. The incidence of CPCs is 50% in fetuses with trisomy 18, but only 10% of fetuses with trisomy 18 will have CPCs as the solitary identifiable indicator on USG.[1] Even though the number of cysts and the cysts' distribution does not change the risk, but it is seen that cysts with diameters less than 5 mm may not be associated with aneuploidy and large cysts with diameter more than 10 mm may bear a higher risk of aneuploidy.[2]

A detailed anatomic survey for other markers of Trisomy 18 like strawberry head, clenched hands, cardiac abnormalities, talipes, early fetal growth restriction (FGR) and polyhydramnios should be performed in cases of CPC noted on USG. The likelihood of isolated CPC being linked with Trisomy 18 is 7 and for Trisomy 21 is 1.9. [1]Invasive genetic testing is not required in case of an isolated CPC after thorough targeted anomaly USG and biochemical screening for aneuploidy.[3] Hence, isolated CPC are now regarded as normal variants. In cases of CPC coupled with other anomalies, aneuploidy is expected in 2.1% cases and Trisomy 18 is more often than not detected in all such cases, therefore invasive testing is necessary in these cases prior to MTP.[4] Due to lower detection rates, Noninvasive prenatal test (NIPT) is not considered the finest option for Trisomy 18.[5]

Generally by the third trimester, as high as ninety percent of CPC generally disappear and on very rare instances they persist in postnatal period. There is no proven neurological injury or any concern regarding cognitive/motor behavior by isolated CPC. The parents need to be counseled and reassured of an excellent prognosis for such cases of isolated CPC. In general, isolated CPC does not merit follow up USG and overall there is no difference in obstetric management in these cases.[1]

Conclusion:

Choroid plexus cysts discovered during the prenatal ultrasound should warrant a meticulous USG examination for associated anomalies and other soft markers for aneuploidy. Counseling the parents is important with the option to offer invasive genetic testing based on USG features and a priori risk.

Prenatal Diagnosis and follow up of a Giant Fetal Sacrococcygeal Teratoma

Case

A 30 year old primigravida was referred to fetal medicine clinic upon detection of 2.8 x 2 cm solid-cystic sacrococcygeal teratoma at routine anomaly ultrasound examination at 20 weeks period of gestation (POG) as depicted in figure 2(A). On further evaluation, fetal MRI revealed 3x2.8x1.5cm sacrococcgeal teratoma with no pelvic extension. Follow up with serial ultrasound was done regularly to monitor the size and vascularity of tumor, to detect fetal anemia by doppler velocimetry of middle cerebral artery peak systolic velocity or signs of hydrops and to assess fetal cardiac function. By 32 weeks, 6.2 x 6.3 x 6.3 cm solid cystic tumor with a total voume of 137.1 cm^3 with increased vascularity was noted on ultrasound examination as depicted in the figure 2(B). There was no associated placentomegaly, polyhydramnios, no evidence of hydrops or any other anomaly. The tumor volume to fetal weight ratio was 0.07 and the solid component constituted 32% of the tumor bulk. By 36 weeks, the size of the tumor progressively increased to 9 x 8.5 cm. She underwent an elective caesarean at 36 weeks and a female baby weighing 2.7 Kg with an apgar score of 9, 9 was delivered. On fourth postnatal day, total surgical excision of the tumor was performed. Post operative period was uneventful and was discharged in a healthy condition. On follow up, histopathology examination revealed immature teratoma and resected part of coccyx was free of tumor. Four cycles of chemotherapy with cisplatin, bleomycin, etoposide have been planned for the baby.

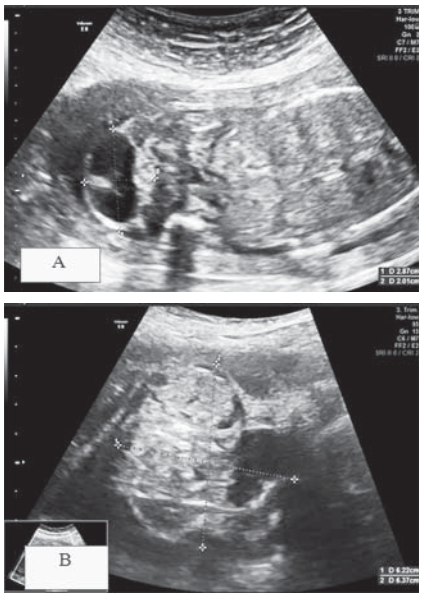

Figure 2: Ultrasound images show presence of sacrococcygeal teratoma measuring 2.8 x 2 cm at initial presentation **(A)** and 6.2 x 6.3 cm by 32 weeks**(B)**.

Discussion

Sacrococcygeal teratoma is a tumor derived from the primitive streak located at the base of the coccyx. It is a rare tumor seen in 1:40000 live births. Large tumours may result in fetal anemia leading to high output heart failure and hydrops which is usually associated with placentomegaly, polyhydramnios and maternal mirror syndrome.[6] Apart from perinatal complications, there is a high chance of fetal demise due to tumor rupture, dystocia and vascular steal from a rapidly growing solid vascular tumor. Thus, the course of these tumors can be unpredictable with a variable outcome. Various poor prognostic factors include large size, solid consistency, increased vascularity, high tumor to fetal weight ratio, presence of other associated anomalies, polyhydramnios, cardiomegaly, hydrops fetalis and intrapelvic extension of tumor.[7] Upon diagnosis, there is no need for any invasive prenatal testing as the incidence of chromosomal defects or genetic syndromes is not increased. Therefore after diagnosis, only serial evaluation every 2-3 weeks with ultrasound including doppler studies such as measurement of fetal middle cerebral artery peak systolic velocity and fetal echocardiography is performed to monitor fetal growth, amniotic fluid volume, tumor size, assessment of cardiac function and development of cardiac failure or hydrops in order to decide about need for any intervention or early delivery. In case of doubt due to similar appearing lesions on ultrasound, fetal MRI may be performed to establish the diagnosis. Very rarely, in utero ultrasound guided laser coagulation or radiofrequency ablation of vessels within the tumor or fetal blood transfusions may become necessary. Prenatal diagnosis is important as early diagnosis may necessitate mode, timing and place of delivery.[8] Although elective caesarean delivery is recommended for tumor more than 5 cm due to risk for traumatic injury, rupture or hemorrhage, but vaginal delivery is acceptable for small tumors. There is no increased risk of recurrence. Mature teratomas are most common and usually have excellent prognosis. Perinatal morbidity and mortality is mostly attributed to associated prematurity, hydrops or difficult surgery, especially with tumors with intrapelvic extension.

Conclusion

Sacrococcygeal teratoma remains a congenital anomaly associated with a high perinatal and infant mortality rate. Prenatal diagnosis of SCT should prompt referral for comprehensive fetal imaging to evaluate the tumor anatomy, vascularity, fetal cardiac function and to rule out associated fetal anomalies, all of which are vital in determining the prognosis and hence counselling the patient. Close antepartum surveillance, planning

of elective delivery and adequate surgical treatment in the postnatal period at a tertiary care centre with good nursery facilities is of vital importance to reduce perinatal mortality.

Successful Management of an Atypical Presentation of Congenital Pulmonary Airway Malformation by Intrauterine Thoraco-Amniotic Shunt

Case:

A 31 year old, second gravida was referred to fetal medicine clinic with an incidental ultrasound diagnosis of congenital pulmonary airway malformation (CPAM) at 29 weeks. Antenatal period was uneventful and level II ultrasound was normal. On ultrasound evaluation, a dominant monocystic lesion measuring 6.5 x 4.5 x 3.1 cm was noted in the fetal thorax with a CPAM volume ratio (CVR) of 1.49 as depicted in figure 3. There was no hydrops or any other anomaly. The cyst was aspirated under ultrasound guidance but, on follow up the cyst had refilled measuring almost same as the original size. After detailed counselling, intrauterine thoracoamniotic shunt placement was planned. Under continuous ultrasound guidance, a metal cannula with a trocar was introduced transabdominally into the amniotic cavity and inserted through the fetal chest wall into the cyst. The trocar was then removed and the shunt was inserted into the cannula. A short introducer rod was then used to deposit half of the shunt into the cyst. Subsequently, the cannula was gradually removed into the amniotic cavity where the other half of the shunt was pushed by a longer introducer. Follow up serial ultrasound revealed the shunt in appropriate position and did not reveal any re-accumulation of the cyst. A baby weighing 3.2 Kg with an apgar of 9,9 was delivered by elective caesarean and was discharged in a healthy condition on postnatal day 5. The baby was readmitted on postnatal day 18 in view of fast breathing and lethargy. Chest X-Ray revealed right sided CPAM with mediastinal shift and NCCT showed involvement of superior part of right lower lobe. The baby underwent right sided middle and lower lobectomy and was discharged after an uneventful postoperative course.

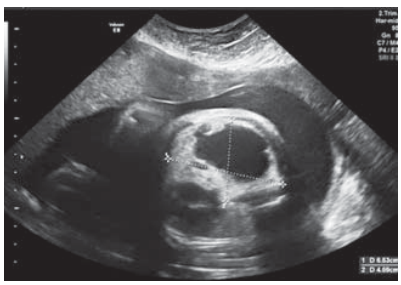

Figure 3: Ultrasound image of the fetal throax (transverse plane) shows CPAM with a dominant cyst measuring 6.5 x 4.5 cm occupying the right hemithorax with the heart pushed to the left.

Discussion:

CPAM is a relatively rare congenital anomaly with an incidence of 1 in 25,000 live births.[9] It has a very wide range of ultrasound appearances depending on the specific type of CPAM. It can present as solid or microcystic, macrocystic with one or more large cysts (>2 cm) and mixed with areas that are solid intermixed with areas containing multiple cysts. It is unilateral in more than 95% of cases and commonly involves one lobe or segment of the lung. The natural antenatal course of CPAM can range from complete regression in utero to life-threatening hydrops. About one third of CPAMs can increase as the gestational age advances until around 26-28 weeks of gestation, after which the growth generally plateaus. There is spontaneous resolution of the lesions in more than three-fourth cases, which may also be due to inability to identify the lesion by ultrasound as the normal lungs also become echogenic. Thus, even in these cases, postnatal chest X-ray and/or CT scan is recommended. The role of antenatal ultrasound is not only helping in determining the anatomical location of the lesion, number and size of the cysts and any coexisting pulmonary lesions such as pulmonary sequestration in case of a hybrid lesion but also for following the course of the disease by serial 2-4 weekly monitoring of CVR, measurement of amniotic fluid and detection of signs of evolving hydrops. The various modalities for in-utero fetal therapy include thoraco-amniotic shunting, open fetal surgery with excision of the lesion in cases associated with hydrops or maternal administration of steroids which may also lead to resolution of hydrops in some cases. The intrauterine thoraco-amniotic shunting can be offered in macrocystic lesion with fetal hydrops or signs of evolving hydrops, cases with a large cyst causing mediastinal shift, in non hydropic cases with CVR more than 1.6 or for lesions rapidly increasing in size.[10] The baby should be delivered in a hospital with neonatal intensive care and pediatric surgery facilities and the mode and timing of delivery is same as for other obstetric indications unless there is fetal hypoxia or hydrops. Though fetuses with CPAM usually have a favorable outcome in majority of cases, however the prognosis of rare cases with large lesions with CVR more than 1.6 with or without hydrops or mediastinal shift, and need for prenatal intervention is remarkably worse.[11] There is no increased risk of recurrence as there is no genetic basis for CPAM and the incidence of chromosomal abnormalities or genetic syndromes

is not increased. The only long term consequences of concern are risk of infection and malignant transformation such as pleuropulmonary blastoma and bronchioloalveolar carcinoma.

Conclusion:

Antenatal ultrasound is a valuable, safe, cost-effective imaging modality which is indispensable in the diagnosis of CPAM. Antenatally diagnosed CPAM have a fair prognosis in the absence of hydrops. CVR can aid in identifying the fetuses at risk for intrauterine or postnatal death, need for fetal intervention. Intrauterine shunting and planned delivery in a tertiary care center are recommended in cases with a large marcocystic CPAM or cases with hydrops.

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Answer: July Issue

Crossword

Right to left

1. Random
2. Hyponatremia
3. Vaptans
4. Corifollitropin Alfa
5. Progesterone
6. Freeze All
7. Agonist

Top to down

1. Letrozole
2. Vegf
3. Antagonist
4. Cyclophosphamide
5. Breast
6. Pergoveris
7. Critical
8. T-Helper
9. NK cell

Pictorial Quiz

1. Physiological ICSI
2. In Vitro Maturation Needal
3. Bicornuate Uterus with pregnancy in Rt. horn

Fetal Interventions: Diagnostic and Therapeutic

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

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

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

Diagnostic Procedures

1. Amniocentesis

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

1.1 ***What are the Indications for amniocentesis?***

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

1.2 ***What Pre-procedure Counselling should be offered to the couple before diagnostic tests?***

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

1.3 ***What are we looking for in the amniotic fluid ?***

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

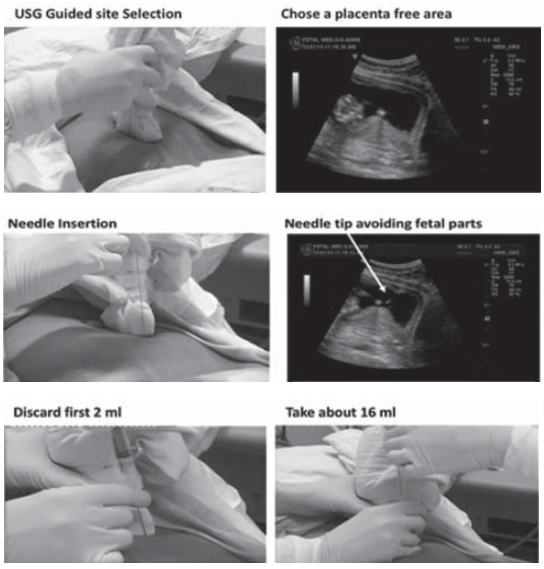
1.4 ***What is the optimal gestation for performing Amniocentesis?***

It is technically possible at any gestational age after approximately 11 weeks of gestation. Optimally it should be performed at 16 to 17 weeks of gestation. Before 15 weeks (ie, early amniocentesis) is associated with higher fetal loss and complication rates, including culture failure.

1.5 ***How is amniocentesis done?***

- Site selection: Avoid placenta as far as possible. Although some studies have suggested an increased rate of fetal loss in transplacental procedures, this has not been substantiated. Also, the lateral quadrants of abdomen should be avoided.
- Needle specification: a 22G spinal needle is used.

• Local anaesthesia usually not necessary In a study by Dadhwal et al it was found that, though pre-procedure pain and anxiety levels are high, most patients experience less pain and anxiety after the procedure.



1.6 ***What are the components of the post procedure care?***

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

1.7 ***What are the possible complications of the procedure ?***

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

b) Bloody tap: It is seen in < 1 % when done under ultrasound guidance blood is almost always of maternal origin and does not adversely affect amniotic cell growth.

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

2. Chorion Villus Sampling:

2.1 ***What are the Indications for CVS***

CVS can be done for all indications of amniocentesis:

Cytogenetic Analysis

Metabolic : in born errors of metabolism

Molecular: hemoglobinopathies, hemophilia, muscle dystrophy

The preopertative counselling should be done as described for amniocentesis

2.2 ***What is the optimal gestation for performing Amniocentesis?***

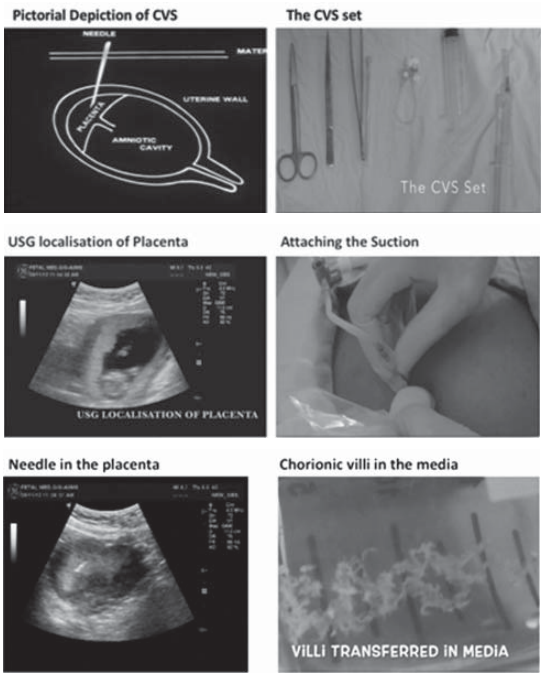
CVS can be done after 10 weeks, usually 10-13 weeks. Therefor it can be performed at earlier gestations than amniocentesis.

2.3 ***What is the advantage of CVS over amniocentesis ?***

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

2.4 ***How is CVS done?***

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



2.5 ***What are the post procedure instructions?***

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

2.6 ***What are the complications?***

Fetal loss rate of CVS has been reported to be 0.7 % within 2 weeks. Total pregnancy loss rate after transabdominal CVS is comparable to amniocentesis, only trans-cervical CVS is slightly higher.

3. Cordocentesis

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

3.1 ***What are the indications for cordocentesis?***

Cordocentesis is performed for diagnosis of:

- Chromosomal abnormalities
- single gene defects
- anemia, thrombocytopenia
- infection

3.2 How is Cordocentesis done?

Placenta and cord insertion are localised. Using USG guided, freehand technique umbilical vein is punctured, fetal blood sample is aspirated.

3.3 What are the complications ?

- Fetal loss rate of 0.2-9.9%has been reported.
- Bradycardia may result from the handling of the cord
- PPROM/ PTL
- Cord hematoma
- Chorioamnionitis
- Umbilical thrombosis
- Fetal-maternal hemorrhage.

Therapeutic Procedures:

4. Intrauterine Transfusion (IUT)

4.1 ***What are the indications for IUT***

The primary indication of intrauterine transfusion (IUT) is fetal anemia. It can be due to various causes such as

- Rh isoimmunization (most common),
- Sensitization to other blood group antigens (Kell, Duffy),
- Parvovirus B19 infection,
- Fetal or placental tumors,
- Fetal arteriovenous malformations,
- TTTS or feto-maternal hemorrhage.

Middle Cerebral Artery –Peak Systolic Velocity > 1.5 MOM indicates that the pregnancy is at risk of significant fetal anemia and mother is offered IUT.

4.2 ***What is the pre-procedure counselling ?***

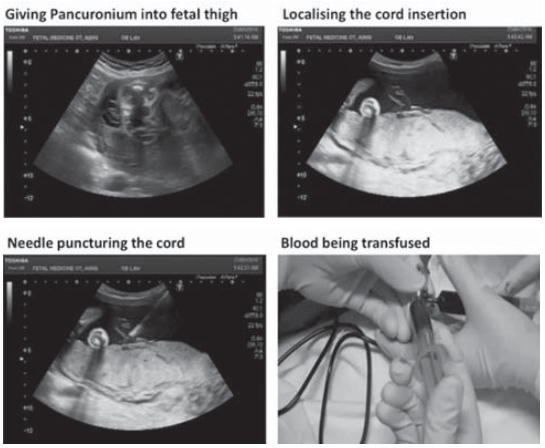
Patient is counselled regarding the benefit of IUT and risks associated such as preterm labor, PPROM, chorioamnionitis, cord accidents (cord hematoma, hemorrhage from the cannulation site, umbilical artery spasm) and requirement of emergency caesarean section if a viable fetus develops severe bradycardia.

4.2 ***How is the procedure performed ?***

- Steroid cover (in viable fetus) is given.
- O negative, leucocyte depleted, irradiated blood with hematocrit of about 80% and cross matched with maternal blood is used.
- The volume of blood to be transfused is calculated using the formula – $V_{fetoplacental} \times (Hematocrit_{final} - Hematocrit_{initial}) /$

Hematocrit$_{transfused\ blood}$. V$_{fetoplacental}$ is calculated by Mandelbrot formula wherein fetoplacental volume (ml) = 1.046 + fetal weight (g) X 0.14. If the fetus is hydropic, about half of the calculated volume is transfused in one setting.

- A single dose injectable antibiotic and intramuscular progesterone is given preoperatively.
- Ultrasound is done to assess the placenta and cord insertion site. Mapping of needle path is done to enter at cord insertion (preferably) or free loop or intrahepatic part of umbilical cord, if insertion site IUT is not feasible.
- It is preferable to puncture umbilical vein , as puncturing umbilical artery is more likely to be associated with fetal bradycardia.
- Fetal paralysis is obtained using injection pancuronium or vecuronium intramuscularly into fetal thigh or into the umbilical vein depending upon the position of placenta and accessibility of cord.
- A long 20G needle is introduced under continuous ultrasound guidance using free hand technique



- Fetal blood is drawn and transfusion started. Immediately fetal haemoglobin is estimated in the OT and requisite amount of blood volume is calculated and transfused.
- After this, blood for post transfusion hematocrit is aspirated after discarding the first 2-3 ml.
- Fetal heart is monitored on CTG for about one hour after the procedure.
- Following first IUT, the rate of fall in hematocrit is estimated to be 1% per day, the next IUT is planned accordingly when the estimated fetal haematocrit is 30% or less.
- Last IUT is generally performed at 33-34 weeks, so that pregnancy can be carried to term, unless technically difficult.
- After 34 weeks, the risk of procedure outweighs the risk of delivery and a preterm delivery may be indicated if needed.

With the use of IUTs, survival rated are about 95%

Fetal Reduction By Intracardiac KCL

5.1 ***What are the indications for fetal reduction by intracardiac KCL***

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

5.2 ***What is the pre-procedure counselling ?***

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

5.3 ***What is the ideal time for performing the procedure ?***

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

5.4 ***Which fetus should be reduced ?***

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

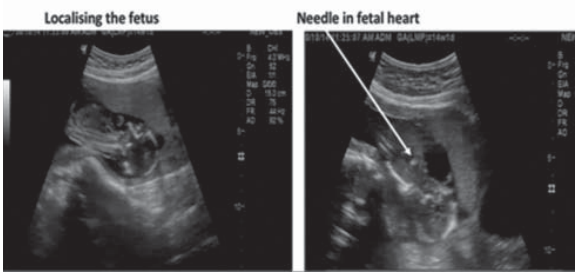
5.4 ***How is the procedure done ?***

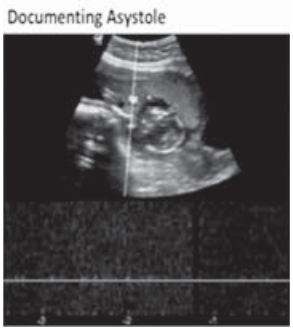
- A single dose of injectable antibiotic and intramuscular progesterone injection can be given before the procedure.
- Amniotic cavity of selected fetus is entered transabdominally under ultrasound guidance using a 22G needle avoiding a transplacental entry if possible.
- Intracardiac or intrathoracic, 1-2 ml KCL (2 mEq/ml) is injected.
- Cardiac asystole is obtained as KCL enters the coronary circulation. Further dose may be required if asystole does not occur after initial injection.

- Needle is withdrawn only after asystole is observed for one minute.

A check scan preferably on the following day to avoid missing a failed attempt is recommended.

Complications can be PPROM, accidental entry into nontargeted sac or complete pregnancy loss.





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

5. Fetal Reduction in monochorionic twins

5.1 *What are the indications for Selective Fetal Reduction?*

Selective Fetal Reduction in monochorionic pregnancy is indicated in cases of

1) Fetal anomaly
2) TRAP sequence
3) TTTS when laser photocoagulation of placental anastomotic vessels is not available or not possible.

Several techniques are available out of which ultrasound guided bipolar cord coagulation and ablation of intra-fetal vessels by laser or radiofrequency are being used more frequently because of their less invasive nature compared to endoscopic procedures.

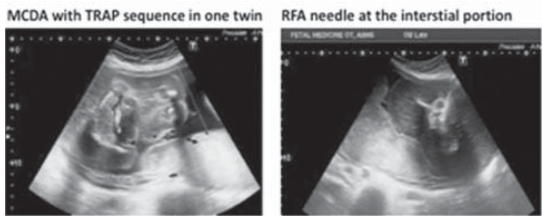
5.2 How is Radiofrequency ablation done ?

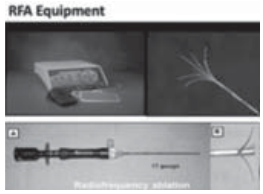
Radiofrequency ablation of intra-fetal vessels is the most commonly used method in our center.

In RFA, changes in alternating current at very high frequencies (200-1200 kHz) is generated between the tines of a needle. As the current alternates in various directions between the tines, tissue ions attempt to align with the electrical field and become agitated, generating very high temperatures which lead to tissue coagulation and necrosis.

- After informed consent, procedure is done under local anesthesia by trained fetal medicine specialists.
- Injectable antibiotic and progesterone are given preoperatively.
- Under continuous ultrasound guidance, a 17G RFA needle is introduced transabdominally into the fetal abdomen at the level of umbilical cord insertion while avoiding the placenta wherever possible.
- Radiofrequency energy is applied by the generator until an average temperature of 100°C is achieved in all three tines for 3 minutes.
- It can be repeated after a cooling period of 1 minute till cessation of blood flow is demonstrated in the umbilical cord.
- Asystole in the targeted fetus and normal cardiac activity in the other fetus is documented by a repeat ultrasound on the same or next day.
- Post procedure MRI of the surviving fetus is done after three weeks to look for any transfusion related injury that might have occurred.

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





6. Laser for TTTS

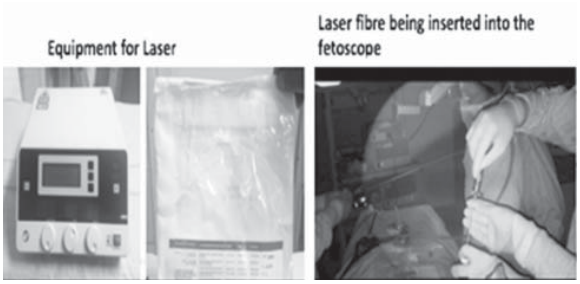
TTTS complicates about 8-10% of MCDA pregnancies. Laser in TTTS has emerged as the intervention of choice as it is the only method which targets the underlying pathology. It involves photocoagulation of vascular anastomoses which cross from one side of placenta to the other so that placenta can be functionally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

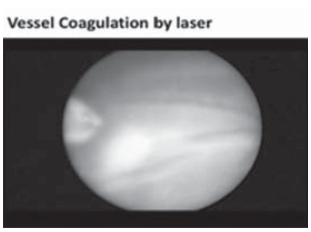
6.1 *How is Laser photocoagulation performed ?*

- The procedure can be done under regional or local anesthesia.
- A fine 3mm trocar is inserted percutaneously under ultrasound guidance into recipient sac.
- Usually, a 0° fetoscope is used for posterior placenta while a 30° fetoscope is used for anterior placenta.
- Photocoagulation is carried out using laser energy while adjusting the delivery watts as required to achieve vessel coagulation. This can be achieved by selective laser ablation of placental anastomoses where all visible intertwin anastomoses and vessels with uncertain course are coagulated if they cross the equator.
- At the end of the procedure, amnioreduction is performed in the recipient sac.

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

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





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Journal Scan

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BJOG 2019;126:556–567.

Vaginal Progesterone, Oral Progesterone, 17-OHPC, Cerclage, and Pessary for Preventing Preterm Birth in at-Risk Singleton Pregnancies: An updated systematic review and network meta-analysis

A Jarde, O Lutsiv, J Beyene, SD McDonald

The leading cause of child mortality globally is complications related to preterm birth. Preterm babies have an increased risk of short-term consequences such as problems related to respiratory, gastrointestinal, central nervous system, hearing, vision, and long term neuro-developmental disability such as cerebral palsy and impaired learning disorders. Various interventions have been attempted to reduce the risk of preterm birth in women at increased risk, including progesterone, cervical cerclage, and cervical pessary. Therefore, it is the need of the hour to update ourselves on the recent progesterone trials on use of combination of interventions to prevent preterm birth which will aid in providing optimal care to both mother and the fetus.

Objectives: To provide an up-to-date network meta-analysis comparing the effectiveness of different types and routes of administration of progesterone, cerclage, and pessary for preventing preterm birth in women at risk overall, and in specific populations such as women with a previous preterm birth and women with a short cervix.

Materials and methods: Medline, EMBASE, CINAHL, Cochrane CENTRAL, and Web of Science were searched up to 1 January 2018. Randomised controlled trials comparing progesterone, cerclage or pessary with a control group or another intervention for the prevention of preterm birth and/or associated adverse outcomes in at-risk singleton pregnancies were included. Women were considered at risk based on their history of preterm birth, cervical length or other factors as defined. Studies with any type of progesterone (natural or 17-OHPC) and route (PV, PO or IM), and any type of cerclage (McDonald or Shirodkar) were included. The comparison group could have received placebo, bed rest, treatment as usual or a different type/route of the intervention. A piloted data extraction form was used and bayesian random-effects network meta-analyses with 95% confidence intervals, as well as pair wise meta-analyses, rating the quality of the evidence using GRADE approach was performed. Primary outcomes were preterm birth <34 weeks (PTB <34 weeks) and <37 weeks (PTB <37 weeks), overall or specified as spontaneous. Our main infant secondary outcome was neonatal death (NND) and other outcomes included important infant and maternal adverse outcomes.

Results: A total of 40 trials were included which comprised 11,311 women. In at-risk women overall, vaginal progesterone reduced preterm birth <34 weeks (OR 0.43, 95% CI 0.20–0.81) and <37 weeks (OR 0.51, 95% CI 0.34–0.74), and neonatal death (OR 0.41, 95% CI 0.20–0.83). PO progesterone did not significantly reduce PTB <34 weeks, PTB <37 weeks or NND, and IM 17- OHPC significantly reduced only PTB <37 weeks (OR 0.61, 95% CrI 0.39–0.92; NNT 9). Upon comparison between two groups of cerclage into McDonald and Shirodkar cerclage, neither type had a significant effect on PTB <34 weeks, PTB <37 weeks or NND.

In the subgroup of women with a 'previous preterm birth' (regardless of cervical length), progesterone (any type and route) significantly reduced the odds of PTB <34 weeks, PTB <37 weeks, and NND, compared with control. No study assessed pessary in this subpopulation and only two studies assessed cerclage, resulting in no significant benefit. On comparing the route of progesterone in women with a previous preterm birth, PV progesterone reduced PTB <34 (OR 0.29, 95% CI 0.12– 0.68; NNT 8) and <37 weeks (OR 0.43, 95% CrI 0.23–0.74; NNT 6), but not NND. In addition, statistically significant differences in PTB <37 weeks between the studies using PV progesterone with a dose of ≤200 mg/day (OR 0.67, 95% CI 0.40–1.13) and those using a higher dose (OR 0.18, 95% CI 0.05–0.58). PO progesterone significantly reduced PTB <34 weeks (OR 0.42, 95% CI 0.22–0.83; NNT 5) but not PTB <37 weeks or NND. IM 17-OHPC reduced PTB <37 weeks (OR 0.53, 95% CrI 0.27–0.95; NNT 7), as well as NND (OR 0.39, 95% CI 0.16–0.95; NNT 24). None of the studies including women with a previous preterm birth assessed the effect of IM 17-OHPC on PTB <34 weeks.

In the subgroup of women with a cervical length ≤25 mm (regardless of history of preterm birth), the only statistically significant result was the reduction of PTB <34 weeks in women receiving progesterone (specifically PV progesterone) compared with control (OR 0.45, 95% CI 0.24–0.84).

Conclusion: Progesterone, especially when administered by vaginal route was the only intervention with consistent effectiveness for preventing preterm birth in singleton at-risk pregnancies overall and in those with a previous preterm birth. In women with short cervix , despite some benefit no clear conclusion could be made.

Editors Comments: Globally, about 15 million pregnancies each year end in preterm birth i.e. before the 37th week of gestation, which is a major cause of morbidity and mortality in children. Progesterone is the key hormone in maintaining a pregnancy through several closely linked mechanisms by promoting uterine quiescence and inhibiting of pro-inflammatory cells.With the advances in knowledge, a variety of interventions have been tried to reduce the risk of preterm birth including progesterone which can be natural or synthetic, cervical cerclage, and cervical pessary in women at risk of preterm birth. Previous spontaneous preterm birth is one of the most important risk factors for recurrent preterm birth. Supplementation with progesterone in such cases is associated with a significant reduction in the risk of perinatal mortality. Also in patients with a short cervix, vaginal progesterone is associated with reduction in the risk of preterm birth and other adverse neonatal events. However, progesterone is not a panacea and it should be used only when indicated as it is not efficacious for all preterm birth indications. Further research is required to explore PV progesterone's heterogeneity, examine interventions for short cervices and to randomly investigate the combination of therapies in preventing preterm birth and their associated complications.

Fetal Diagn Ther 2018;44(3):210-220.

Prognostic Features and Long-Term Outcome in Patients with Isolated Fetal Ventriculomegaly

Alice Winkler, Sandra Tolle, Giancarlo Natalucci, Barbara Plecko, Josef Wisser

The diagnosis of fetal ventriculomegaly (VM) represents only the tip of the iceberg as it can be associated various underlying conditions. Counselling the couple is a challenge because of the uncertainty of long term neurodevelopmental outcome. Without proper counselling and evaluation, pregnancy termination rates of 3.6% for mild isolated VM up to 52% for severe isolated VM have been reported.

Aims and Objectives: The primary aims was to identify the characteristics of prenatal isolated VM (IVM) as predictive factors for adverse postnatal outcome, to determine their predictive value, and to evaluate the accuracy of prenatal sonography by postnatal confirmation and postnatal diagnosis of additional brain anomalies.

The secondary aim was to study the subgroups with unfavorable neurodevelopmental outcome due to postnatal detection of additional anomalies.

Materials and methods: This was a retrospective cohort analysis over a 13-year period from January 1999 until December 2011 in a tertiary perinatal care center at University Hospital Zurich. Antenatal and obstetric data were collected from scan reports and clinic charts of the pregnant women. Postnatal data were collected by consultation of medical records, cranial ultrasound scans, magnetic resonance imaging (MRI), and developmental and neurological assessments. Properties of VM (ventricular diameter, intrauterine evolution, symmetry, and laterality) were modeled on dichotomized or trichotomized scores of outcome parameter categories. Associations between fetal VM characteristics and outcome parameters were calculated in the cohort and in subgroups with values <0.05 were considered as statistically significant.

Results: After a careful scrutiny of inclusion and exclusion criteria, fifty-five fetuses with confirmed IVM remained in the prenatal follow-up group. There were 20 cases with mild VM, 14 cases with moderate VM, and 21 cases with severe VM. 78% of the fetuses had bilateral VM (n = 43) and 22% had unilateral VM (n = 12). 65% showed symmetrical VM (n = 36) and 35% asymmetrical VM (n = 19). Termination of pregnancy was opted by parents in 14.6%, all in the moderate or severe VM group and there was no termination of pregnancy due to mild VM in this study. The median duration of postnatal follow-up was 7.2 years (range 2.1–14.6).

Postnatal resolution of VM occurred in 18% (n = 7/38), especially in mild and moderate VM cases and in 1 case with confirmed severe VM. Additional cerebral anomalies were diagnosed postnatally in 42% and genetic disorders in 12% of 45 live births.

Although, the degree of atrial width was predictive of intrauterine progression (p = 0.000), postnatal confirmation by ultrasound or autopsy (p = 0.029), need for surgery (p = 0.003), and postnatal detection of a genetic anomaly with a significant association (p = 0.017), however interestingly there was no association between the degree of VM and neurologic outcome variables, developmental outcome variables or emotional-behavioral problems. Also, neither symmetry nor laterality was predictive of the assessed outcome parameters. Furthermore, on subgroup analysis it was noted that if cerebral or genetic anomalies are not found in the postnatal period, a favorable outcome may be expected in cases of VM. Even though the postnatal finding of a genetic or cerebral anomaly is a predictor of outcome, these postnatal diagnoses were not significantly associated with prenatal degree of VM nor with prenatal progression of VM.

Conclusion: The diameter and intrauterine progression in IVM are not significantly associated with most outcome parameters. Cerebral anomalies and genetic disorders may contribute to an unfavorable outcome. Therefore, counselling and prognostication in a fetus with IVM remains a challenge as outcome may be favorable irrespective of its degree of dilatation. Nevertheless, fetuses with severe VM are more likely to have underlying genetic syndromes with a higher risk of adverse outcomes.

Editors Comment: The diagnosis of fetal ventriculomegaly has important implications because of its high prevalence and high risk of association with other brain abnormalities and underlying genetic syndromes. The widely used definition of fetal VM is a measurement of ≥10 mm at any stage of pregnancy at the level of transventricular plane of the fetal head. It is believed that if other structural CNS abnormalities are found in conjunction with VM, there is a high risk of a poor neurologic and/or developmental outcome. Therefore, in case of IVM it is important to perform systematic pre- and postnatal brain MRI, the latter with an adequate interval from birth, to identify additional cerebral anomalies that may impact developmental outcome. However, when VM is the only abnormal finding and the fetus is known to be euploid, counseling parents was partly based on the severity of dilatation of ventricles as increasing size of the ventricles is associated with a higher risk of poor outcome. However, upon literature review it was found that the degree of fetal IVM per se did not correlate with neurodevelopmental outcome, behavioral problems, or postnatal detection of brain anomalies and could not predict learning problems as was noted in this article also.

Future advances in research with defined neurosonography protocols with fetal follow-up, fetal and postnatal MRI with an adequate interval from birth, application of formal neurological and developmental tests with control groups until school age, and application of uniform definitions of neurodevelopmental delay will guide in a better way to counsel the couple about the long term outcome of ventticulomegaly.

Clinical Proceedings of AOGD Clinical Meeting held at All India Institute of Medical Science, New Delhi on 26st July, 2019

Fertility Outcome in Borderline Ovarian Tumour - Expanding Indications and Reducing Radicality

Swati Tomar, Reeta Mahey, Garima Kachhawa, Neerja Bhatla

Case History

A 29-years $G_2P_{0+0+1+0}$ presented at 6 weeks amenorrhea with imaging showing a large complex right ovarian mass. The detailed history revealed that in 2016, during evaluation for primary infertility, she was diagnosed to have bilateral complex adnexal masses and underwent diagnostic laparoscopy and biopsy from surface deposit on the ovarian mass. The histology showed serous borderline tumor and with this patient was referred to AIIMS. MRI revealed large bilateral complex ovarian masses with irregular walls. Serum CA 125 level was 94.6 U/mL. PET-CT showed mild ill-defined uptake confined to left ovary. She underwent fertility-sparing staging laparotomy with left salpingo-oopherectomy, right cystectomy and pelvic lymph node dissection. The final diagnosis was bilateral serous borderline tumour stage 1C2.

Three months later she conceived spontaneously and had live right tubal ectopic pregnancy with serum bhCG level 51,129 mIU/ml. Patient opted for medical management in view of nulliparity and single tube. She received intravenous Methotrexate 100 mg and ultrasound-guided intra-sac potassium chloride injection. Serial monitoring of hCG was done, and it became negative over 10 weeks. Her AMH level was now 0.2ng/ml and fertility was the concern. She was advised donor oocyte IVF for future conception but she was not willing and adopted a baby.

Two years later, she conceived spontaneously and presented with an intra-uterine pregnancy and a large recurrent adnexal mass. Ultrasound showed a 6-week singleton pregnancy and right solid-cystic adnexal mass (13x10cm) with thick septations and small nodularities. Surgery was planned in the second trimester. MRI at 16 weeks' gestation revealed a large multi-loculated pelvic mass, measuring 17 cm with papillary projections and thin septations. Serum CA 125 level was 28.5 U/mL. Due to the high suspicion of malignancy, a staging laparotomy was done at 16 weeks POG. Intraoperatively there was a large solid cystic 20x20 cm tumour of the right ovary. Right salpingo-oophorectomy along with peritoneal washings was performed. The final histology was suggestive of borderline ovarian tumour of serous variety. At present the patient has an ongoing pregnancy of 29 weeks.

Discussion

Borderline ovarian tumours (BOTs) are a distinct histological entity and they account for nearly 10%–20% of all ovarian epithelial tumors. Previous studies in pregnant patients with adnexal masses have reported an incidence of BOTs ranging from 0% to 8%. Risk factors include nulliparity, obesity, unopposed estrogen and infertility or infertility treatment.

Management depends on the age of the patient, desire for fertility, stage of the disease, and presence or absence of invasive implants. A multidisciplinary team including obstetrician, gynae-oncologist, medical oncologist, geneticist and neonatologist should evaluate the patient and plan appropriate management to ensure good oncological outcomes along with fulfillment of the patient's wishes. Conservative surgery can be done in a young patient who desires future fertility. This includes staging laparotomy including peritoneal washings, multiple peritoneal biopsies, resection of implants, omentectomy, unilateral salpingo-oopherectomy in unilateral tumour or unilateral salpingo-oopherectomy and contralateral cystectomy in bilateral tumour. Conservative surgery should be done only after documentation on frozen section. The patients should be counseled regarding the risk of recurrence and need of follow-up. Although most recurrences are indolent and can be readily cured by a second surgical procedure, the risk of progression to invasive carcinoma is 2-3%. Pregnancy following these surgeries is usually uneventful, but occasionally the need to deliver these babies preterm may arise.

The present case emphasizes the need of thorough evaluation of adenexal masses and the feasibility of conservative fertility sparing surgery in a multidisciplinary setting in young patients with borderline tumours desirous of future fertility.

An Unusual Cause of Secondary Postpartum Haemorrhage Unit II

Aarthi S Jayraj, Seema Singhal, Sunesh Kumar, Jyoti Meena, Vatsla Dadhwal, Vidushi Kulshrestha

Case report:

A 30-year-old P1L1 female patient presented to our outpatient clinic with backache and secondary PPH following an emergency LSCS done 30 days back. Ultrasonographic examination revealed a hypo-echoic mass along the anterior wall of uterine cavity, suggestive of retained products of conception. Her serum b-hCG was 0.12 mIU/mL. Patient underwent uterine evacuation and histopathological examination showed a poorly differentiated neoplasm. She presented to our clinic again after a period of 5 days with another episode of PPH and underwent a repeat evacuation. Histopathology of products of evacuation were reported as Non Hodgkin's lymphoma (pleomorphic mantle cell lymphoma). Subsequently, the patient developed left periorbital swelling with loss of sensation over chin and features suggestive of conus medullaris with worsening backache. 18F-PET/CT showed osteolytic metabolic lesion in left frontal sinus with destruction of roof of left orbit, L3-L5 lesion with intra-spinal extension. She was treated with palliative radiotherapy to the spine and chemotherapy with R-CHOP regimen, completed 5 cycles. Her cord compression symptoms resolved and bleeding per vaginum abated following the first cycle of chemotherapy. Her follow up 18F-PET/CT scan has shown resolution of all lesions, except for a focal lesion in L3 vertebrae which is showing less uptake as compared to the previous scan. She has been planned for a further 2 cycles of chemotherapy followed by autologous stem cell transplantation (ASCT).

Secondary PPH is defined as haemorrhage from the genital tract after 24 hours of delivery and up to 12 weeks postpartum. Once in a while, we come across very unusual causes of PPH such as pregnancy associated cancer (PAC). The most common PACs are cervical cancer, breast cancer, malignant melanoma and hematological cancers (leukemia and lymphoma). Uterine involvement in a case of Non Hodgkin's lymphoma is a rare entity. Very few cases have been reported and most of the patients are elderly, unlike our patient who was young. The prognosis of such patients remains dismal. Multimodality approach with prompt interdisciplinary review with gynaecologist, pathologist, radiologist, medical oncologists, radiation oncologists, palliative therapists is necessary for these patients to individualize the treatment, which should adhere as much as possible to standard care.

Laparoscopic Assisted Cervicovaginoplasty: A Challenging Domain

Juhi Bharti, Vinod Nair, Anamika Das, Kallol Kumar Roy

Case Summary

A 13 year old unmarried girl presented with the chief complaint of cyclical pain in lower abdomen for 4 months, though she never had revealed menses. On examination, she had mild pallor. Her secondary sexual characters were well developed. There was no palpable mass per abdomen. External genitalia appeared normal and there was no hymenal bulge or discolouration. On separating the labia, only the vaginal dimples were seen. On per-rectal examination, a globular bulge was felt anteriorly suggestive of bulky uterus. An ultrasonography of pelvis followed by MRI (*Fig-1)* was ordered which revealed haematometra with absent cervix and vagina. After counselling and written informed consent, the patient was taken up for "Laparoscopic haematometra drainage and cervicovaginolasty" under general anaesthesia.

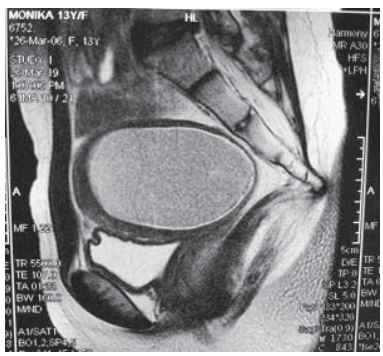

Figure 1: MRI depicting haematometra with cervical and vaginal agenesis.

On laparoscopic examination, the uterus was found to be 10 weeks size with a prominent bulge posteriorly. A small incision (1 cm) was made on the posterior wall at the thinnest site to drain around 200ml of chocolate coloured inspissated blood. After draining the haematometra a laparoscopic suction cannula was inserted into the endometrial cavity to indent the most dependent portion. Simultaneously, another surgical team performed Mc-Indoe's vaginoplasty and a uterovaginal anastomosis was established using

suction cannula as guide. A stent made up of silicon Malecot's catheter along with vaginal mould was inserted into the neovagina such that the Malecot's catheter was placed in the endometrial cavity. The patient received antibiotics and analgesics for one week and perineal hygiene was ensured. The mould was changed after 7 days and intra-uterine stent was trimmed (*Fig-2).* Patient is on follow up and she is relieved of pelvic pain and is menstruating regularly.

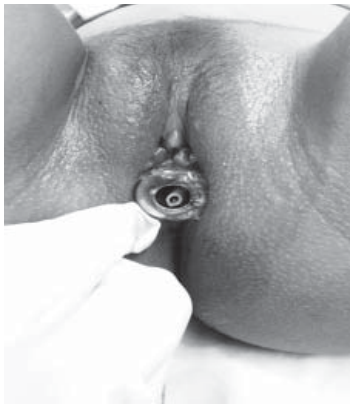

Figure 2: Final outcome: Vaginal mould and intrauterine stent in place

Discussion

Cervical agenesis is a grey area due to rarity of the malformation and also due to scarcity of literature on it. It is a very rare developmental anomaly with an incidence of around 1: 80,000 to 100,000. There can be associated complete or partial vaginal agenesis.

Cervical agenesis is quite challenging not only for the gynaecologist, but also for the patient. These patients are young teenage girls with a mean age at diagnosis of 15 years. This has a huge psychological impact on the patient. For the gynaecologist, differentiating between a high transverse vaginal septum and cervical agenesis can be difficult. MRI can diagnose cervical agenesis with 80% accuracy. However, there can be fallacies. If there is a diagnostic dilemma, it will be prudent to do an examination under anaesthesia and diagnostic laparoscopy.

There are no definite management guidelines. The surgical approach can be either conservative or radical. In radical approach, a hysterectomy is performed and vaginoplasty can be deferred till the patient intends to get married, where as in conservative approach cervicovaginoplasty is done either by laparotomy or with laparoscopic assistance. For maintaining the patency of uterocevical anastomosis, either a Foley's catheter or a self-retaining Malecot's catheter can be used. It should be changed at periodic intervals and can be discontinued after one year.

Historically, hysterectomy has been considered the treatment of choice for cervical agenesis because of the possibility of restenosis and subsequent risk of hysterectomy in conservative approach. However, there have been case reports and case series in the literature describing successful outcome in terms of regular menstruation, sexual activity and even pregnancy which is quite encouraging.

Conclusion

Cervical agenesis is a very rare Mullerian anomaly which is quite devastating for the patient as well as her parents. Cervicovaginoplasty is the treatment of choice in the present era. A thorough pre-operative evaluation and definitive planning of surgery are the keys to success.

The Maze of Knowledge

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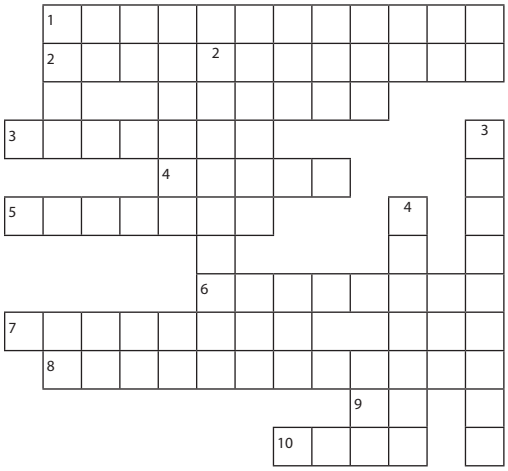
CROSSWORD



Horizontal Clues:

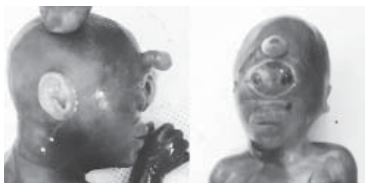
1. The syndrome consisting of encephalocele, dysplastic kidneys and polydactyly (12)
2. The course of this vessel is affected in case of agenesis of corpus callosum (12)
3. The landmark trial that changed our concepts of Foetal growth restriction (7)
4. The trial that evaluated the effectiveness of vesicoamniotic shunting in foetal life (5)
5. DOC for transplacental therapy in long VA tachyarrhythmia (7)
6. The ultrasonographic sign that distinguishes cervical pregnancy from inevitable abortion: (7)
7. The teratogenic drug used for anticoagulant prophylaxis in prosthetic cardiac valves (8)
8. Posterior fossa abnormality: (11)
9. First degree fetal heart block can be diagnosed using …… interval on fetal echocardiography (2)
10. The historical trial that has shown promising results in open foetal surgery. (4)

Vertical Clues:

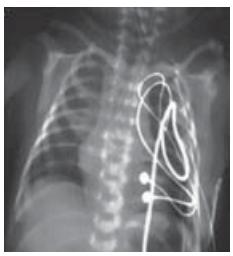
1. A method for performing cell free DNA testing: (Please give abbreviation) (3)
2. Grading for PAS : (7)
3. The drug in clue 7 above causes ……of epiphysis as a manifestation of its teratogenicity (9)
4. Flat facial profile/ …….. phenotype is said to be a marker for aneuploidy. (7)

PICTORIAL QUIZ

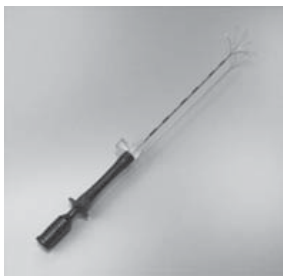
Q1. Identify the condition



Q2. This picture shows the management of a condition amenable to diagnosis in utero
1. Name the disease.
2. Name one maternal disease associated with this congenital manifestation



Q3. 1. Name the equipment shown.
2. Mention one antenatal complication that can be managed using this instrument.



Watsapp your answers to **9211656757.**
Names of first three correct entries will be mentioned in the next issue

Refer page 49 for previous answer key.

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