NEWSLETTER OF THE INDIAN COLLEGE OF OBSTETRICIANS & GYNAECOLOGISTS

ISSUE April 2017 | Pages 20

ICOG CAMPUS

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EDUCATION & HEALTHCARE PRACTICES

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Caring for the Unborn Patient

President's Address

Dr. Rishma Dhillon Pai
President FOGSI

Greetings to all !

It gives me great pleasure to share with you all that the first ICOG E-Newsletter has been appreciated by one and all. The revival of 'ICOG campus' in form of this e-newsletter has proved to be a vital tool for the college to communicate with all the fellows and members.

Having dealt with the important issues of high risk pregnancy, this April issue deals with the other important aspect pertaining to obstetricians i.e. the fetus. The topics have been wisely chosen and cater to the important dilemmas faced in the field of fetal medicine.

I wish Dr Mala Arora and Dr Monika Gupta all the success for this continuum of education. I sincerely hope that they keep bringing forth even more intriguing topics of contention every month and match up to the expectations of Fogsians.

"Education is the most powerful weapon which you can use to change the world"

-Nelson Mandela

Chairperson's Address

Dr. Mala Arora
Chairperson ICOG
chairpersonicog@gmail.com

Esteemed Fellows & members of ICOG

Greetings on the occasion of World Health Day

One of the unique challenges of the Obstetrician is to look after the health & well being of the unborn patient. To ensure that the fetus is healthy, free of congenital malformations and is attaining adequate growth parameters, we rely on biochemical markers and ultrasound imaging besides clinical assessment.

Non invasive prenatal testing (NIPT) by analyzing cell free fetal DNA is now widely available and is reducing the need for invasive testing.

Refinement in imaging machines helps us to identify anomalies in the first trimester scan. It is also possible to document various soft markers for chromosomal abnormalities. A pictoral journey is presented in this issue.

Clinical algorhithm for the management of Fetal growth restricted baby is presented along with a stimulating section on brain teasers which I am sure you will enjoy !

Secretary's Message

Dr. S. Shantha Kumari
Secretary ICOG

Dear Friends

Greetings from ICOG

Monitoring fetal health is an important aspect of antenatal care as the final outcome of pregnancy is always a composite of both maternal and fetal wellbeing. With advances in fetal medicine, the parameters to assess fetal wellbeing have been redefined in every stage of pregnancy. While early assessment is mostly aimed at screening for potential problems, fetal tests in the later half of pregnancy are aimed at diagnosis, risk stratification and prognostication of fetuses at risk such that appropriate care plans are constituted and time delivery affected ensuring better perinatal survival. The present issue of the newsletter has a set of topics highlighting theses aspects on the recent advances in tests for fetal wellbeing.

With warm regards

From the Editor's Pen

EDITOR-IN-CHIEF

Dr. Monika Gupta

MD, DNB, FICOG, MAMS

Associate Professor, Obgyn

VMMC & Safdarjung Hospital, New Delhi

FOGSI-Kamini Rao Yuva Orator Awardee 2016

ICOG Travel Fellowship (ART) Awardee 2016

Joint Secty, AOGD 2015-16

drmonikagupta@hotmail.com

09312796171

www.icogonline.org

Greetings to All!

I thank everyone from the core of my heart for welcoming our academic endeavor of "ICOG Campus" with all the warmth and appreciation. The inaugural issue on high risk pregnancy has been read widely and the positive feedbacks and suggestions which we received, gave our team an assurance that we are treading the right path.

We intend to pursue our responsibilities with full diligence and dedication. We are committed to cater to improvement in the health of both mother and child. Our next step in order to further this goal is this issue on "Caring for the Unborn Patient"

Topics of great clinical interest dealing with fetal medicine have been dealt with in this issue. The article on Non-invasive Prenatal diagnostics is a simplified attempt to clarify all doubts regarding this much talked about antenatal investigation. The feature on First trimester anomalies has been incorporated as a ready reference guide for practicing obstetrician.Keeping in mind the dilemmas in management of Fetal growth restriction an evidence based approach has been presented. Journal scan covers interesting newer researches in the field of fetal medicine and the brainteasers at the end will prove refreshing for the readers.

With this, on behalf of the Editorial team, I would like to wish happy reading to all of you.

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Non-invasive Prenatal Diagnosis: in a nutshell

Dr. Seema Thakur
Senior Consultant Genetic and Fetal Med, Fortis Hospital,
Professor, Genetic Medicine, Apollo Hospital, Delhi

INTRODUCTION

One of the major breakthroughs in the obstetrical care has been the advent of prenatal genetic diagnosis by amniocentesis and chorionic villus sampling. However, these procedures are associated with 0.5-1% procedure related risk of abortion. Hence the quest for noninvasive approaches for prenatal genetic screening and diagnosis continued. Until recently, noninvasive prenatal screening for aneuploidy relied on measurements of maternal serum analytes and/or ultrasonography which have a false-positive rate of approximately 5% and detection rates of 50–95%. Advances in genomic technologies led to noninvasive prenatal screening that relies on the presence of cell-free DNA. In 2011, cell free fetal DNA became available. This introduction has a paradigm shift on the detection of Down syndrome. The major reason NIPT is increasingly being used is due to high detection rate (98-99%) and high positive predictive value (50-80%).

WHAT IS CELL FREE FETAL DNA (CFDNA)?

Both the mother and the fetal-placental unit produce cfDNA. The primary source of fetal cfDNA in the maternal circulation is from placental cells (syncytiotrophoblast), while maternal hematopoietic cells are the source of most maternal cfDNA. Since the fetus and the placenta originate from a single fertilized egg, they are usually genetically identical.

WHAT IS THE METHODOLGY OF CFDNA?

Massive parallel sequencing of maternal and fetal fragments of DNA occurs simultaneously. Sequencing with quantification can be random, targeted, and followed by quantification or exploitation of single-nucleotide polymorphisms. The available methods are:

1. **"Shotgun sequencing"** randomly sequences cfDNA fragments and requires approximately 10 million mapped fragments to obtain a reliable test result
2. **"Targeted sequencing"** approach allows mapping of fewer targeted fragments of interest (eg, chromosome 21, 18, 13, X, and Y) which undergo a preliminary step of enrichment. This requires approximately one million mapped fragments to obtain a reliable test result.
3. Another method uses over 10,000 highly polymorphic **single nucleotide polymorphisms (SNPs)**. Maternal white cell SNP genotypes are compared with the corresponding genotypes of the mixture of cfDNA from the mother and fetus in the plasma sample.

The SNP genotyping method cannot be used in cases of **egg donor, transplant recipient, or surrogate mother** because additional confounding chromosomes (SNPs) are present in the maternal plasma.

WHAT IS MEANT BY FETAL FRACTION?

- The placental fraction accounts for approximately 10% of all cell-free DNA in maternal circulation.
- Fetal cfDNA can be isolated from maternal blood as early as five weeks of gestation and almost always by nine weeks of gestation
- The relative concentration of fetal cfDNA increases modestly (0.1 percent per week) with gestational age.
- An adequate amount of fetal cfDNA must be present to obtain a reliable test result usually 4%

WHAT ARE THE INDICATIONS OF NIPT?

NIPT is commonly used as secondary screening test after positive biochemical screen or soft markers on ultrasound which suggest high risk for Down syndrome. These include:

- Maternal age 35 years or older at delivery
- Fetal ultrasonographic findings indicating an increased risk of aneuploidy
- History of a prior pregnancy with a trisomy
- Positive test result for aneuploidy, including first trimester, or a quadruple screen.
- Parental balanced Robertsonian translocation with increased risk of fetal trisomy13/21

RECOMMENDATIONS OF PROFESSIONAL SOCIETIES

At least eight professional organizations have issued seven practice guidelines for noninvasive prenatal aneuploidy screening using cfDNA. In general, all acknowledge that cfDNA testing has a high detection rate and low false-positive rate for identifying trisomy 21, 18, and 13, and that such testing should be routinely offered to women at high risk of these disorders (maternal age at delivery of ≥35 [or 37] years of age, a positive serum/ultrasound screening test, relevant family history).

The American College of Medical Genetics and Genomics and the International Society for Prenatal Diagnosis recommendations go further and allow for testing in the general obstetric population.

Although only a few recommendations address expanded chromosome testing, several suggest making testing optional

Table 1: Screening Performance of NIPT

Condition	DR	FPR	FNR
Down syndrome	98.6 %	1.01%	1.4 %
Trisomy 18	94.9 %	0.14 %	5.1%
Trisomy 13	91.3%	0.14%,	8.7%

(DR- Detection Rate, FPR- False Positive Rate, FNR - False Negative Rate)

(sex chromosome testing) or not routine (microdeletion testing).

INTERPRETATION OF NIPT RESULTS

Screen-positive — Even with the high performance of cfDNA screening, invasive diagnostic testing (preferably amniocentesis) should be offered to confirm screen-positive test results.

Screen-negative — A screen-negative result means the fetus is at a reduced risk of having one of the aneuploidies in the test panel. Screen-negative women are not offered invasive diagnostic testing.

No result — This occurs in 1 to 5 percent of cases. Obese women are at increased risk. Options in this setting:

1. Repeat the cfDNA test. Repeat testing is successful in 50 to 80 percent of cases
2. Standard serum marker/ ultrasound screening.
3. Invasive diagnostic procedure (amniocentesis, CVS)

CAUSES OF FALSE POSITIVE NIPT

1. **Confined placental mosaicism** – Since the primary source of «fetal» cfDNA in the maternal circulation is placental cells (syncytiotrophoblast), the cfDNA test will provide results relevant to the placenta, which may be discordant with fetal tissue.
2. **Demised twin** – A demised twin can cause a false-positive result if the demised twin was having aneuploidy.
3. **Maternal cancer** – The occurrence of more than one aneuploidy is rare and may suggest occult maternal malignancy in which tumor DNA is shed into the maternal circulation.
4. **Maternal aneuploidy** –Some women may have a non-mosaic sex chromosome abnormality (eg, 47XXX) and appear normal. Maternal aneuploidy can be diagnosed by karyotyping peripheral blood lymphocytes.
5. **Technical issues** – As with all laboratory testing, occasional sample mix-ups or other technical errors could lead to false-positive (or false-negative) test results.
6. **Transplant recipient**
7. **Recent blood transfusion** – Maternal blood transfusion from a male donor performed <4 weeks prior to the blood draw for cfDNA

CAUSES OF FALSE NEGATIVE CFDNA

1. **Borderline low fetal fraction** – A borderline low fetal fraction (eg, between 4 and 5 percent) results in a very small difference in the expected (normal reference) versus observed percentage of chromosome fragments (eg, chromosome 21 fragments). Causes of low fetal fraction are:
   a. Obesity
   b. Early gestational age
   c. Suboptimal sample collection

   Data suggest that the lower limit of cell-free fetal DNA for a reliable result is approximately 4%.
2. **Confined placental mosaicism** – The primary source of "fetal" cfDNA in the maternal circulation is placental cells (syncytiotrophoblast), which may be discordant with fetal tissue. It is possible that a fetus could be aneuploid even though the placenta is euploid.

SCREENING PERFORMANCE

Screening performance of NIPT is described by detection rate (DR) and false-positive rate (FPR). It is important to note that 1 to 5 percent of cfDNA screening tests fail (ie, no result).

Trisomy 21, 18, and 13 — The overall DR for trisomy 21, 18, and 13 screening by cfDNA is 97 percent, with an FPR of 1.25 percent; cfDNA is the most sensitive screening option for these aneuploidies. Performance varies by trisomy (Table 1).

NIPT IN TWIN PREGNANCY

In pregnancies with multiple gestations and/or donor oocytes, testing laboratories should be contacted regarding the validity of NIPS before it is offered to the patient as a screening option.

STRATEGY FOR IMPLEMENTING NIPT IN THE PRACTICE

Contingent screening protocol for implementing cfDNA (after combined screen test) as suggested by Nicolaides (2016)

High risk	Intermediate risk	Low risk
>1 in 100	**1:100-1:2500**	**>1:2500**
Invasive/ cfDNA testing	***cfDNA testing or no further testing***	***No further testing***

CONCLUSION

Screening for fetal trisomies by cfDNA analysis of maternal blood, contingent on the results of the combined test, can be implemented easily in routine clinical practice. NIPT has potential to change the practice of obstetricians. An updated information is most important for pretest and post-test counselling.

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3. Noninvasive prenatal screening for fetal aneuploidy. 2016 update: a position statement of the American College of Medical Genetics and Genomics
4. Gil MM, Revello R, Poon LC, Akolekar R,Nicolaides KH. Clinical implementation of routine screening for fetal trisomies in the UK NHS: cell-free DNA test contingent on results from first-trimester combined test. Ultrasound Obstet Gynecol. 2016;47(1):45-52. doi: 10.1002/ uog.15783

ILLUSTRATIONS

Illustration 1: Normal NIPT report

Test Name	In Range	Out of Range	Reference Range	Lab
QNATAL(TM) ADV (QUEST INDIA)				EZ
Number of Fetuses?	1			
Advanced Maternal Age?	NG			
Abnormal MSS?	NG			
Abnormal US?	NG			
Personal/Fam History?	NG			
Interpretation	SEE BELOW			
This specimen showed expected repreaentation of chromosome 21, 18, and 13 material.				
Trisomy 21 (T21)	Negative			
Trisomy 18 (T18)	Negative			
Trisomy 13 (T13)	Negative			
Sex Chromosome	No aneuploidy			
Sex Chromosome Interp	SEE BELOW			
No apparent abnormality was detected. See "Limitations" below.				
Microdeletion	Not detected			
Microdeletion Interp	SEE BELOW			
No apparent abnormality was detected. See "Limitations" below.				
Gestational Age (in weeks)	18			
Gestational Age (in days)	1			
Fetal Fraction	11.50%			
Laboratory Comments	SEE BELOW			
Laboratory results and submitted clinical information reviewed by Bernard				

Illustration 2: NIPT positive for triple X

QNatal™ Advanced

Interpretation Summary — **Lab: EZ**

=>This specimen showed an abnormal representation of sex chromosome material (see "Sex Chromosomes" section below). Follow-up genetic counseling and diagnostic testing is suggested. An expected representation of chromosome 21, 18, and 13 material was seen.

Chromosome Results

Chromosome Tested	Results
Trisomy 21 (T21)	=>Negative
Trisomy 18 (T18)	=>Negative
Trisomy 13 (T13)	=>Negative

Fetal Sex Result

=>Y Chromosomal material Opted out	=>Fetal sex testing not performed per clinician request.

Pregnancy Data

=>Fetal Fraction	Sufficient
=>Number of Fetuses	1
Gestational Age	
=>Weeks	22
=>Days	0

Additional Chromosome Results

Chromosome Tested	Results	Interpretation
Sex Chromosome	=>Increased Risk	=>Findings are suggestive of a 47,XXX chromosome aneuploidy.
Microdeletion	=>Not detected	=>No apparent abnormality was detected. See "Limitations" below.

Laboratory Comments — **Lab: EZ**

=>Addendum: New or additional information added to previously reported result
This sample yielded an abnormally high Z score for Chromosome X, which is likely caused by maternal duplication of all or a segment of Chromosome X. At present, this assay cannot discern whether the fetus inherited this variation. Copy number variant detection by microarray testing is recommended in the mother, if clinically warranted, to better define the variation and genes involved. Similarly, microarray testing of the fetus is recommended to determine if this variant has been inherited or whether other copy number variants may be present. Genetic counseling is recommended.
Laboratory testing supervised and results monitored by Charles Strom, M.D., Ph.D., FACMG, FAAP, HCLD.
(*** RESULT AMENDED ON 10/21/2015 ***)

The pursuit of knowledge is never-ending.
The day you stop seeking knowledge is the day you stop growing.

- Brandon Travis Ciaccio

First Trimester Anomaly Scan : Visual Recap

Dr. Kuldeep Singh
Consultant Ultrasonologist,
New Delhi

INTRODUCTION

Routine ultrasound scanning is offered increasingly during the first trimester. Diagnostic ultrasound has played an important role in a better understanding of human development and has opened up immense possibilities to study morphology and physiology from conception to end of first trimester. The assessment of the first trimester starts from intra-uterine gestational sac and viability up to 13+6 weeks of gestation. Transvaginal scanning allows ultrasound imaging of early fetal development. The first trimester emryo looks completely different from the second trimester fetus with changes in appearance from week to week

FIRST TRIMESTER ASSESSMENTS

1. Uniform embryonic development
2. Balanced proportion between embryonic and extra-embryonic structures
3. Small dysmorphic structures instead of normal embryo

TRANSIENT MARKERS

1. Significant deviation of yolk sac growth
2. Significant deviation of amniotic cavity volume
3. Abnormal fetal heart rate especially bradycardia
4. Nuchal translucency thickness

SONOGRAPHIC FINDINGS OF EARLY PREGNANCY FAILURE

1. No embryonic cardiac activity with a crl > 5 mm
2. Gestational sac larger than 8 mm without a yolk sac
3. Gestational sac larger than 16 mm without an embryo

SONOGRAPHIC FINDINGS OF IMPENDING EARLY PREGNANCY FAILURE

1. Mean sac diameter minus CRL is < 5 mm
2. Poor sac growth
3. Large yolk sac
4. Abnormally large or floppy amniotic sac

WEEK BY WEEK ANALYSIS

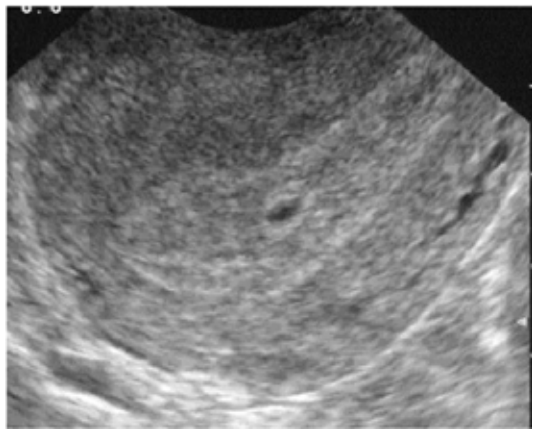


Fig 1 : 04-05 weeks (gestational sac visible from 4w 3d as a round or oval anechoic structure)

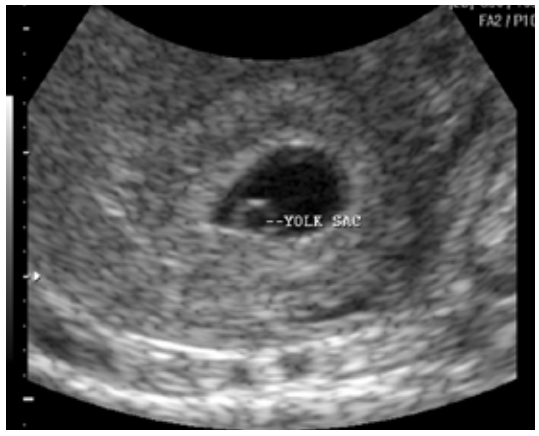


Fig 2 (2D & 3D) : 05-06 weeks (yolk sac is seen at the beginning of the week)

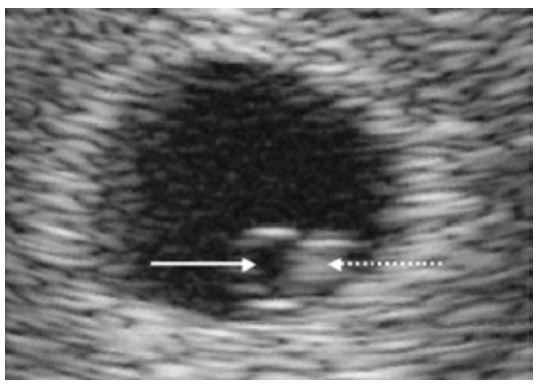


Fig 3: 05-06 weeks (embryonic pole is seen during the second half of the week)

Cardiac activity can be seen in the middle of 5th week as peristalsis and at the end of the 5th week the frequency is about 100 bpm

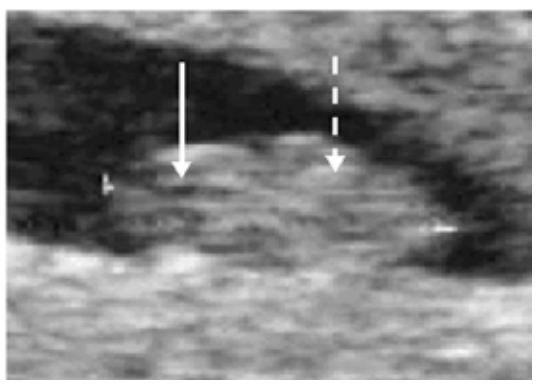


Fig 4 : 07-08 weeks (The embryo looks like an ovoid and a triangle in the sagittal section)

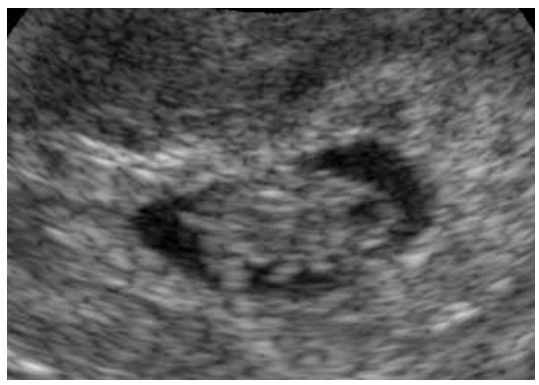


Fig 5 : 07-08 weeks (brain vesicles appear in the developing brain)

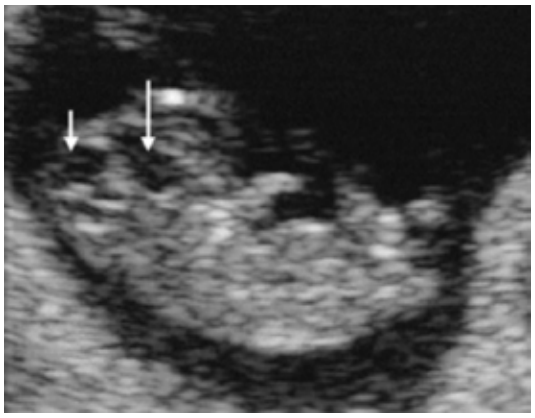
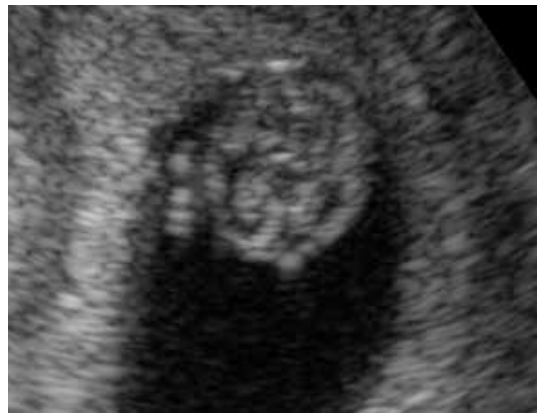


Fig 6 : 08-09 weeks (the cavities in the brain are seen as large anechoic areas in the fetal head; blood flow in the fetal heart, aorta, umbilical artery and intracranial flow visualised)



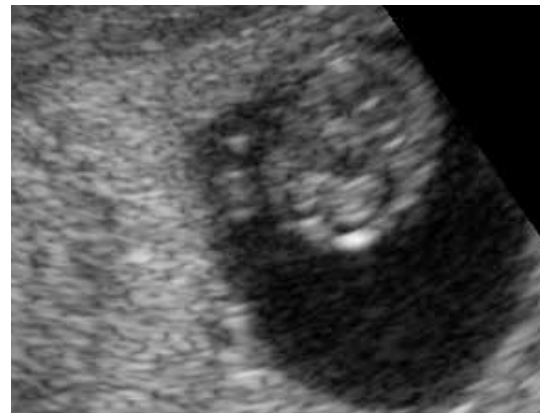


Fig 7 : 09-10 weeks (echogenic choroid plexuses can be seen filling the lateral ventricles)

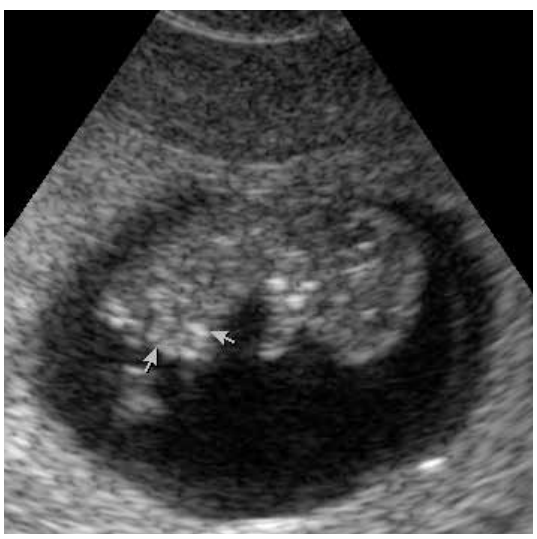
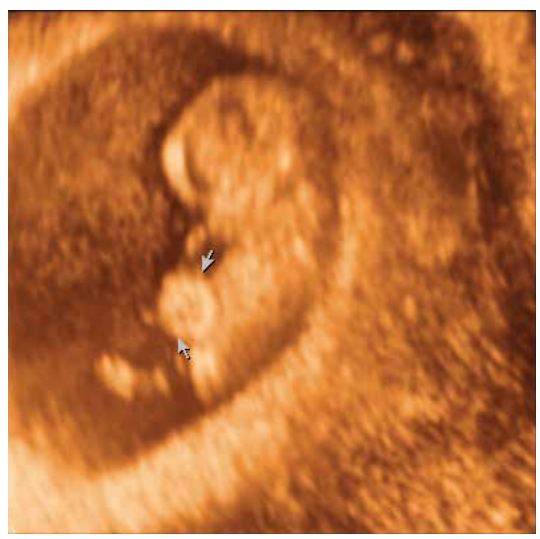


Fig 8 : 09-10 weeks (Bowel Herniation seen commonly)



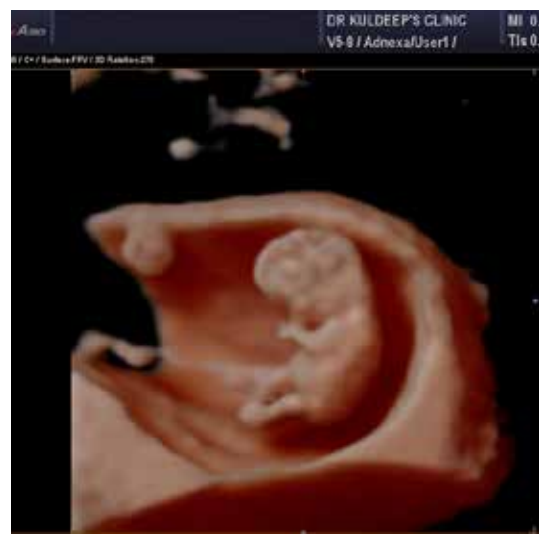
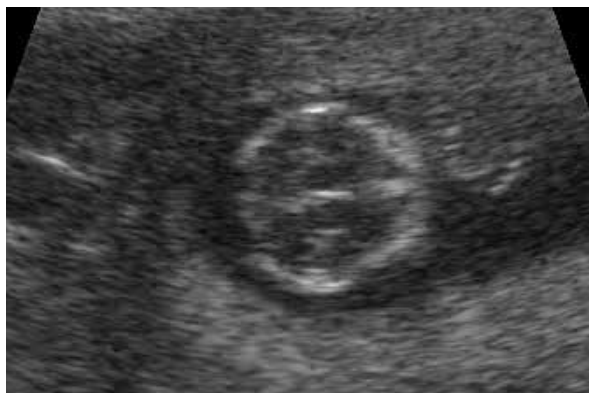


Fig 9 : 3D of 9 weeks 4 days fetus



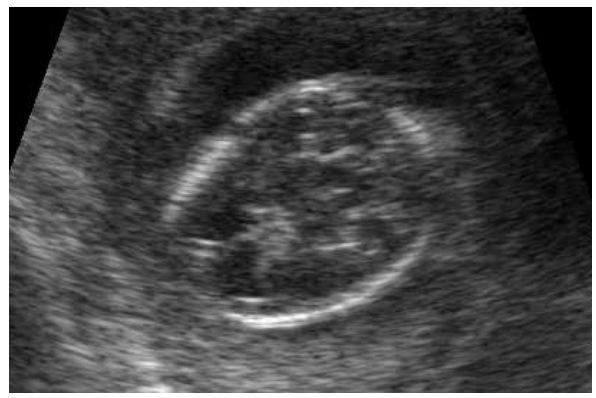
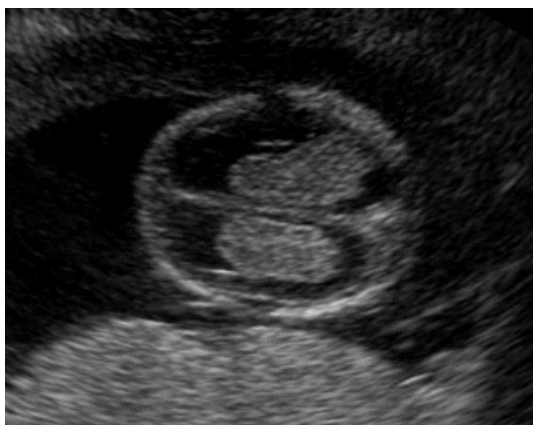


Fig 10 : 10-14 weeks (SKULL: look for completeness to exclude acrania, anencephaly and encephalocele)



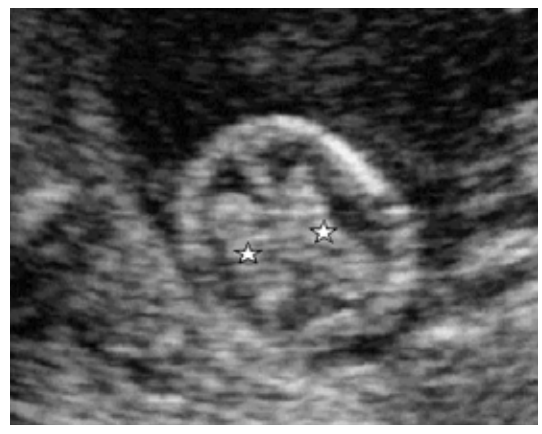


Fig 11 : 10-14 weeks (BRAIN: look for butterfly choroid plexus)

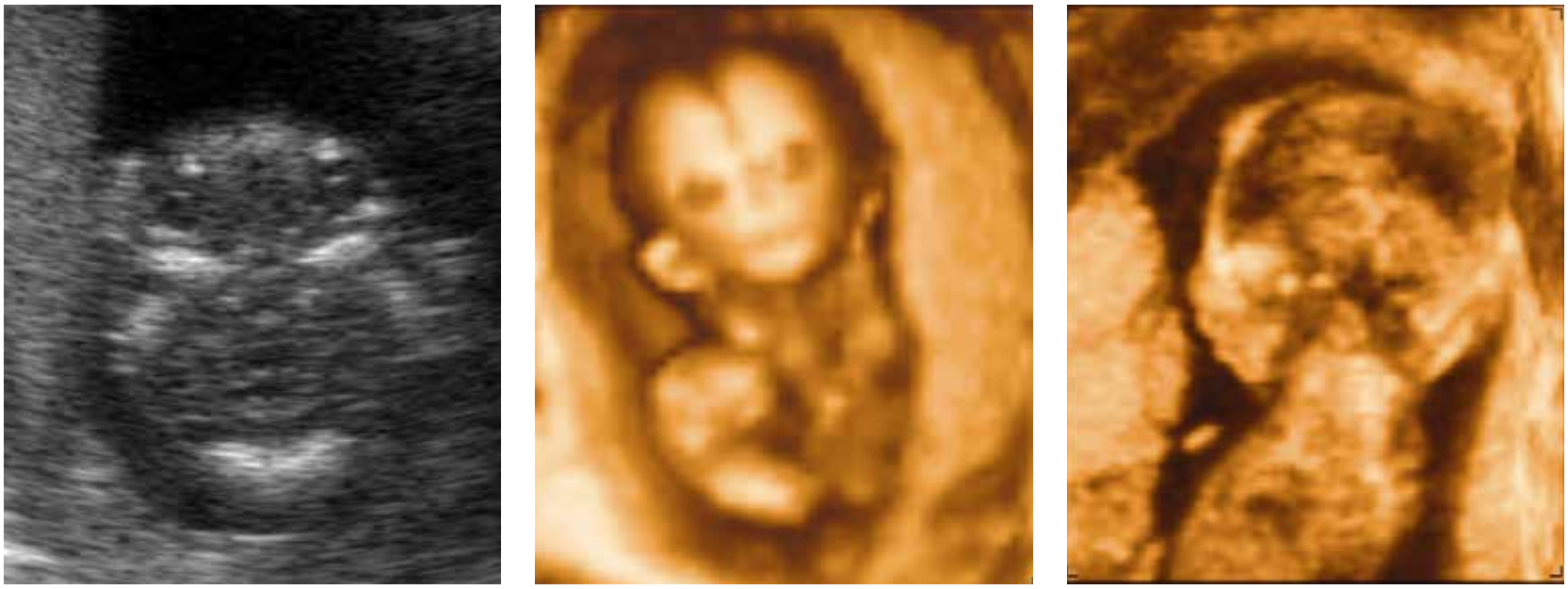


Fig 12: 10-14 weeks (FACE: evaluate orbits, nasal bone and facial profile)

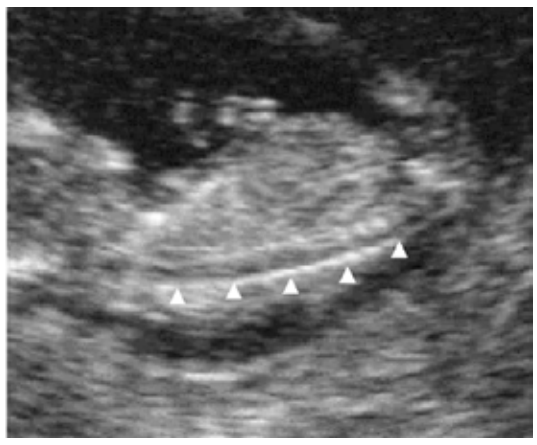


Fig 13 : 10-14 weeks (SPINE: look for alignment and any dysraphic disorganisation)

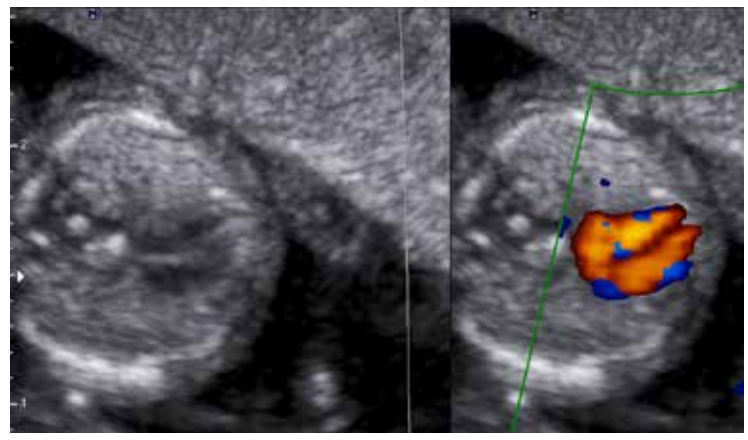


Fig 14 : 10-14 weeks (HEART: look for FOUR CHAMBER view AND GREAT VESSELS on 2D and color flow mapping)

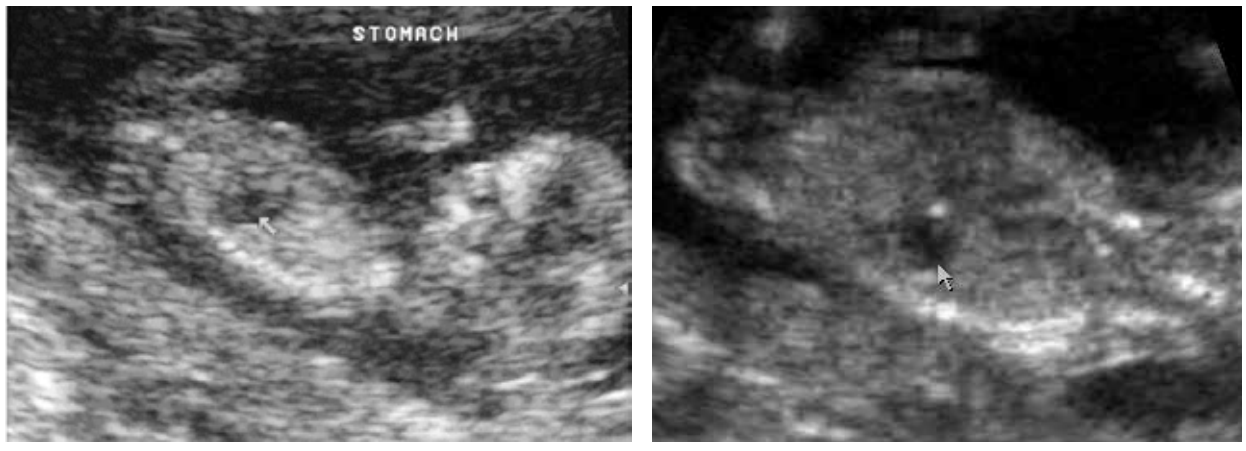


Fig 15 : 10-14 weeks (STOMACH: look for FILLING and emptying)

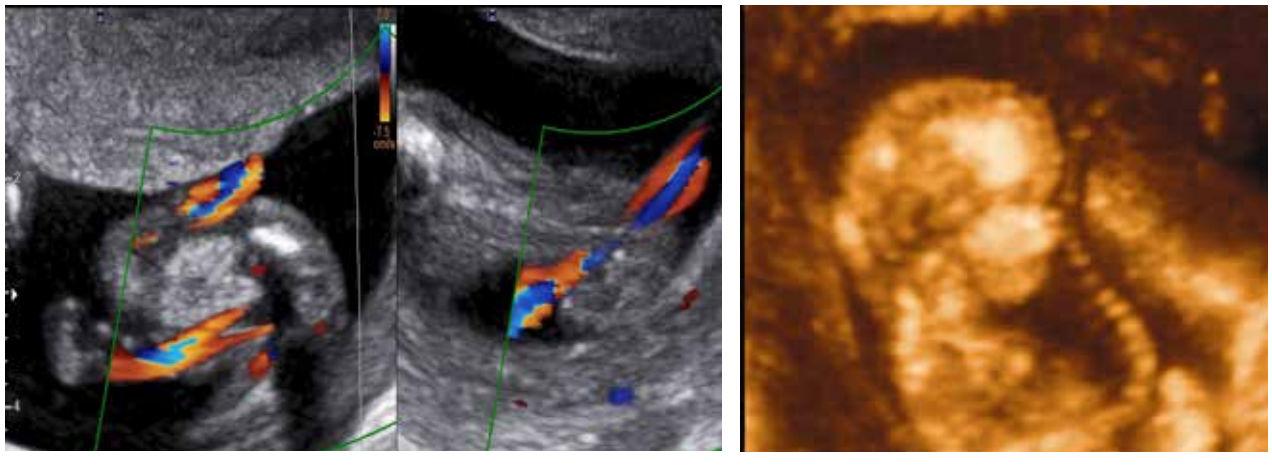


Fig 16 : 10-14 weeks (ABDOMEN: UMBILICAL CORD INSERTION and number of vessels)

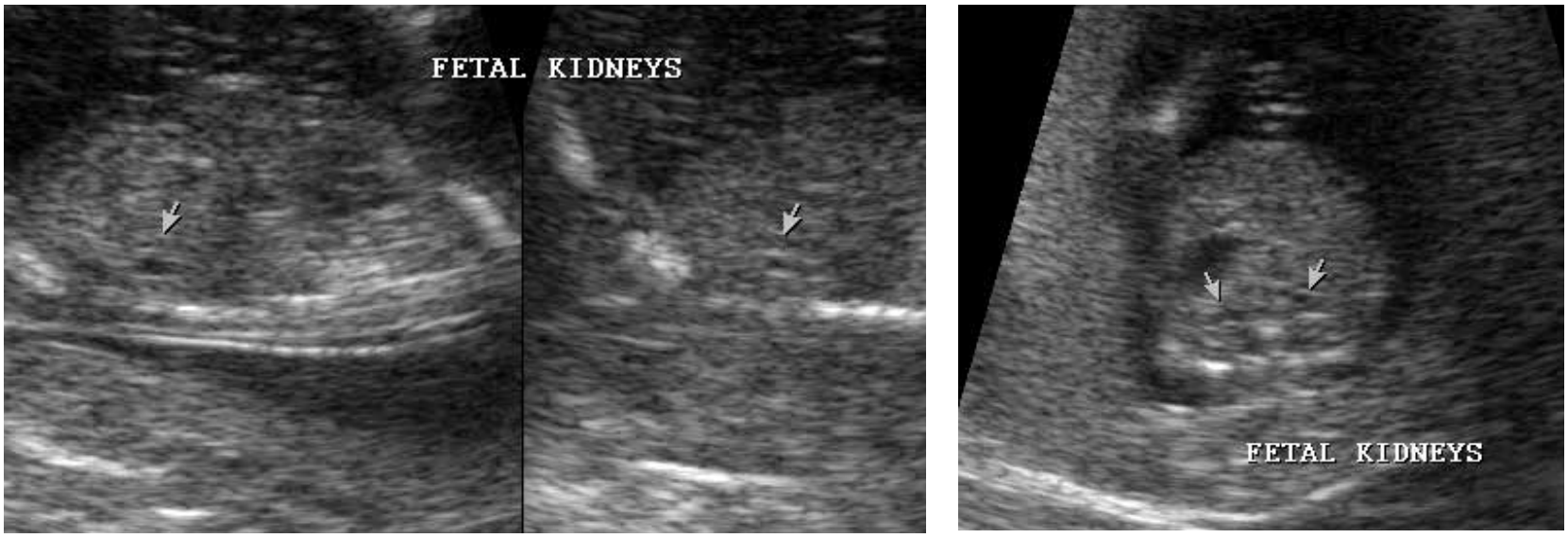


Fig 17: 10-14 weeks (KIDNEYS: VISUALISATION on both sides)

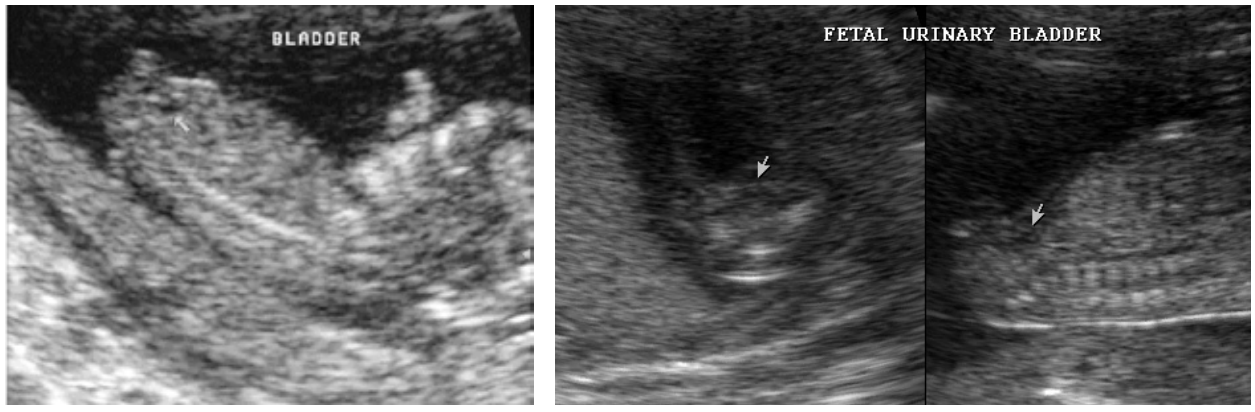


Fig 18: 10-14 weeks (BLADDER: FILLING and emptying)

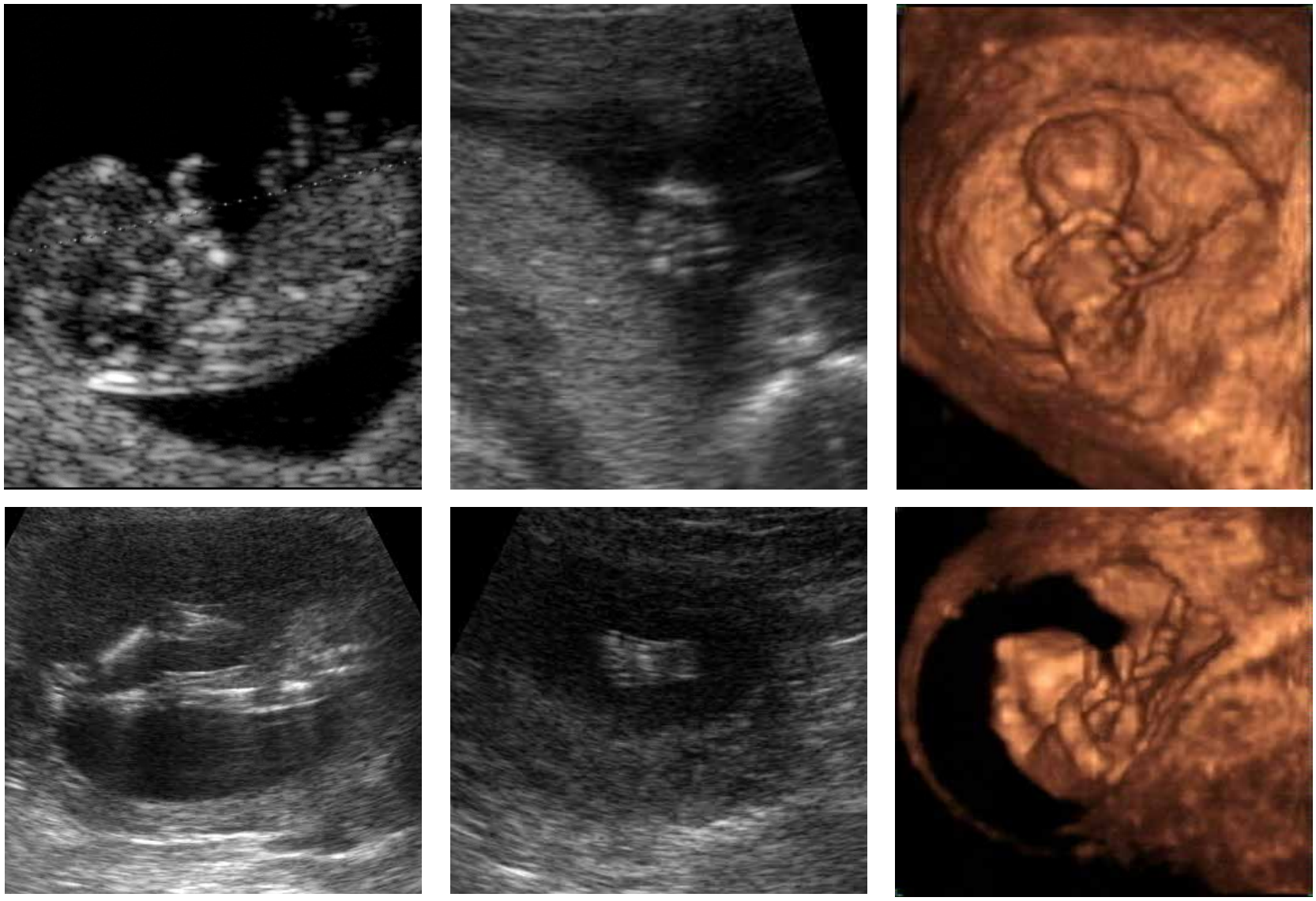


Fig 19 : 10-14 weeks (EXTREMITIES: Long Bones And Movements)

ANOMALIES

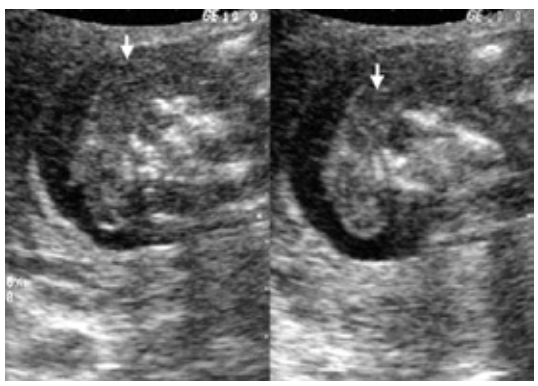


Fig 20: ACRANIA

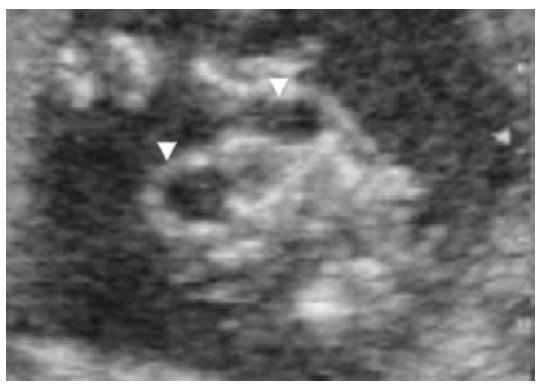


Fig 21: ANENCEPHALY

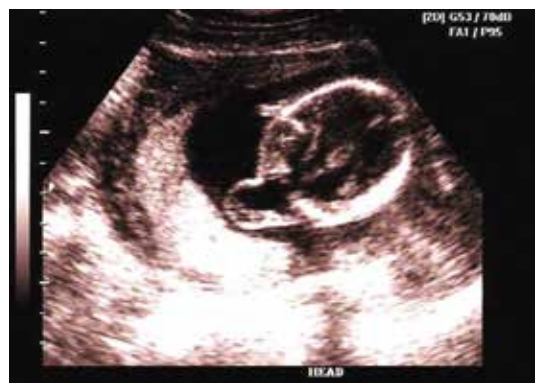


Fig 22 : ENCEPHALOCELE

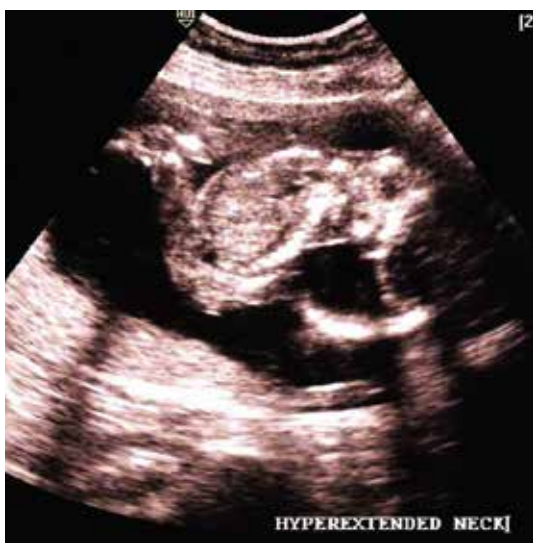


Fig 23 : INIENCEPHALY

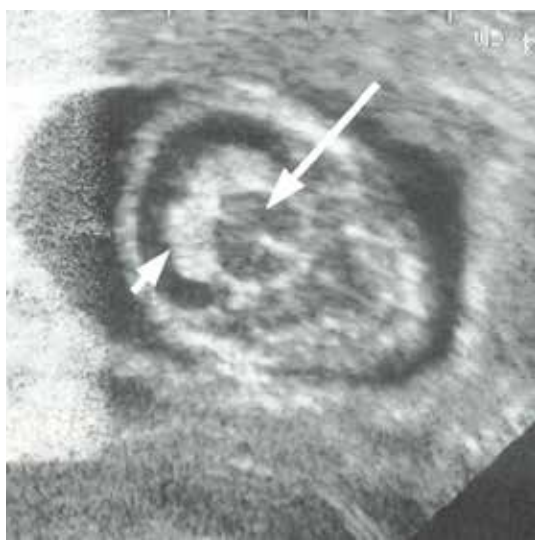


Fig 24 : HOLOPROSENCEPHALY

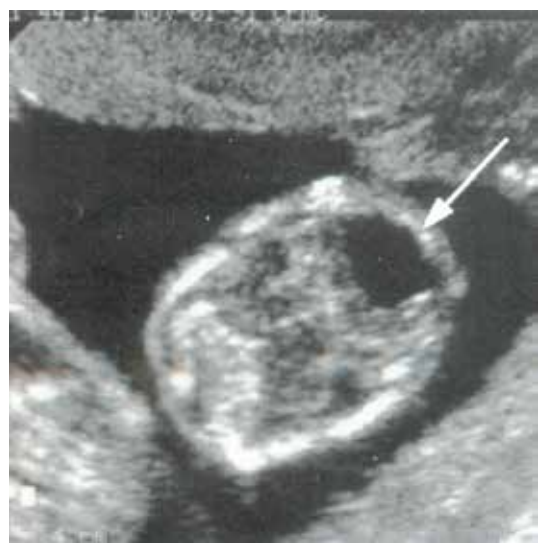


Fig 25 : DANDY WALKER MALFORMATION

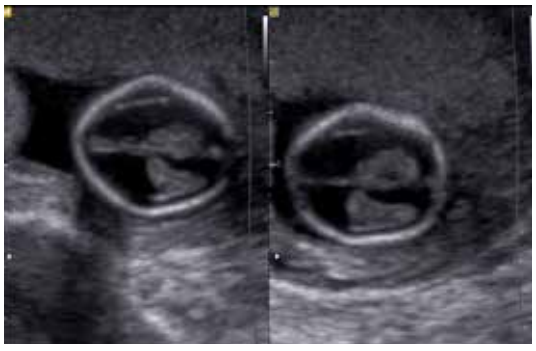
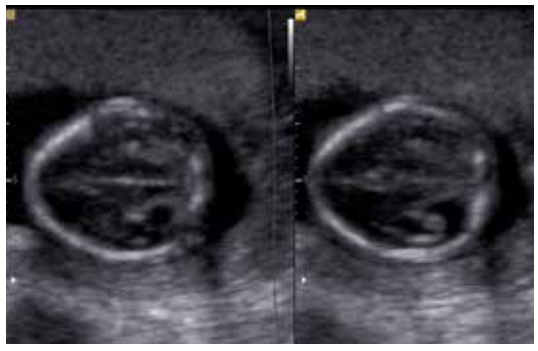


Fig 26 : VENTRICULOMEGALY



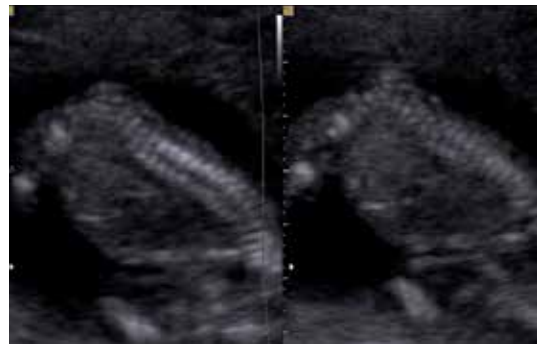


Fig 27 : FETAL SPINE : meningomyelocele

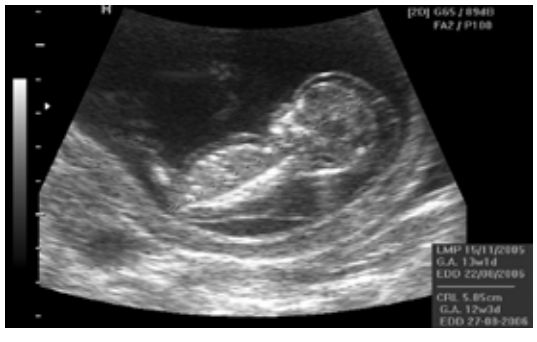
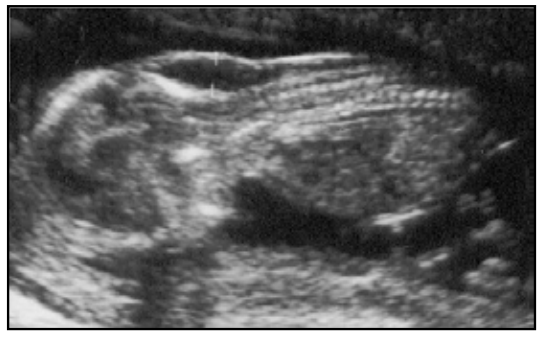
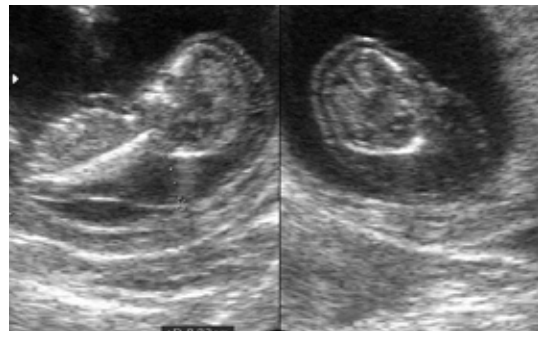
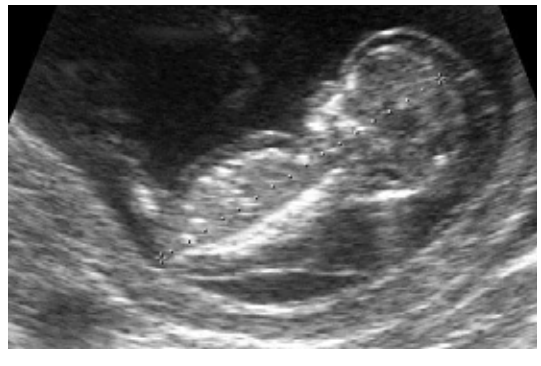


Fig 28 : CYSTIC HYGROMA enveloping the cranium and trunk







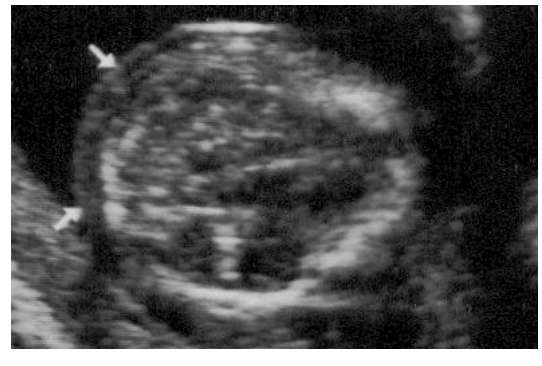


Fig 29: NUCHAL TRANSLUCENCY thickened. Evaluate for karyotypic abnormalities and cardiac defects

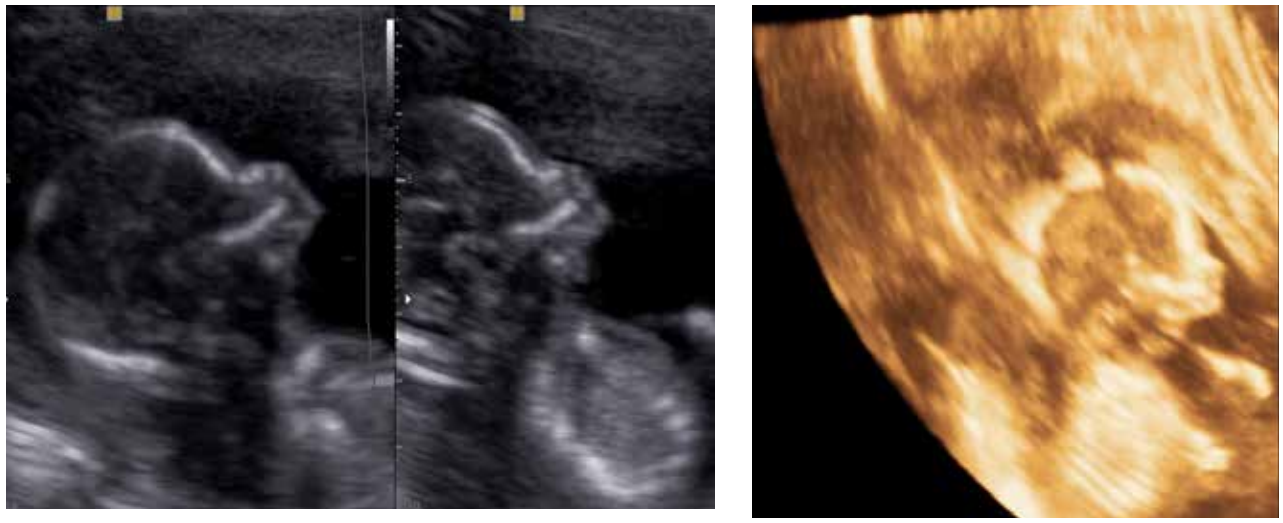


Fig 30: FACIAL ANOMALIES : Micrognathia

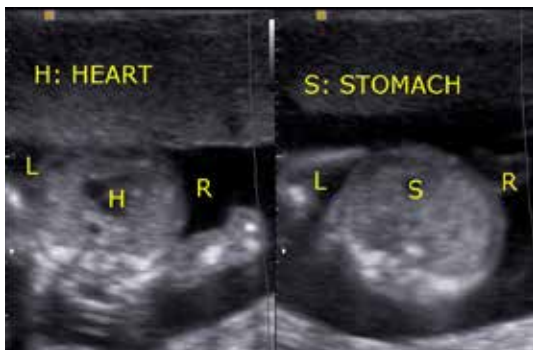


Fig 31: SITUS ANOMALIES : Heart and stomach on opposite sides

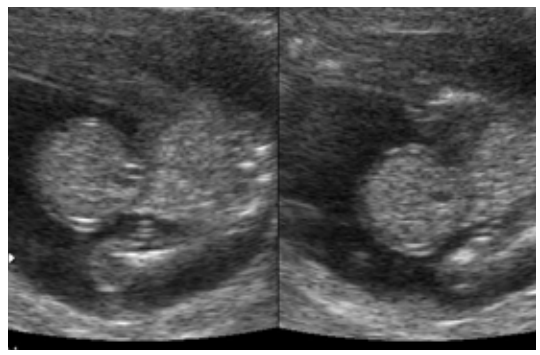


Fig 32: OMPHALOCELE with liver herniating

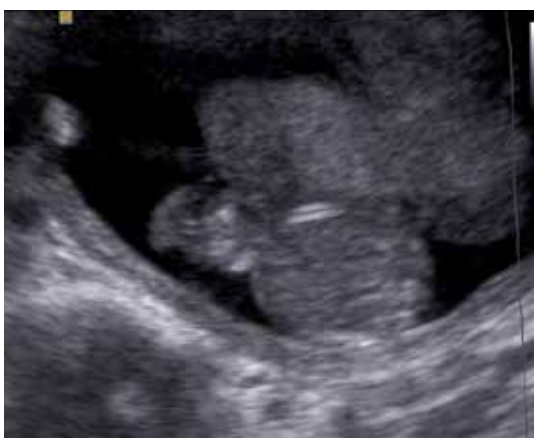
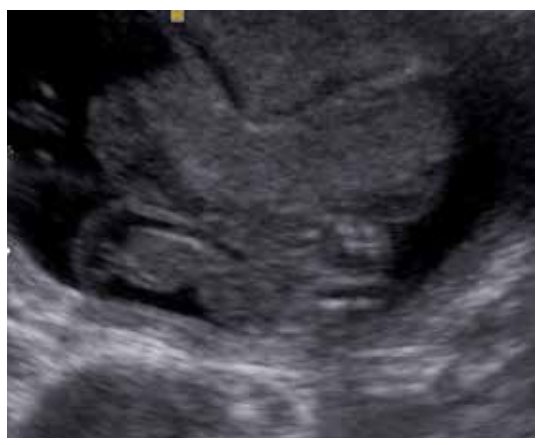


Fig 33: Gastroschisis



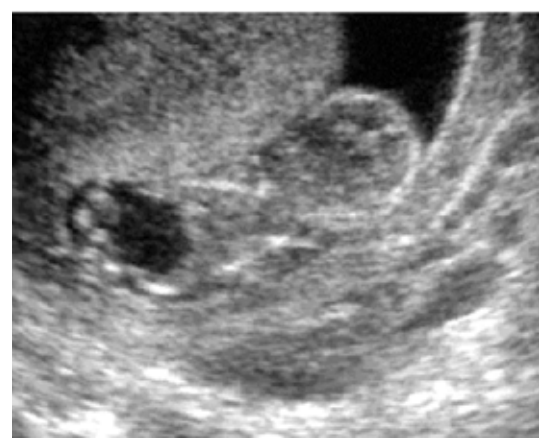
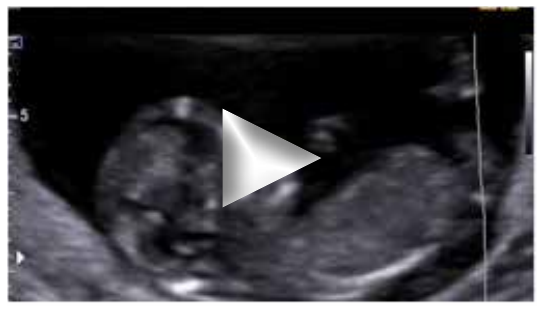


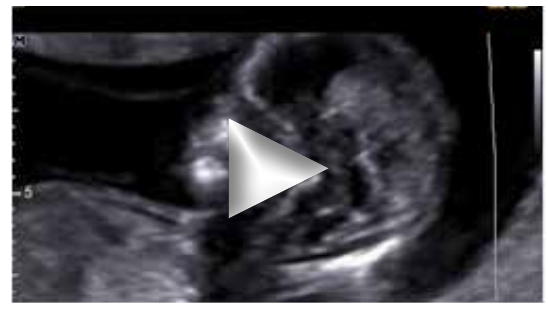
Fig 34: MEGACYSTIS.

VIDEOS

Video : Nuchal translucency, nasal bone and Intracranial translucency in the same view



Eyeballing for a proper Nuchal Translucency



Nuchal translucency, nasal bone and Intracranial translucency in the same view

Intrauterine Growth Restriction: Evidence based Management Algorithm

Lt Col (Dr) Reema Kumar
MS, DNB, FICOG
Consultant, Obst /Gyne & Fetal Maternal Medicine,
Army Hospital (Research and Referral),
New Delhi

Dr. Monika Gupta
MD, DNB, FICOG, MAMS
Associate Professor, Obgyn
VMMC & Safdarjung Hospital,
New Delhi

DEFINITION AND DIAGNOSIS OF FGR

The American College of Obstetricians and Gynecologists (ACOG). defines FGR as an estimated fetal weight less than the 10th centile.[1] The Royal College of Obstetricians and Gynaecologists (RCOG) uses fetal abdominal circumference (AC) or estimated fetal weight (EFW) <10th centile to diagnose a FGR fetus.[2] More recently, early FGR has been defined by a consensus committee of international fetal medicine experts with solitary parameters either EFW <3rd centile, AC <3rd centile or absent umbilical artery end diastolic flow.[3]

Early FGR by definition is diagnosed at or below 32 weeks and differs from late onset FGR also in terms of its clinical manifestations, association with hypertension, patterns of deterioration and severity of placental dysfunction.

Despite being one of the most relevant and most commonly studied conditions in modern obstetrics, there has not been consensus among International Guidelines regarding the optimal management of early onset FGR in terms of monitoring and recommended gestational age at delivery, which can be due to the lack of comparability among studies and the paucity of randomized controlled trials available.[4] Importantly, gestational age is the most significant determinant of both survival and intact survival.[5]

FETAL DOPPLER IN FGR

The fetal vessels that are more commonly examined include umbilical artery, middle cerebral artery, and ductus venosus. Early-onset FGR is associated with high impedance utero placental perfusion which in turn leads to elevated umbilical artery blood flow resistance once villous damage exceeds 30%. Late-onset FGR is more common but less severe with absent or mild placental abnormalities; umbilical artery Doppler may be normal, but fetuses may react with decreased middle cerebral artery (MCA) impedance in response to hypoxemia.[6]

DV has been demonstrated to be the single strongest Doppler parameter to predict the short term risk of fetal death in early onset FGR and there is good correlation between abnormal DV waveform and late stage acidemia.[7] Absent or reversed A-wave have been reported to be associated with increased risk of intrauterine fetal death (40–70%) independently of the gestational age at delivery; DV PI >95th centile also confers higher risk of adverse outcome, although at lesser extent than that of reversed or absent A- wave.[8]

The cerebroplacental ratio (CPR) quantifies the redistribution of cardiac output by dividing the Doppler indices of the middle cerebral artery (MCA) with that of the umbilical artery. The PORTO study demonstrated the association between redistribution, either isolated or associated with umbilical artery PI >95th centile, and adverse perinatal outcome [20]. More recent data have shown significantly lower MCA PI and CPR among fetuses with EFW <10th centile diagnosed gestation beyond 32 weeks who experienced adverse perinatal outcomes in terms of intrapartum distress and abnormal cord pH.[9]

STAGE BASED MANAGEMENT OF FETAL GROWTH RESTRICTION

While strong evidence is lacking to support firm recommendations on the timing of delivery, a protocol that integrates the best available evidence can help reducing clinical practice variation. A stage-based management protocol suggested by Figueras et al recommend fetal monitoring twice weekly up to 34 weeks if umbilical artery AEDF, every 24 to 48 h up to 30 weeks if reverse diastolic flow in the umbilical artery (REDV) or DV-PI > 95th centile, and every 12 to 24 h up to 26 weeks if spontaneous FHR decelerations, reduced STV (<3 ms) in the computerised cardiotocography, or reverse atrial flow in the DV.[10]

Stage I FGR (Severe Smallness or Mild Placental Insufficiency)

- Either UtA, UA or MCA Doppler, or the CPR are abnormal.
- In the absence of other abnormalities, low risk of fetal deterioration before term.
- Labor induction beyond 37 weeks is acceptable
- Cervical induction with Foley catheter is also recommended.
- Weekly monitoring seems reasonable.

Stage II FGR (Severe Placental In-sufficiency)

- UA absent-end diastolic velocity (AEDV) or reverse Aortic Isthmus.
- Delivery recommended after 34 weeks.
- Risk of emergent cesarean section at labor induction exceeds 50%; elective cesarean section is a reasonable option.
- Monitoring twice a week is recommended.

Stage III FGR (Advanced Fetal Deterioration, Low-Suspicion Signs of Fetal Acidosis)

- Reverse absent-end diastolic velocity (REDV) or DV PI >95th centile.
- Higher risk of stillbirth and poorer neurological outcome.
- Reasonable to delay elective delivery to reduce possible effects of severe prematurity.
- Delivery should be recommended by cesarean section after 30 weeks.
- Monitoring every 24–48 h is recommended.

Stage IV FGR (High Suspicion of Fetal Acidosis and High Risk of Fetal Death).

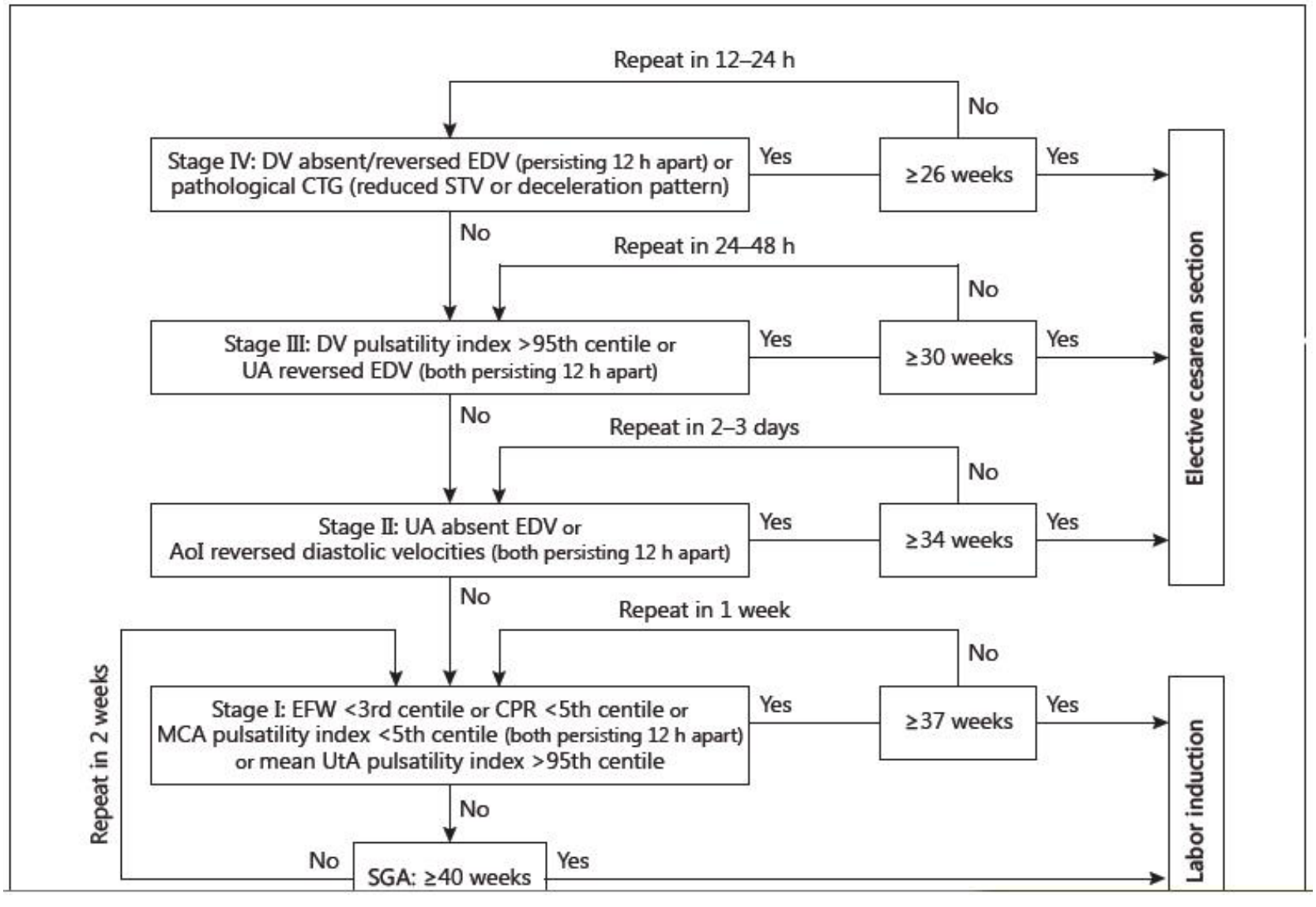
- Spontaneous FHR decelerations, reduced Short Term Variability (<3 ms) in the cCTG, or reverse atrial flow in the DV Doppler.
- Spontaneous FHR deceleration if persistent, may justify emergency cesarean section..
- Deliver after 26 weeks by cesarean section at a tertiary care center under steroid treatment for lung maturation.
- Intact survival exceeds 50% only after 26–28 weeks; before this threshold parents should be counseled by multidisciplinary teams.
- Monitoring every 12–24 h until delivery is recommended.

STAGE BASED CLASSIFICATION AND MANAGEMENT OF FGR

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

All Doppler signs described above should be confirmed at least twice, ideally at least 12 h apart. GA = Gestational age; LI = labor induction; CS = cesarean section. * Recommended intervals in the absence of severe preeclampsia. If FGR is accompanied by this complication, strict fetal monitoring is warranted regardless of the stage. ** Lower GA threshold recommended according to current literature figures reporting at least 50% intact survival. Threshold could be tailored according to parents' wishes or adjusted according to local statistics of intact survival.

DECISION ALGORITHM FOR THE MANAGEMENT OF FGR



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7. Figueras F, Gratacos E. Update on the Diagnosis and Classification of Fetal Growth Restriction and Proposal of a Stage-Based Management Protocol. Fetal Diagn Ther. 2014;36:86–98.

8. Lees CC, Marlow N, van Wassenaer-Leemhuis A, Arabin B, Bilardo CM, Brezinka C, Calvert S, Derks JB, Diemert A, Duvekot JJ, Ferrazzi E, Frusca T, Ganzevoort W, Hecher K, Martinelli P, Ostermayer E, Papageorghiou AT, Schlembach D, Schneider KT, Thilaganathan B, Todros T, Valcamonico A, Visser GH, Wolf H, TRUFFLE study group. 2 year neurodevelopmental and intermediate perinatal outcomes in infants with very preterm fetal growth restriction (TRUFFLE): a randomised trial. Lancet. 2015;385(9983):2162–72.

9. Figueras F, Savchev S, Triunfo S, Crovetto F, Gratacos E. An integrated model with classification criteria to predict small-for-gestational-age fetuses at risk of adverse perinatal outcome. Ultrasound Obstet Gynecol. 2015;45(3):279–85.

10. Figueras F, Gratacos E. Stage-based approach to the management of fetal growth restriction. Prenat Diagn. 2014;34:655–9.

We are likely to become morbid
and
look constantly on the dark side of life,
and
spend entirely too much time considering
and
brooding over what we can't do, rather than what we can do.....

Let us rejoice at the many unexplored fields
in which there is unlimited fame
and
fortune to the successful explorer
and
upon which there is no color line, simply the survival of the fittest.

- George Washington Carver

Dr. Sharda Patra
Professor, Department of Obstetrics & Gynecology, Lady Hardinge Medical College & Smt SK Hospital, New Delhi

Dr. Puneet K Kochhar
Consultant Gynecologist & IVF Specialist
Elixir Fertility Centre,
Gujranwala Town, Delhi

1. **First-trimester chorionic bump--Association with fetal aneuploidy in a high-risk population.**

   Wax JR, Cartin A, Litton C, Pinette MG, Lucas FL.

   J Clin Ultrasound. 2017 Jan;45(1):3-7. doi: 10.1002/jcu.22417. Epub2016 Nov 3.

OBJECTIVE: To determine the relationship between the first-trimester chorionic bump and fetal aneuploidy.

METHODS: This retrospective cohort study included all singleton pregnancies with chromosomal analysis and sonographic examination performed between 5 0/7 and 13 6/7 weeks from January 1, 2010 through August 15, 2015. Interobserver and intraobserver agreement for identifying a chorionic bump was evaluated by the Kappa statistic. Pregnancies with and without a chorionic bump were compared regarding patient characteristics and fetal karyotypes.

RESULTS: Six hundred ninety subjects were included, 16 (2.3%) having a bump. The kappa coefficients for interobserver agreement were 0.88 (95% confidence interval [CI]: 0.71-1.00) and 0.94 (95% CI: 0.82-1.00); those for intraobserver agreement were 0.81 (95% CI: 0.61-1.00) and perfect agreement. One hundred seventeen fetuses (16.9%) were aneuploid, of which five (4.3%) had a bump. The odds of aneuploidy in the presence of a chorionic bump were higher than those in the absence of a chorionic bump, although this difference was not statistically significant (odds ratio [OR] 2.3, 95% CI: 0.8-6.7). In subgroup analyses, odds of aneuploidy were four times higher in the bump group than in the no bump group among those with a sonographically isolated bump (OR 4.5, 95% CI: 1.5-13.5) and 15 times higher among those with an isolated bump and increased first-trimester aneuploidy risk (OR 15.0, 95% CI 2.4-93.3).

CONCLUSIONS: Agreement in identifying chorionic bumps is near-perfect. A sonographically nonisolated chorionic bump is not associated with significant additional aneuploidy risk, whereas a sonographically isolated chorionic bump confers a significantly increased likelihood of aneuploidy in high-risk fetuses.

2. **The IONA® Test: Development of an Automated Cell-Free DNA-Based Screening Test for Fetal Trisomies 13, 18, and 21 That Employs the Ion Proton Semiconductor Sequencing Platform.**

   Crea F, Forman M, Hulme R, Old RW, Ryan D, Mazey R, Risley MD.

   Fetal Diagn Ther. 2017 Feb 8. doi: 10.1159/000455025. [Epub ahead of print]

OBJECTIVE: To develop a screening test for fetal trisomy 13, 18, and 21 using cell-free DNA from maternal blood with an automated workflow using the Ion Proton sequencing platform.

METHODS: An automated next-generation sequencing workflow was developed using the Ion Proton sequencing platform and software developed for straightforward bioinformatic analysis. An algorithm was developed using 239 samples to determine the likelihood of trisomy, using DNA fragment counts and a fetal fraction validity check; the results were compared with those from invasive diagnostic procedures. A further 111 samples were used to assess the tests' sensitivity (detection rate) and specificity (1 minus false-positive rate).

RESULTS: The 110 of a possible 111 valid samples used to verify the IONA® test gave 100% sensitivity and specificity, compared with invasive diagnostic procedures; one failed the fetal fraction validity check giving a sample failure rate of 0.29% across all 350 analysed samples.

CONCLUSION: The data indicate that the IONA test provides a robust, accurate automated workflow suitable for use on maternal blood samples to screen for trisomies 13, 18, and 21. The test has the potential to reduce the number of unnecessary invasive procedures performed and facilitate testing by screening laboratories.

3. **Genomic Array as Compared to Karyotyping in Myelodysplastic Syndromes in a Prospective Clinical trial.**

   Stevens-Kroef MJ, Olde Weghuis D, ElIdrissi-Zaynoun N, van der Reijden B, Cremers EM, Alhan C, Westers TM, Visser-Wisselaar HA, Chitu DA, Cunha SM, Vellenga E, Klein SK, Wijermans P, de Greef GE, Schaafsma MR, Muus P, Ossenkoppele GJ, van de Loosdrecht AA, Jansen JH.

   Genes Chromosomes Cancer. 2017 Feb 25. doi: 10.1002/gcc.22455. [Epub ahead of print]

BACKGROUND: Karyotyping is considered as the gold standard in the genetic sub classification of myelodysplastic syndrome (MDS). Oligo/SNP-based genomic array profiling is a high-resolution tool that also enables genome wide analysis.

METHODS: We compared karyotyping with oligo/SNP-

based array profiling in 104 MDS patients from the HOVON-89 study.

RESULTS: Oligo/SNP-array identified all cytogenetically defined genomic lesions, except for subclones in two cases and balanced translocations in three cases. On the other hand oligo/SNP-based genomic array profiling had a higher success rate, showing 55 abnormal cases, while an abnormal karyotype was found in only 35 patients. In 9 patients whose karyotyping was unsuccessful because of insufficient metaphases or failure, oligo/SNP-based array analysis was successful. Based on cytogenetic visible abnormalities as identified by oligo/SNP-based genomic array prognostic scores based on IPSS/-R were assigned. These prognostic scores were identical to the IPSS/-R scores as obtained with karyotyping in 95-96% of the patients. In addition to the detection of cytogenetically defined lesions, oligo/SNP-based genomic profiling identified focal copy number abnormalities or regions of copy neutral loss of heterozygosity that were out of the scope of karyotyping and fluorescence in situ hybridization. Of interest, in 26 patients we demonstrated such cytogenetic invisible abnormalities. These abnormalities often involved regions that are recurrently affected in hematological malignancies, and may therefore be of clinical relevance.

CONCLUSIONS: Our findings indicate that oligo/SNP-based genomic array can be used to identify the vast majority of recurrent cytogenetic abnormalities in MDS. Furthermore, oligo/SNP-based array profiling yields additional genetic abnormalities that may be of clinical importance.

4. **Pre-conceptual and prenatal supplementary folic acid and multivitamin intake, behavioral problems, and hyperkinetic disorders: A study based on the Danish National Birth Cohort (DNBC).**

   Virk J, Liew Z, Olsen J, Nohr EA, Catov JM, Ritz B.

   Nutr Neurosci. 2017 Mar 9:1-9. doi: 10.1080/1028415X.2017.1290932. [Epub ahead of print]

OBJECTIVE: To evaluate whether early folic acid or multivitamin supplementation during pregnancy prevents diagnosis of hyperkinetic disorders (HKD), treatment for attention deficit hyperactivity disorder (ADHD), and ADHD-like behaviors reported by parents participating in the DNBC for children at age 7.

METHODS: HKD diagnosis and ADHD medication use data were obtained from the Danish National Hospital, Central Psychiatric and Pharmaceutical registers. We estimated hazard ratios (HRs) for HKD diagnosis and ADHD medication use and risk ratios (RRs) for parent-reported ADHD behavior collected with the Strength and Difficulties Questionnaire (SDQ), comparing children whose mothers took folic acid or multivitamin supplements early in pregnancy defined as starting periconceptionally (4 weeks prior to their last menstrual period (LMP)) through 8 weeks after their LMP (4-8 weeks), to children whose mothers indicated no supplement use for the same entire period.

RESULTS: We identified 384 children (1.1%) with a hospital diagnosis for HKD and 642 children (1.8%) treated with ADHD medication. We found no association between risk of HKD diagnosis or intake of ADHD medication and early maternal folic acid use. However, early multivitamin use was associated with an approximately 30% reduction in risk for HKD diagnosis (aHR: 0.70, 95% CI: 0.52-0.96) and 21% reduction in treatment with ADHD medication (aHR: 0.79, 95% CI: 0.62-0.98). We observed a reduced risk in parent-reported ADHD behaviors, but these results were attenuated after adjustment.

CONCLUSION: Our data suggest that multivitamin use in early pregnancy may reduce risk for HKD diagnosis and treatment for ADHD in the offspring.

5. **Noninvasive Prenatal Screening of Fetal Aneuploidy without Massively Parallel Sequencing.**

   Xu C, Wang T, Liu C, Li H, Chen X, Zhu H, Chen S, Xin Q, Tao J, Huang L, Jiang Z.

   Clin Chem. 2017 Feb 14. pii: clinchem.2016.266247. doi: 10.1373/clinchem.2016.266247. [Epub ahead of print]

BACKGROUND: Noninvasive prenatal screening (NIPS) using plasma cell-free DNA has gained tremendous popularity in the clinical assessment of fetal aneuploidy. Most, if not all, of these tests rely on complex and expensive massively parallel sequencing (MPS) techniques, hindering the use of NIPS as a common screening procedure.

METHODS: We have developed and optimized an MPS-independent noninvasive genetic test that can rapidly detect fetal aneuploidy at considerably lower costs. We used the high-throughput ligation-dependent probe amplification (HLPA) assay with standard z score statistics to identify the minute copy number change of targeted chromosomal regions. HLPA was modified from multiplex ligation-dependent probe amplification to allow quantification of up to 200 genomic loci in a single multiplex PCR. As a proof of principle, we conducted Down syndrome screening in 1182 women with singleton pregnancies [maternal age (SD): 32.7 (4.6)] using whole-genome sequencing-based NIPS and our method.

RESULTS: Nineteen fetuses with trisomy 21 were detected by both methods and confirmed by karyotyping of amniotic fluid. Overall, our method showed 100.0% sensitivity (19/19) and 99.7% specificity (1076/1079) in trisomy 21 screening, generating a positive predictive value of 86.4% (19/22) and a 7.1% (84/1182) no-call rate.

CONCLUSIONS: Our technique potentially opens new avenues for the development of inexpensive, yet effective, prenatal aneuploidy tests. The simplicity and accuracy of this method make it a good candidate for clinical implementation as a standard screening procedure.

6. **Are First Trimester Nuchal Septations Independent Risk Factors for Chromosomal Anomalies?**

   Mack LM, Lee W, Mastrobattista JM, Belfort MA, Van den Veyver IB, Shamshirsaz AA, Ruano R, Sanz Cortes M, Espinoza A, Thiam Diouf A, Espinoza J.

   J Ultrasound Med. 2017 Jan;36(1):155-161. doi: 10.7863/ultra.16.01066. Epub 2016 Nov 28.

OBJECTIVES: There is conflicting information regarding the role of nuchal septations during first-trimester genetic screening. This study was designed to determine whether nuchal septations are risk factors for chromosomal anomalies, independent of increased nuchal translucency (NT), in the first trimester of pregnancy.

METHODS: This retrospective cohort study included all women who underwent first-trimester genetic screening between November 2011 and December 2014. The 95th percentile for the NT measurement was calculated for each gestational week. A multivariable logistic regression analysis was performed to determine whether the visualization of nuchal septations was an independent risk factor for chromosomal analysis while controlling for confounding variables. $P < .05$ was considered significant.

RESULTS: Chromosomal abnormalities were present in 1.0% of the population (33 of 3275). The prevalence of chromosomal abnormalities was significantly higher among fetuses with nuchal septations compared to fetuses with normal NT without septations ($P < .001$) and those with NT above the 95th percentile without septations ($P < .001$). The sonographic evidence of septations was associated with high risk of chromosomal abnormalities (odds ratio, 40.0; 95% confidence interval, 9.1-174.0) after controlling for NT measurements and other confounding variables.

CONCLUSIONS: Visualization of nuchal septations during first-trimester genetic screening is a powerful risk factor for chromosomal anomalies, independent of increased NT.

7. A new method to predict the need for a Rashkind procedure in fetuses with dextro-transposition of the great arteries.

Słodki M, Axt-Fliedner R, Zych-Krekora K, Wolter A, Kawecki A, Enzensberge C, Gulczyńska E, Respondek-Liberska M; International Prenatal Cardiology Collaboration Group.

Ultrasound Obstet Gynecol. 2017 Mar 14. doi: 10.1002/uog.17469. [Epub ahead of print]

OBJECTIVE: Prenatal congenital heart disease classification system specifies critical d-TGA with restriction of the foramen ovale (which requires Rashkind procedure) and planned d-TGA. However, current prenatal diagnostic criteria for post-delivery foramen ovale (FO) restriction in d-TGA are inadequate, resulting in a high false negative rate. We aim to find an echocardiographic feature to predict the need for Rashkind procedure.

METHODS: 98 patients from 2 European centers diagnosed prenatally with fetal d-TGA from 2006 to 2013 were analyzed and two groups were compared: 1) those in which the Rashkind procedure was performed within the first 24 hours of life; and 2) those who did not undergo a Rashkind procedure before cardiac surgery. The exclusion criteria were: 1) no fetal echocardiography three weeks before delivery (n = 18); 2) delivery before 36 weeks of gestation (n = 6); 3) improper or lack of measurements (n = 10); 4.) no follow up data (n = 9); 5) Rashkind procedure in second or more days after delivery (n = 4).

RESULTS: Finally 51 patients met the inclusion criteria: 29 with Rashkind procedure and 22 without. There were no differences between the two study groups in maternal age, gestational age at the time of fetal echo, fetal biometric measurements, estimated fetal weight, rate of cesarean delivery, newborn weight and Apgar scores at 1 minute. There were also no differences during prenatal life between the two study groups in terms of fetal cardiac size, rate of disproportion between left and right ventricle, foramen ovale (FO) size and FO Vmax. However, the maximum speed of blood flow in the pulmonary veins was significantly higher in the group requiring a Rashkind procedure (47.62 ± 7.48cm/s vs. 32.21 ± 5.47cm/s; $p < 0.001$). The cut-off value 41 cm/s provided maximal specificity and PPV (100%) at only a slight expense of sensitivity and NPV (86%). The prenatal appearance of the FO (flattened valve) was also differed between the groups.

CONCLUSIONS: Prenatal sonographic findings of an increased pulmonary venous blood flow and flattened FO valve were more frequently associated with the postnatal need for a Rashkind procedure within 24 hours of life.

8. Non-invasive prenatal diagnosis of beta-thalassemia by semiconductor sequencing: a feasibility study in the sardinian population.

Saba L, Masala M, Capponi V, Marceddu G, Massidda M, Rosatelli MC.

Eur J Hum Genet. 2017 Mar 8. doi: 10.1038/ejhg.2017.26. [Epub ahead of print]

BACKGROUND: β-Thalassemia is the most common autosomal recessive single-gene disorder in Sardinia, where approximately 10.3% of the population is a carrier. Prenatal diagnosis is carried out at 12 weeks of gestation via villocentesis and is commonly aimed at ascertaining the presence or absence of the HBB variant c.118C>T, which is the most common in Sardinia.

METHODS: In this study, we describe for the first time the application of semiconductor sequencing to the non-invasive prenatal diagnosis of β-thalassemia in 37 couples at risk for this variant.

RESULTS: In particular, by using a haplotyping-based approach with a hidden Markov model (HMM) and a dedicated pipeline, the two parental haplotypes most likely inherited by the foetus could be established in 30 out of 37 cffDNA samples. Specifically, the paternally inherited haplotype was correctly determined in all 30 of the samples, while the maternal haplotype was incorrectly predicted in six of the 30 genotyped samples. The lack of informative SNPs hampered the inference of both parental haplotypes in the remaining seven samples.

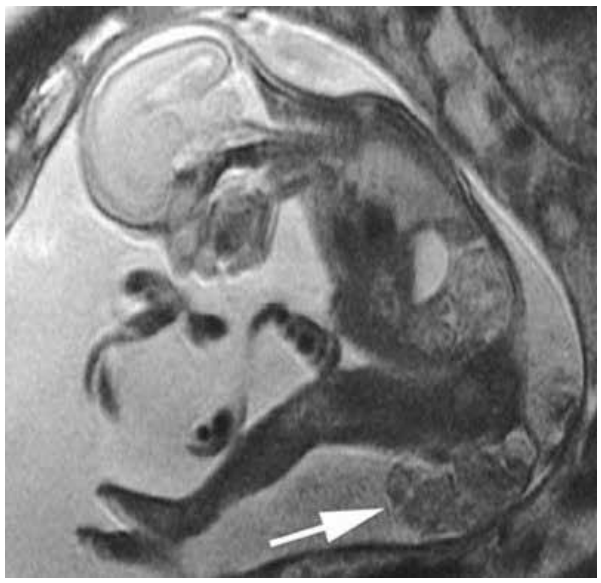
CONCLUSIONS: As shown in previous studies, we have confirmed that the haplotyping-based approach represents a valuable resource, as it improves the detection of both parental haplotypes inherited by the foetus. In general, our results are encouraging, as we have proven that NIPD is also feasible in couples who are at risk for a monogenic disorder and share the same variant.

Brain Teasers

Dr. Abha Rani Sinha

Associate Professor, Obst & Gynae, Patna Medical College, Patna,
Chairperson Quiz committee FOGSI (2015-2017)

Q1. Identify the anomaly seen in the fetal MRI



Q2. Identify the tool used for diagnosing fetal cardiac rhythm disorder?

Q.3. In monochorionic twin of discordant size, , increase NT in at least one fetus indicates early manifestation of .....

Q.4. What is the most commonly used diagnostic modality to monitor fetus exposed to anti RO antibodies?

Q.5. As an isolated ultrasonographic soft marker , which marker is associated with a) highest risk of aneuploidy b) lowest risk of aneuploidy?

ANSWERS TO BRAIN TEASERS – FEBRUARY ISSUE

Ans 1:

- Aplasia cutis congenita.
- Methimazole (anti-thyroid drug).

Ans 2: Contrast-enhanced CT shows a large area of arterial infarction,a secondary right subcapsular haematoma and segmental Budd -Chiari Syndrome

Ans 3: 1%

Ans 4: Single donor platelets transfusion raises the platelet count by 30-60,000 in contrast to 1 unit of RDP which raises it by 5000-10,000

Ans 5: Fetal tone

You never change things by fighting the existing reality.
To change something, build a new Model
that makes the existing model obsolete

- R Buckminster Fuller