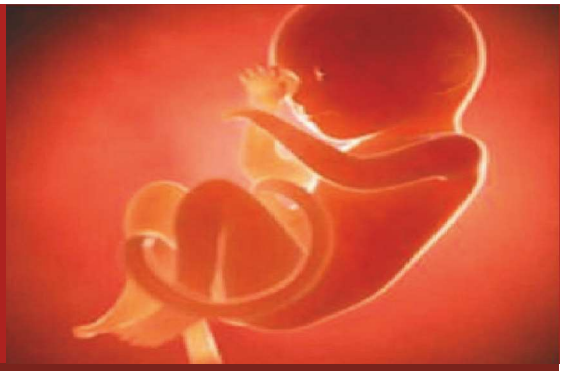
Society of Fetal Medicine



NEWSLETTER OF THE DELHI STATE CHAPTER

Vol 2, May 2023

IN THIS EDITION

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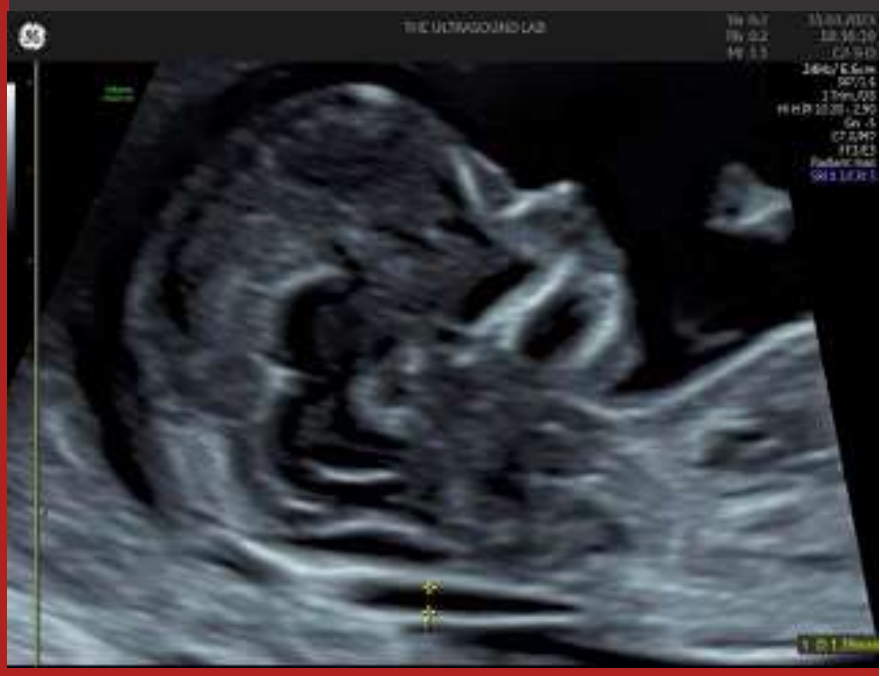

SFM DELHI CHAPTER EXECUTIVE COMMITTEE

From the Secretary's Desk

As we look through the magnifying glass in the first trimester, the base of the inverted pyramid has a clear timeline-based approach toward screening for fetal and maternal morbidity. If there is one field where we do not endeavor to score a century is maternal mortality, where a declining trend is praise worthy indeed. This newsletter is an endeavor to bring you up to date on the guidelines-based actions in the first trimester toward optimizing maternal-fetal outcomes. It has been put together by the hard work of our contributors and brought to final fruition by our editors. I am confident you will find it a ready reckoner and practical manual.

I also invite you to join our quarterly meetings for crisp academic bytes. The next one is planned in the month of June.

Happy browsing!

Sumitra Bachani
Secretary
SFM Delhi Chapter

From the Editors' Desk

Dear Readers,

We are privileged to share with you the second issue of our newsletter, which is dedicated to the fetus in the first trimester. With the increasing emphasis on early diagnosis of fetal abnormalities and the opportunity to screen and prevent the dreaded disease preeclampsia, the first trimester presents a golden opportunity to the sonologist, and it's only befitting that we dedicate a whole issue to it.
As with the previous issue, there is another Crossword in this issue to rattle your fetal medicine-hardwired brain cells! There is an image collage from last quarter's SFM meetings.

The response to our request for contributions has been overwhelming, and we hope that it remains so. The newsletter would be impossible without the valuable contributions of our readers. We thank you all for your input and look forward to continuing to receive articles.

Dr Alok Varshney

Dr Chanchal

FIRST TRIMESTER EVALUATION OF FETAL HEART

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Screening of fetal heart during a first trimester screening (FTS) ultrasound between 11–14 week is highly recommended in every patient regardless of a priori risk for congenital heart defect. A first-trimester evaluation does not replace the second-trimester cardiac screening or fetal echocardiography. However, major cardiac defects can be potentially detected with 75% sensitivity and 99% specificity in the first-trimester.[1]

TECHNIQUE

Evaluation is usually performed transabdominally using high frequency convex or linear transducers. Transvaginal scanning provides an excellent resolution of the fetal heart structures. Hence, it may be preferable in high-risk pregnancies, fetuses with suspected anomalies or if transabdominal scan is not able to provide good views of the fetal heart, e.g., in high BMI patients. The routine use of color Doppler or HD- flow power Doppler adds significantly to our ability to diagnose congenital heart disease by demonstrating blood flow events, flow direction and as an indirect method for structural assessment of the chambers and great vessels.[2]

The crucial planes for a screening examination are (Fig. 1)[3]:

1. Axial section through the fetal upper abdomen (to evaluate fetal situs)
2. The 4-chamber view
3. The three vessel-trachea view for outflow tracts

These planes can be obtained in almost 100% of fetuses between 12 and 14 weeks of gestation.[4]

The left and right ventricular outflow views, longitudinal views for aortic and ductal arches may be taken as a part of detailed cardiac evaluation.

OPTIMIZING FIRST TRIMESTER CARDIAC IMAGING

Gray scale

1. High-frequency transducers
2. Narrow sector width
3. Image magnification
4. High contrast image settings
5. Fetus in dorso-posterior position (NT position)

Color Doppler

1. Optimize gray-scale
2. Narrow color box
3. Mid velocity range (20-30 cm/sec)
4. Mid filter levels
5. Mid-to -high color persistence
6. Low color gain
7. Use of HD-flow & Slow-flow, if available

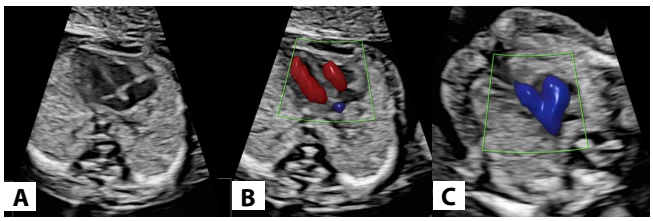

Figure 1: Axial images of fetal heart from a 13 weeks fetus (transvaginal ultrasound). **A.** 4-chamber view on gray-scale. **B.** 4-chamber view with color doppler showing two AV stripes **C.** Three-vessel-trachea view on color Doppler showing a V-shape, equal sized vessels and same direction of flow.

ASSESSMENT OF FETAL HEART

Situs

FTS fetal situs evaluation relies on identification of the stomach bubble and the cardiac apex being on the same side. Situs ambiguous (Fig.2) is often related to cardiac anomalies and/ or Isomerism. Diagnosing situs inversus totalis is challenging but noting the fetal presentation i.e.

cephalic or breech while evaluating fetal situs is helpful.[5]

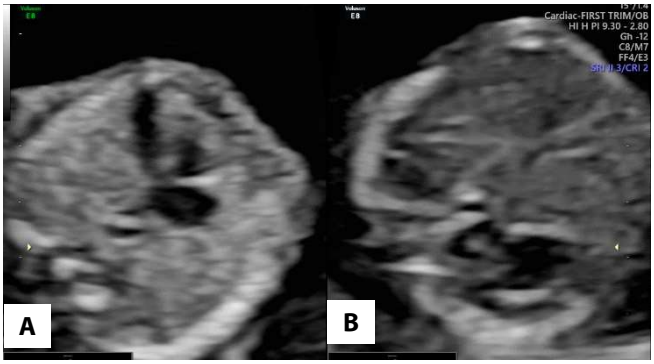

Figure 2: Axial images of fetal chest **A**. and upper abdomen **B.** from a 13 weeks fetus showing the fetal cardiac apex and the stomach on different sides (Situs Ambiguous). Note linear insertion of the atrio-ventricular valves in 4-chamber view suggestive of atrio-ventricular septal defect.

4 Chamber view

Position: Intrathoracic heart position with the heart in the middle of the chest. If the heart appears displaced towards one side, congenital diaphragmatic hernia may be suspected (Fig.3 A).

Cardiac axis: Normal cardiac axis in first trimester is 34.5 to 56.8 degrees.[6] Abnormal cardiac axis, i.e. mesocardia or excess levorotation (Fig.3 B) is a highly sensitive marker for cardiac defects (74% sensitivity).[7]

Size: One-third of thoracic space

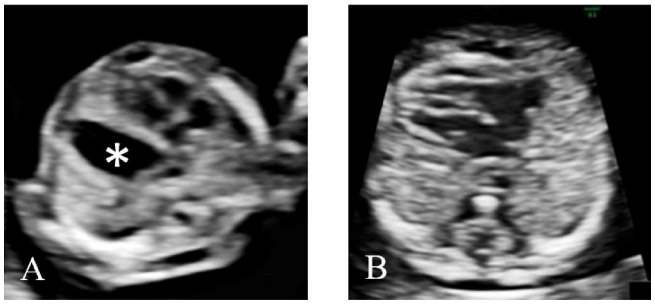

Figure 3: A. Axial images of fetal chest from a 13 weeks fetus showing the fetal heart displaced towards the right side due to fetal stomach (*) herniated inside the left chest (Congenital diaphragmatic hernia). **B.** Marked levo-rotation of the fetal heart in a 12 weeks fetus, which resulted in a discovery of Tetralogy of Fallot.

Symmetry : Two distinct equal sized ventricles on grayscale. Flow across both AV valves on color Doppler (two atrio-ventricular color stripes). Chamber asymmetry, particularly when only one AV stripe is visible, is a sign of serious defect such as HLHS (Fig. 4) or tricuspid atresia.

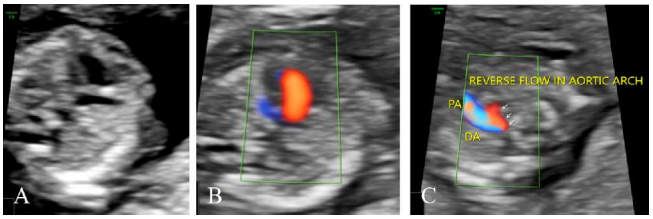

Figure 4: A. 12 weeks fetus showing asymmetry of cardiac chambers in 4-Chamber view in which the left ventricle appears very small. **B.** Only one color-stripe on color Doppler suggesting no flow across the mitral valve **C.** Three-vessel-trachea view showing reverse flow in the aortic arch. Diagnosis: Hypoplastic left heart syndrome.

Septal defect : No gross defect in the septum between the two halves of the heart. Large Atrioventricular septal defects (Fig. 5 A) are better visible in diastole than in systole.[8] Gray scale evaluation confirming the presence of an interventricular septum is crucial to exclude single ventricle defects such as double inlet left ventricle in which presence of two atrioventricular stripes on color Doppler may be misleading (Fig. 5 B &C).[9]

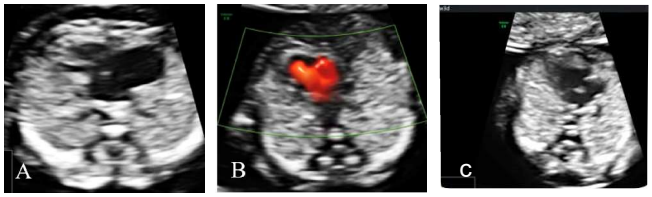

Figure 5: A. A large defect in the atrio-ventricular septum (AVSD) in a 13 weeks fetus. **B.** 12 weeks fetus showing two atrio-ventricular stripes on color Doppler. **C.** Gray scale image shows both atrio-ventricular valves opening into a single ventricle (Double inlet left ventricle)

Regurgitation: No regurgitation from the center of the heart or from either atrioventricular valve. Though mild regurgitation is seen in approx. 5% of fetuses, gross tricuspid regurgitation originating from near the apex of the heart is indicative of Ebstein's anomaly (Fig 6 A & B). Regurgitation from the center of the heart is suggestive of AVSD (Fig. 6 C).

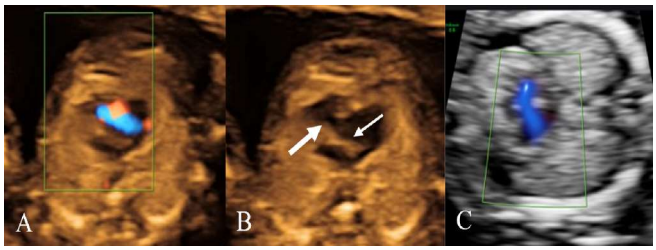

Figure 6: A. 12 weeks fetus. Severe tricuspid regurgitation which appears to be originating near the cardiac apex. **B.** Apical insertion of the septal leaflet of the tricuspid valve (large arrow) away from the crux (small arrow) in a case of Ebstein's anomaly. **C.** Regurgitation from the center of the heart in a 12 weeks fetus due to atrio-ventricular septal defect.

THREE-VESSEL-TRACHEA VIEW

Due to their small size, the great vessels may not be distinctly identified on gray-scale. Color Doppler or HD flow greatly aids in identification with greater accuracy. Three vessel trachea view displays a typical V-shape formed by the aortic and ductal arches and their confluence on the left side of the fetal spine. This view demonstrates the presence, number and size of the great vessels, their anatomic relationship and the direction of blood flow, along with the continuity of the ductal and aortic arches, ruling out of most complex anomalies affecting the great vessels.[10] Visualization of a single vessel instead of a V may be indicative of great vessel malposition e.g. Transposition of great arteries (Fig. 7), corrected transposition, double outlet right ventricle, malposition associated with a univentricular heart etc. Other differential diagnoses include common arterial trunk, pulmonary atresia with ventricular septal defect and Aortic atresia.

If instead of a typical V a 'U' appearance is seen in the three-vessel-trachea view, a right aortic arch with left sided ductus arteriosus can be diagnosed (Fig.8). However, these cases require exclusion of a double aortic arch on follow-up studies.

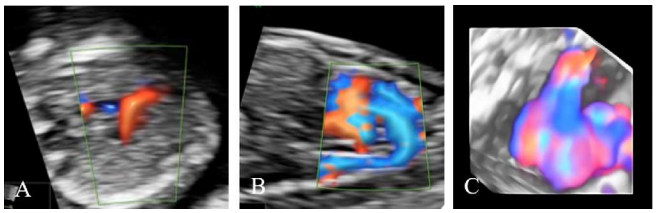

Figure 7: 12 weeks fetus **A.** Single vessel in upper chest. **B.** Parallel great vessels in sagittal view with no crossover **C.** 3D volume rendering of the HD-flow showing parallel great vessels arising from the ventricles. Findings are suggestive of Transposition of great vessels.

When one of the limbs of the V appear smaller in caliber than the other, this may be due to a small aorta (Coarctation) or a small pulmonary artery, usually seen in Tetralogy of Fallot (TOF). In TOF the narrow pulmonary artery typically joins the aortic arch at an angle (Y sign) (Fig. 9).[11]

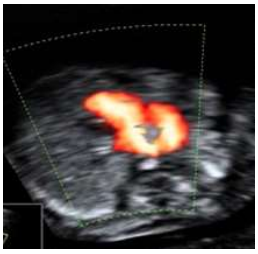

Figure 8: 14 weeks fetus. U sign suggestive of right aortic arch with left ductus.

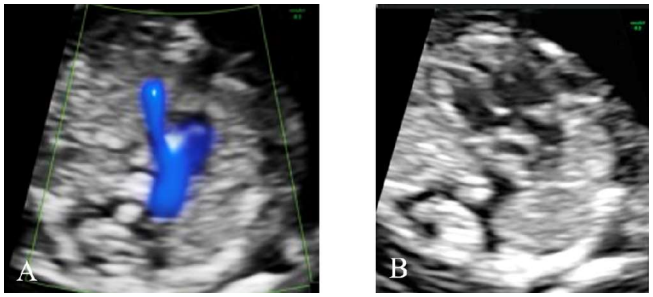

Figure 9 : 13 weeks fetus A. Narrow pulmonary artery joining the aorta at an angle (Y sign). B. Ventricular septal defect with overriding aorta. Findings typical of Tetralogy of Fallot.

FIRST TRIMESTER CARDIAC EXAMINATION CHECKLIST

- Heart activity present with regular heart rhythm
- Establish normal situs
- Intrathoracic heart in the center of the chest
- Normal cardiac axis
- Equal sized two sides of the heart
- Flow present across both AV valves
- No gross defect in the atrio-ventricular septum.
- No significant regurgitation from AV valves
- Normal appearing V-sign of 3 vessel-trachea view
- Cross-over of the great vessels present.
- Antegrade ductus venosus A-wave on pulsed-wave Doppler

CONCLUSION

With advancing technology and use of standard cardiac examination protocol during a routine first-trimester screening, it is possible to detect a majority of major cardiac defects at an earlier gestational age.

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"Excellent!' I cried. "Elementary," said he.

- Arthur Conan Doyle, The Complete Sherlock Holmes

SCREENING FOR PREECLAMPSIA

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Pre-eclampsia (PE) affects 2%–5% of pregnant women and is one of the common causes of perinatal morbidity and mortality especially in early onset disease.[1] The pathogenesis involves a two stage theory. First stage pertains to abnormal invasion of the trophoblast leading to inadequate remodelling of the spiral arteries. This leads to the second stage which involves the maternal response to abnormal endothelial function resulting in an imbalance between anti-angiogenic and angiogenic factors causing features of the pre eclampsia.[2]

As per ISSHP3 guidelines, PE is defined as systolic blood pressure at ≥140 mm Hg and/or diastolic blood pressure at ≥90 mm Hg on at least two occasions measured 4 hours apart in a woman who was previously normotensive and is accompanied by ≥1+ of proteinuria or any other maternal organ dysfunction, abnormal fetal dopplers with growth restriction or intrauterine fetal death. It is challenging to monitor women with PE while balancing the need to achieve fetal maturation in utero with the maternal risks associated with the continuation of pregnancy. The latter include eclampsia, HELLP (hemolysis, elevated liver enzyme,[3,4] low platelet) syndrome and placental abruption.[4] Women with PE are also at risk of death from future cardiovascular diseases, diabetes, hypertension, renal dysfunction, stroke and metabolic syndrome.[5,6] Fetal risks include higher infant mortality and morbidity, cerebral palsy, bronchopulmonary dysplasia, thrombo-cytopenia and an increased likelihood of chronic diseases in adulthood, particularly type 2 diabetes, obesity and cardiovascular diseases.[7,8]

National Institute for Health and Care Excellence (NICE) and American College of Obstetricians and Gynecologists (ACOG) have suggested screening for preeclampsia based on maternal risk factors. In this approach, each risk factor has a separate screening test with additive detection and screen-positive rate.[9,10,11] Preeclampsia screening based on the ACOG and NICE approach has suboptimal performance, as the NICE recommendation only achieves detection rates of 41% (preterm PE) and 34% (term PE), with a 10% false-positive rate, ACOG recommendation can only achieve detection rates of 5%(for preterm PE) and 2% (term PE), with false-positive rate of 0.2% .[12]

Maternal characteristics, obstetric history and medical history for screening of pre-eclampsia in the first trimester[14]: ACOG has classified it into high risk and moderate risk factors.

HIGH RISK FACTORS

- Previous pregnancy with PE
- Chronic hypertension
- Renal disease
- Diabetes mellitus: type 1, type 2
- Systemic lupus erythematosus or antiphospholipid syndrome
- Multifetal gestation

Abbreviation: PE, pre-eclampsia.

MODERATE RISK FACTORS

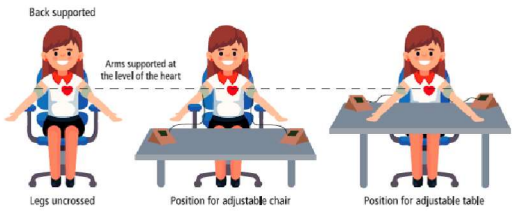
- Age > 35 years
- Nulliparity
- Interpregnancy interval > 10 years
- BMI >30 kg/m2
- Family history of PE (mother or sister)
- History of SGA or adverse outcome
- Sociodemographic characteristics (African American race or low socioeconomic status)

Fetal Medicine Foundation (FMF) first trimester prediction model for PE (the triple test), includes combination of maternal factors , mean arterial pressure, serum placental growth factor and uterine artery pulsatility index. It's detection rates are 90% and 75% for the prediction of early and preterm PE, respectively, with a 10% false-positive rate(FPR). The administration of low-dose aspirin, has been shown to reduce the rate of preterm preeclampsia by 62% in high risk women based on this prediction model. It entails that 250 women need to be screened to prevent 1 case of preterm preeclampsia .[13]

A) Mean arterial pressure(MAP): It is calculated from systolic (sBP) and diastolic blood pressure (dBP) readings. The measured sBP and dBP is converted to MAP by the risk calculator.

MAP = dBP+(sBP−dBP)/3.

Blood pressure should be measured simultaneously in both arms with validated automated blood pressure devices using correct size cuffs. A total of 2 readings should be recorded from each arm at least 1 minute apart. The final MAP is calculated from the average of the 4 measurements.[14] Maternal factors together with MAP can increase detection rates to 50.5% for preterm preeclampsia, at 10% FPR.[15]



Correct positioning of a woman for blood pressure measurement. Courtesy of PerkinElmer Life and Analytical Sciences.

B) Uterine artery pulsatility index (UtA-PI)

To measure UtA-PI a sagittal section of the uterus and internal cervical os is located on ultrasound. The probe is tilted to both the lateral sides of the cervix and color doppler flow mapping is done to identify the corresponding uterine arteries at the this level. The pulsed wave doppler is performed with the sampling gate set at 2 mm and angle of insonation of less than 30°. The UtA-PI and peak systolic velocity (PSV) are measured automatically when 3 similar consecutive waveforms are obtained. The PSV should be at >60 cm/s to ensure that measurement is performed at the level of the internal os.(Fig 1)The transverse approach is not the approved technique according to FMF; however, it can be used in challenging cases.[17,18]The first-trimester abnormal UtAPI is defined as >90th percentile, with detection rate of 48% and 8% FPR for the prediction of early-onset PE. The detection rate for predicting late-onset PE is lower.

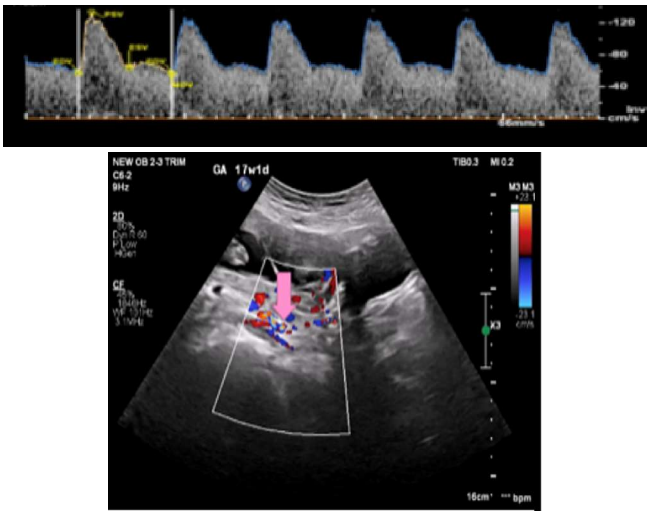


Figure 1: Uterine artery doppler, measuring the PI

C)Maternal Serum Analytes:

Placental growth factor(PLGF): It is a glycosylated dimeric glycoprotein secreted by villous and extravillous cytotrophoblasts and belongs to angiogenic vascular endothelial growth factor (VEGF) family. It binds to VEGF receptor1(VEGFR-1)which increases during normal pregnancy. Changes in the levels of PLGF or its inhibitory receptors have been implicated in the causation of PE. PLGF alone has a detection rate of 55% (early onset PE)and 33% (late-onset PE) respectively, at 10% FPR.[19,20]

Pregnancy-associated plasma protein A(PAPPA): A metalloproteinase insulin-like growth factor (IGF) binding protein secreted by the syncytiotrophoblasts and plays an important role in placental growth and development. It enhances the mitogenic function of the IGFs. Low level of circulating PAPP-A are seen in pregnancy

complicated by PE, which is due to the reduced availability of unbound IGFs to fulfil their functional role on a cellular level. PAPP-A MoM value <5th percentile (0.4 MoM) is seen in 8%–23% of women with PE with an euploid pregnancy. As a single stand alone marker it has a low DR of 16% (9%–28%) at 8% FPR for predicting PE.[21,22,23]

Both PAPP-A and PlGF are affected by gestational age at screening, BMI, race, cigarette smoking, IVF conception, nulliparity and preexisting diabetes mellitus. In addition, serum PlGF is also affected by maternal age.[24] Other markers under evaluation are Inhibin A , Activin , PP13,ADAM 12 ,fbHCG , Cystatin C, Pentraxin 3, P-Selectin and Fetal Hemoglobin. These are thought to be representative of reduced placental perfusion which leads to placental ischemia related damage, thus release of inflammatory factors and abnormal oxidative stress.[25]

COMBINED RISK ASSESSMENT

A woman is considered high risk when the risk is ≥ 1 in 100 based on the first-trimester combined test (maternal risk factors, MAP, PLGF and UTPI) which can be added to online calculators for calculation of the final risk for PE.[19]The first-trimester combined test is more predictive of preterm PE than term PE. When the biochemical markers and/or UTPI cannot be measured (as in low resource settings) the baseline screening test should include combination of maternal risk factors with MAP. PAPP-A is useful if PLGF and UTPI measurements are not available .[26,27]

SECOND AND THIRD TRIMESTER SCREENING

This includes a combination of maternal characteristics and history, biochemical and biophysical markers at 30–33 week's gestation to estimate the risk of developing PE which requires delivery within selected intervals from the time of screening. It uses measurement of MAP, UTPI, PLGF (pro angiogenic), and SFLT (antiangiogenic) at 30–34 week's gestation. The main aim of screening in later trimester is to identify the women that will develop severe PE requiring delivery within next 1–4 weeks. Measurement of serum PlGF or sFlt-to PlGF ratio is highly accurate in identifying the target group.In pregnancies complicated by PE level of serum PlGF is decreased and sFlt-1 is increased. Combined screening by maternal factors, MAP, UTPI, PLGF, and sFLT has a prediction rate of 98% for preterm-PE and 49% for term-PE at a FPR of 5%.[28,29,30,31]

Method of screening	Risk cut-off for PE <37 wk	Preterm PE		Term PE	
		AUC	DR % (95% CI)	AUC	DR % (95% CI)
Maternal risk factors	1 in 62	0.788	44.8 (40.5–49.2)	0.735	33.5 (31.0–36.2)
Maternal risk factors plus					
MAP (baseline)	1 in 61	0.841	50.5 (46.1–54.9)	0.776	38.2 (35.6–40.9)
UTPI	1 in 60	0.853	58.4 (54.0–62.7)	0.733	35.2 (32.6–37.8)
PAPP-A	1 in 61	0.810	48.5 (44.1–52.9)	0.734	35.2 (32.7–37.9)
PLGF	1 in 62	0.868	60.6 (56.3–64.9)	0.745	34.5 (32.0–37.2)
MAP, UTPI	1 in 61	0.891	68.4 (64.1–72.3)	0.772	41.4 (38.8–44.2)
MAP, PAPP-A	1 in 60	0.855	55.8 (51.4–60.1)	0.774	39.1 (36.4–41.8)
MAP, PLGF	1 in 65	0.895	66.1 (61.8–70.2)	0.777	39.3 (36.7–42.0)
UTPI, PAPP-A	1 in 60	0.861	59.2 (54.8–63.5)	0.735	36.3 (33.7–39.0)
UTPI, PLGF	1 in 62	0.892	66.9 (62.7–70.9)	0.744	36.9 (34.3–39.6)
PLGF, PAPP-A	1 in 62	0.869	63.5 (59.2–67.6)	0.745	35.7 (33.1–38.4)
MAP, UTPI, PAPP-A	1 in 61	0.896	68.2 (63.9–72.1)	0.773	40.6 (37.9–43.3)
MAP, PAPP-A, PLGF	1 in 65	0.896	67.3 (63.1–71.3)	0.777	39.3 (36.7–42.0)
MAP, UTPI, PLGF	1 in 66	0.915	74.8 (70.8–78.5)	0.776	41.0 (38.3–43.7)
UTPI, PAPP-A, PLGF	1 in 63	0.892	68.2 (63.9–72.1)	0.745	36.9 (34.3–39.6)
MAP, UTPI, PAPP-A, PLGF	1 in 66	0.916	74.8 (70.8–78.5)	0.777	41.3 (38.7–44.1)

Abbreviations: PE, pre-eclampsia; AUC, area under curve; DR, detection rate; MAP, mean arterial pressure; UTPI, uterine artery pulsatility index; PAPP-A, pregnancy-associated plasma protein A; PLGF, placental growth factor.

Table 1: Detection rates of preterm PE and term PE by maternal factors, biomarkers, and their combination, at screen-positive rate of 10%

PROGNOSIS trial (Prediction of Short-Term Outcome in Pregnant Women with Suspected Preeclampsia Study), has inferred that an sFlt-1/PlGF ratio of ≤ 38 can be used to rule out the risk of developing PE within one week, independently of gestational age. This has a high negative predictive value (99.3%) . Furthermore an sFlt-1/PlGF ratio ≥ 85 is predictive of early-onset PE at (<34 weeks) and 110 for late-onset PE (≥34 weeks).[32] National Institute for Health and Care Excellence (NICE) recommends measurement of sFlt-1/PlGF ratio to exclude PE in women presenting with suspected PE between 20 and 34+6 gestation weeks.[9]

OPHTHALMIC ARTERY DOPPLER

In pregnancies with pre-eclampsia (PE), there is a reduced impedance to flow and an increase in flow velocity in the ophthalmic arteries. Ophthalmic artery doppler at 35-37 weeks' gestation can help in prediction of development of pre-eclampsia, especially within 3 weeks of assessment. Ratio of the second to the first peak of systolic velocity, is the most useful Doppler index of Ophthalmic artery.[33] (Fig 2) Meta-analysis of 3 studies have demonstrated the doppler changes in ophthalmic artery have a sensitivity of 61.0% & specificity of73.2 % for early onset PE prediction.[34, 35]

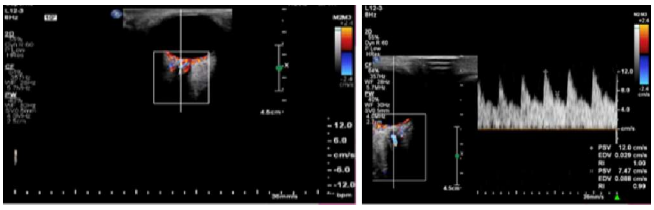
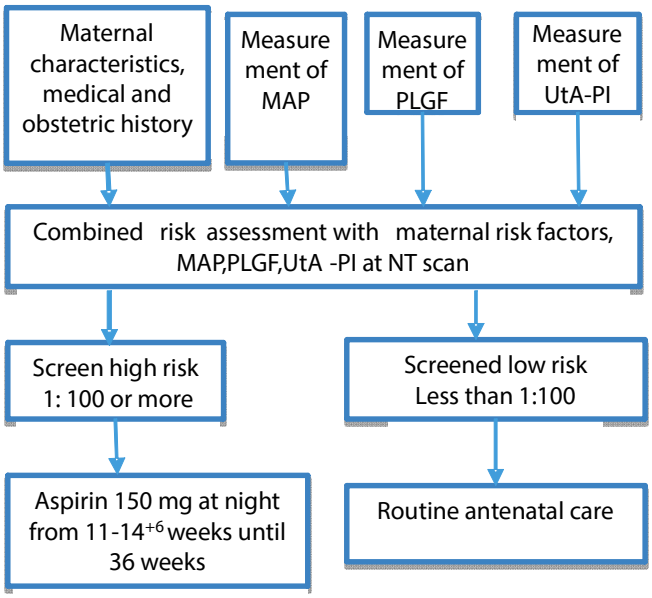


Figure 2: Ophthalmic artery doppler, measuring the ratio of first and second PSV

PREVENTION OF PRE ECLAMPSIA

'US preventive Services Task Forces Recommendation Statement "has recommended Low dose aspirin prophylaxis beginning at 81 mg/d from 12 and 28 weeks 'gestation (optimally at <16 weeks 'gestation), daily until delivery for women with 1 or more high-risk factors or more than 1 of several moderate risk factors. This is also endorsed by the Society for Maternal-Fetal Medicine, ACOG, and American Diabetes Association.(Table 1) However FIGO recommendation which is supported by the evidence from the ASPRE trial, includes aspirin prophylaxis commencing at 11–14+6 weeks of gestation at a dose of ~150 mg daily until either 36 weeks of gestation, when delivery occurs, or when PE is diagnosed, in women identified at high risk following the first-trimester screening.[14]

Low-dose aspirin treatment in pregnancy prevents the PE development by inhibiting the synthesis of placental thromboxane A2.The enzyme cyclooxygenase has an important role in the production of both prostacyclin and thromboxane A2. Aspirin inhibits cyclooxygenase and this process is irreversible in platelets, where the enzyme is inhibited for their entire lifespan. This selective inhibition of cyclooxygenase results in alteration in the prostacyclin to thromboxane A2 ratio in the placenta, which forms the basis of its usage in prevention of PE. ASPRE trial recommends administration of 150mg of Asprin from 14 – 36 weeks of pregnancy in women at high risk for developing preterm PE and reports a 62% reduction in PE < 34 weeks, 78% in PE < 32 weeks.[26]



Pathway of preterm pre-eclampsia screening and prevention

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MY LEARNING CURVE ON ANEUPLOIDY SCREENING

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"Learn continually. There's always "one more thing" to learn."

~ Steve Jobs

These words hold true every single day for a second-year postgraduate resident who has so much to learn in the field of maternal-fetal medicine. I particularly find obstetric ultrasound quite fascinating – the fetus gyrating, sucking its thumb, or playing peekaboo with the examiner, then suddenly revealing its angelic smile. There is also a deeper realization in me that ultrasound is an extremely powerful instrument for feto-maternal evaluation, when placed in properly trained and experienced hands.

As a resident, I am learning the utility of first-trimester ultrasound examinations. The study is used not only to confirm dating, the number of feti, their chorionicity and amnionicity, but also for aneuploidy screening, early diagnosis of fetal anomalies, and help assess the risk of pre-eclampsia and fetal growth restriction[1]. It is a challenging yet rewarding experience. However, the nuances of aneuploidy screening seem quite daunting to a novice like me, considering the choice of tests available today. Here I am sharing my experience while counseling patients for aneuploidy screening in the outpatient department (OPD).

Patient R, aged 35 years, sought counseling for aneuploidy screening. Her prior baby had features suggestive of Goldenhar syndrome, although no molecular confirmation was available. Her combined first-trimester screening (CFTS) done elsewhere suggested a low risk of aneuploidy. But while reviewing the scan images I found that despite multiple images appended to the scan report there was no image depicting an appropriate Nuchal translucency (NT) measurement (Fig 1).

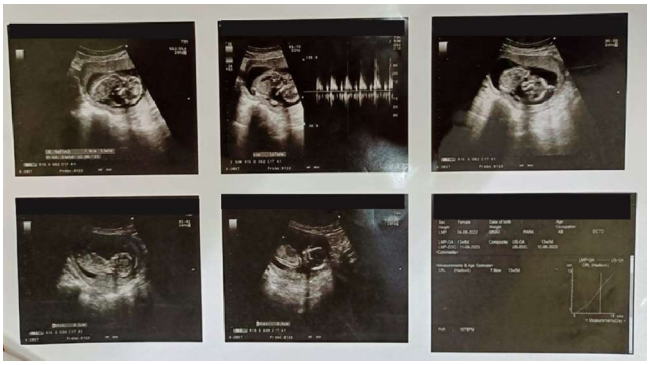
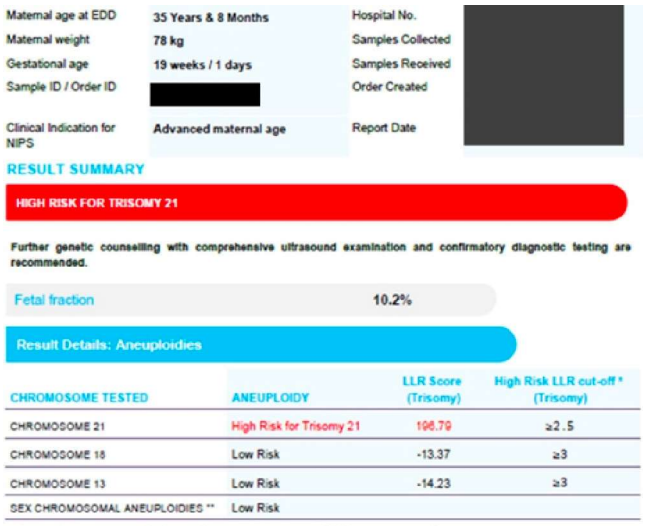


Figure 1: Images from the first trimester ultrasound. No appropriate image for NT is seen



Maternal age at EDD	35 Years & 8 Months	Hospital No.	
Maternal weight	78 kg	Samples Collected	
Gestational age	19 weeks / 1 days	Samples Received	
Sample ID / Order ID	[redacted]	Order Created	
Clinical Indication for NIPS	Advanced maternal age	Report Date	

RESULT SUMMARY

HIGH RISK FOR TRISOMY 21

Further genetic counselling with comprehensive ultrasound examination and confirmatory diagnostic testing are recommended.

Fetal fraction 10.2%

Result Details: Aneuploidies

CHROMOSOME TESTED	ANEUPLOIDY	LLR Score (Trisomy)	High Risk LLR cut-off * (Trisomy)
CHROMOSOME 21	High Risk for Trisomy 21	196.79	≥2.5
CHROMOSOME 18	Low Risk	-13.37	≥3
CHROMOSOME 13	Low Risk	-14.23	≥3
SEX CHROMOSOMAL ANEUPLOIDIES **	Low Risk		

Figure 2 : NIPS report showing high risk for Trisomy 21

In view of her advanced maternal age, upon counselling, she opted for non-invasive prenatal screening (NIPS). Unfortunately, the test showed a high risk for trisomy 21 (Fig 2), which was confirmed by further invasive testing.

The learning point for me is that CFTS is not merely a number; getting into the depth of how that number was reached is equally important to

be able to counsel patients appropriately. The purpose of aneuploidy screening is to pick up pregnancy at a high risk of aneuploidy such as Down syndrome. Advanced maternal age makes the pregnancy a high risk. Hence, a woman with advanced maternal age and low-risk CFTS should still be offered NIPS, which is a superior screening test. A good first-trimester scan followed by NIPS is a more optimal strategy, which, unfortunately, is precluded by the high cost of NIPS for many of our patients.

The next patient who moulded my experience was a 26-year-old primigravida, who presented with a low-risk CFTS, but her NT scan was suggestive of absent nasal bone (ANB) (Fig.3). We confirmed the findings on ultrasound and reviewed her again at 16 weeks when the nasal

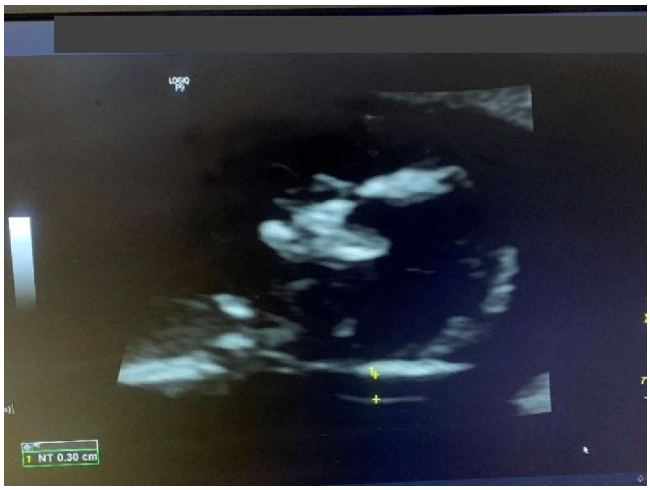


Figure 3: Absent nasal bones

bone continued to remain unossified. In view of this finding the patient was counseled for invasive testing. A quick Fluorescent in-situ hybridization test (for chromosomes 21, 13, 18 and sex chromosomes) followed by chromosomal microarray found no abnormality.

Which test to offer in such cases is controversial. Isolated ANB with a low risk in biochemical screening is rarely associated with aneuploidy and most fetuses with abnormal chromosome results have an associated high risk in biochemical screening, additional aneuploidy markers or associated anomalies[2]. However, though rare, fetuses with an isolated ANB may have chromosomal anomalies[3]. Hence one should counsel and offer invasive testing in this scenario[4]

Lastly, a woman reported for counseling at 21 weeks and 3 days of gestation, whose quadruple marker showed a high risk for trisomy 21 (1:99) (Fig 4). However, even after counseling and despite knowing very well the possibility of

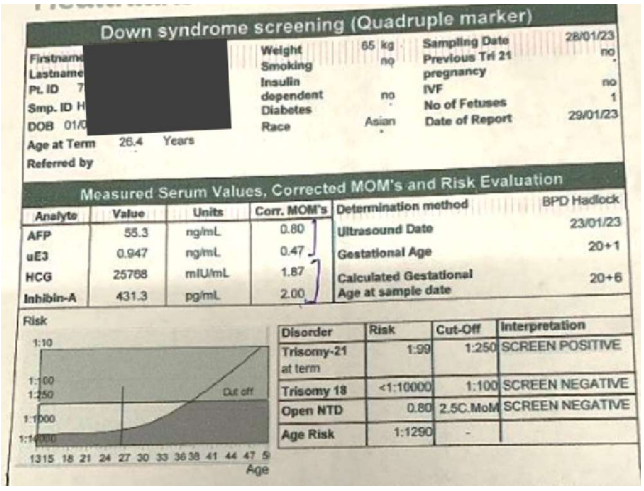


Figure 4: Quadruple test report showing high-risk for trisomy 21.

having a baby with Down syndrome, she opted for no further testing. She was very keen to continue this pregnancy as she had lost a prior child due to antepartum hemorrhage and extremely preterm birth.

I learned that we are facilitators in a family's sojourn of a pregnancy, yet while counselling we must respect their beliefs and choices. Science is a means to alleviate human agony, not to amplify their anxieties.

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FIRST TRIMESTER ULTRASOUND DIAGNOSIS OF ABNORMAL DRAINAGE OF THE UMBILICAL VEIN INTO THE INFERIOR VENA CAVA

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INTRODUCTION: Ductus venosus (DV) is a short conduit that connects the umbilical vein with the inferior vena cava, typically just below the diaphragm. In rare cases there may be agenesis of DV or unusual placement of DV resulting in abnormal drainage of the umbilical vein, which may also be associated with aneuploidies and cardiac defects.

CASE REPORT: As a protocol for first trimester aneuploidy screening, all pregnant women in our fetal medicine unit undergo DV waveform assessment. Among these, two fetuses at a mean gestational age of 12 weeks had an unusual downward presence of a DV-like shunt (Fig. 1), leading to a suspicion of aberrant drainage of the umbilical vein. Pulse wave Doppler in the area of aliasing showed a typical DV-like triphasic waveform. 3-dimensional color Doppler acquisition (Fig. 2) confirmed abnormal drainage of the umbilical vein into the intra-abdominal inferior vena cava with presence of a DV-like shunt at the junction.

Both women underwent a prenatal diagnostic procedure with microarray (750K), followed by detailed anatomical evaluation between 19-20 weeks and fetal echo between 22-24 weeks. All tests were reported as normal. Both fetuses were followed up for any signs of cardiac overload (cardiomegaly, tricuspid regurgitation, or hydrops), portal venous system abnormalities, and the presence of portosystemic shunts. No abnormality was found in the subsequent examinations. Healthy male babies with normal birth weight were born at term gestation with normal postnatal assessment.

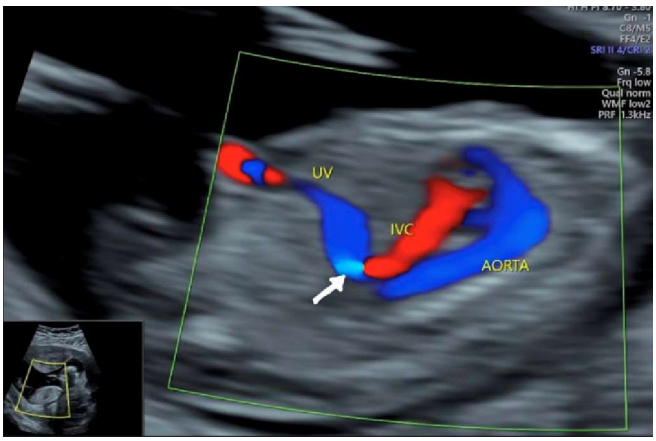

Figure 1: 2-dimensional color Doppler acquisition showing unusual downward placement of ductus venous like shunt (marked by an arrow), UV- umbilical vein, IVC- inferior vena cava

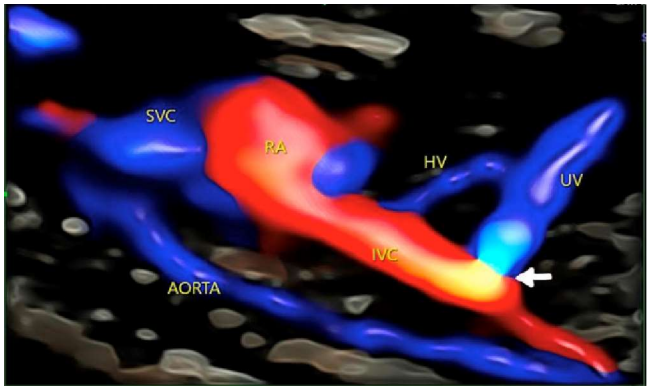

Figure 2: 3-dimensional color Doppler acquisition depicting abnormal drainage of umbilical vein (UV) into inferior vena cava (IVC) via presence of a DV-like shunt at the junction (shown by an arrow), SVC- superior vena cava, RA- right atrium, HV- hepatic veins

DISCUSSION : In fetal circulation the umbilical vein is connected to the portal system via a shunt known as Ductus venosus (DV), which transfers well-oxygenated blood from the umbilical vein towards the left atrium and left ventricle via the foramen ovale, and ultimately to the fetal cerebral and coronary circulation. Rarely, there can be agenesis of DV or unusual placement of DV, resulting in abnormal drainage of the umbilical vein via formation of aberrant vessels or DV-like shunt, which can have intrahepatic or extrahepatic drainage[1]. Published literature, though mainly consisting of case series, reports a higher incidence of chromosomal abnormalities, structural defects (cardiac and non-cardiac),

portal system abnormalities and poor perinatal outcomes in the cases of abnormal drainage of the umbilical vein, especially with an aberrant extrahepatic drainage[2-3].

CONCLUSION: Abnormal drainage of the umbilical vein has been reported with adverse perinatal outcomes. However, with timely identification, a systematic approach, and close monitoring of fetuses favorable outcomes can be achieved, as observed in our cases.

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FIRST TRIMESTER DIAGNOSIS OF AMNIOTIC BAND SYNDROME

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INTRODUCTION: Amniotic band syndrome occurs when string-like bands from a disrupted amnion entrap fetal body parts. These bands can adhere to or form constriction bands or rings over any body part of the developing fetus, inhibiting growth, blood flow, or both. We present a rare case of Amniotic band syndrome suspected during a routine first-trimester ultrasound scan.

CASE REPORT: 27-year-old primigravida came to us for a routine first-trimester scan at 12 weeks of gestation. There was no history of leaking/ bleeding per vaginum or any febrile illness. Nuchal translucency was normal. The anatomical survey was satisfactory for the gestation, with good movements in all four fetal limbs and normal-appearing digits and toes. However, the amniotic sac looked collapsed and the amniotic membranes appeared to be enveloping the fetus (Fig.1). This raised suspicion of Amniotic band syndrome; hence, the patient was called for an early anomaly scan at 16 weeks.

On her anomaly scan, a thin band appeared attached to the right hand of the fetus, restricting its movements (Fig.2). The distal parts of the digits were not seen in the middle and ring fingers of the right hand (Fig.3 & 4), suggesting amputation secondary to the amniotic band. No other fetal part was seen to be attached to the amniotic band. These features were suggestive of Amniotic band syndrome, confirming our provisional diagnosis made in the first trimester.

The couple was explained about the morbidity associated with the condition and the option of post-natal reconstructive surgery/prosthesis. However, they opted for the termination of the pregnancy. They were counseled about the low risk of recurrence in future pregnancies.

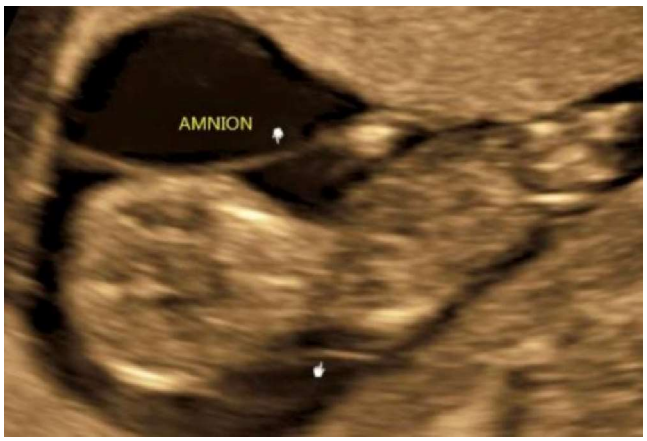

Figure 1: Collapsed Amniotic sac wrapping the fetus like an envelope.

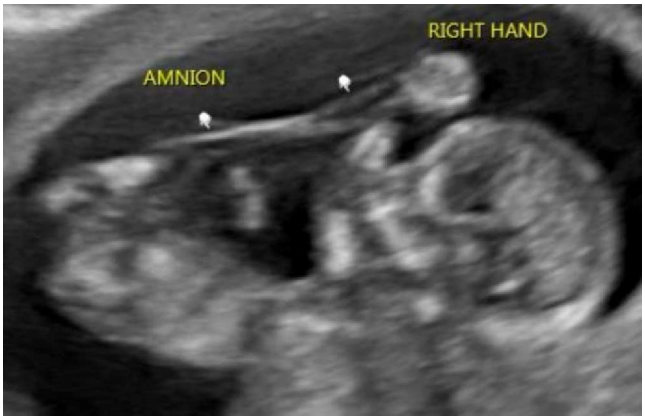

Figure 2: Amniotic band in close relation to the fetal right hand

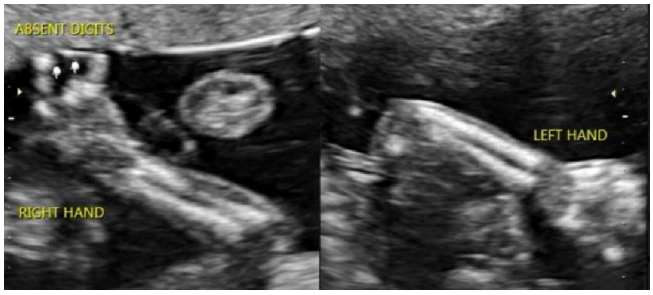

Figure 3: Amputation of the distal parts of the middle and ring fingers of the right hand. The left hand was normal

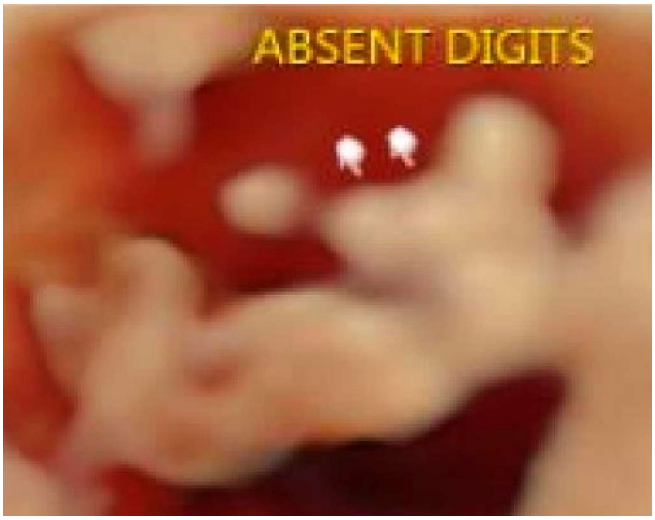

Figure 4: 3D reconstructed image of the right hand

DISCUSSION: Amniotic band syndrome is a lesser-known clinical entity. It can cause limb, facial, cranial, and abdominal wall abnormalities, ranging from mild deformities to serious anomalies causing fetal and neonatal morbidities.[1,2] Ushakov et al have classified the cases of amniotic band syndrome in the first trimester in four main groups:[3]

1. Amniotic net - characterized by multiple amniotic bands, either free-floating or attached to the fetus. These fetuses have multiple, severe asymmetric abnormalities-atypical facial clefts, brain anomalies, thoraco-abdominal facial defects and limb anomalies.
2. Dividing amnion - an intact amniotic membrane divides the fetus into intra-amniotic and extra-amniotic parts.
3. Amniotic connection - an isolated single amniotic band connects the fetus to the chorion. With the progression of the pregnancy, the amniotic band may rupture or disappear.
4. Baby in an envelope - an unusual presentation presenting with reduced volume of amniotic sac in the first trimester, resulting in fetal entrapment and secondary rupture of the sac in the early second trimester. This type is associated with talipes and limb reductions.

These pregnancies with amniotic band syndrome usually have a low risk of recurrence in future pregnancies and thus can be counseled accordingly. With the advent of newer technology of 3D Ultrasound, a better understanding of the pathology is possible.[4]

In this case report, we emphasize on a detailed evaluation in the first trimester for the early detection of the amniotic band syndrome.

CONCLUSION: With a systematic and detailed evaluation, a first-trimester diagnosis of Amniotic band syndrome is feasible. These pregnancies can be followed up with an early anomaly scan to look for the morbidities associated with the condition. This will aid in the management of the present pregnancy and counseling regarding the recurrence risk in future pregnancies.

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FIRST TRIMESTER DETECTION OF ABERRANT RIGHT SUBCLAVIAN ARTERY

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INTRODUCTION: Aberrant right subclavian artery (ARSA) is an important soft marker for aneuploidy screening in the second trimester. With improved technology and the use of color Doppler imaging, it is possible to detect ARSA even in the first trimester. However, its utility in first trimester aneuploidy screening is unclear.

CASE REPORT: First trimester screening examination was performed in a 31-year-old primigravida in accordance with the Fetal Medicine Foundation criteria.[1] Transabdominal scan showed a single live fetus of 13 weeks 4 days by Crown rump length (74.0mm). The Nuchal translucency measured 2.1mm (64th percentile). The nasal bones appeared poorly ossified, hence, classified as absent. The ductus venosus showed normal forward flows and no tricuspid regurgitation was seen. While performing cardiac screening, an axial section of the fetal upper thorax with color Doppler was obtained, which showed an ARSA arising from the posterior part of the aortic arch near the apex of the 'V' formed by the confluence of the aortic and ductal arches and coursing posterior to the trachea from left to right side with a straight course (Fig. 1). An echogenic intracardiac focus (EIF) was also found in the left ventricle of the fetal heart. No fetal structural or cardiac abnormality was found. Combined double marker test showed an intermediate risk of 1 in 232 for Down syndrome. Considering absent nasal bones, ARSA, and EIF, the patient was counselled and further evaluation with amniocentesis with microarray (750 K) was performed at 16 weeks along with a repeat ultrasound for reassessment of the nasal bone, ARSA and fetal heart. Ultrasound done at 16 weeks confirmed the presence of ARSA. No cardiac defect was found. The nasal bone appeared normal. The microarray test was negative for Down syndrome.

DISCUSSION: A developmental abnormality in the branching pattern of the aortic arch results in an anomalous origin of the right subclavian artery, which arises as a fourth branch from the posterior aspect of the aortic arch near its junction with the arterial duct and passes behind the trachea and the esophagus to reach the right upper limb. This is termed as an aberrant right subclavian artery (ARSA). Prenatal ultrasound studies have reported that the incidence of ARSA in the second trimester is much higher (about 35%) in the fetuses with trisomy 21 compared to 1.4% in chromosomally normal fetuses [2]. Hence, ARSA is an important maker for Down syndrome screening in the second trimester. Studies have demonstrated that it is possible to assess the position of the right subclavian artery in about 70-80% of cases at 11 + 0 to 13 + 6 weeks [2,3]. It is important to not confuse the azygos vein with an ARSA.

There are very few studies that have addressed the utility of ARSA in first trimester aneuploidy screening. In one study, the finding of ARSA was helpful in the diagnosis of the aneuploidy in two fetuses, including a fetus with intermediate risk on combined screening and isolated ARSA; the other fetus had a low risk on combined screening but had hypoplastic nasal bone and ARSA[3].

Another study did not find ARSA a useful marker in first trimester screening [2].

CONCLUSION:

Even though it is feasible to detect ARSA in the first trimester, its utility as a soft marker for screening of trisomy 21 is not proven. If ARSA is isolated, no invasive testing is advised. However, in conjunction with any additional markers, structural / cardiac defects or intermediate risk on combined first trimester screening, further testing (NIPT or invasive testing) is warranted.

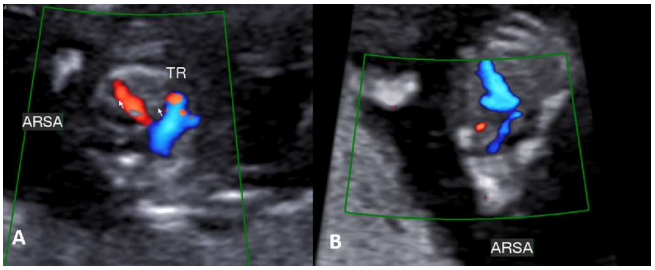

Figure 1 (A &B) : ARSA arising from the posterior part of the aortic arch, coursing behind the trachea (arrow) and showing a straight course towards the right arm

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MULTIPLE ANOMALIES IN A FETUS WARRANTS GENETIC EVALUATION

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INTRODUCTION: Anatomic survey is an integral part of the first trimester ultrasound screening. Multiple anomalies affecting different organ-systems are often associated with aneuploidy or chromosomal/ genetic abnormality. Hence, the fetuses with anomalies must undergo genetic evaluation in order to correctly counsel the couples for the risk of anomalies in future pregnancies.

CASE REPORT: The patient was a second-gravida female, aged 31yrs, with a history of hypothyroidism under control with medicines. No other significant history could be elicited. She presented at a gestational age of 12 weeks 2 days by LMP. Ultrasound findings revealed a single live fetus with a crown rump length of 41.4 mm corresponding to GA of 11weeks 0days +/- 7days. Transabdominal and transvaginal anatomic survey of the fetus showed gross structural abnormalities in the fetus, which included:

1. Acrania: absence of calvarium with fetal brain surrounded by amniotic fluid (Fig.1).
2. Large omphalocele: anterior midline mass with abdominal contents bulging through the base of cord insertion.
3. Rocker bottom feet.
4. Absent nasal bone.
5. Ductus venosus with abnormal flow with reversed 'a' wave.
6. Tricuspid regurgitation.

Fetal nuchal translucency could not be measured. Fetal heart appeared abnormal but could not be fully evaluated. In view of multiple gross fetal anomalies, aneuploidy / chromosomal abnormalities were suspected, most likely

trisomy 18/13. As these anomalies were deemed incompatible with life, the patient was counseled and termination was offered. The examination of the abortus confirmed the ultrasound findings (Fig. 2). The fetal sample was sent for genetic testing (microarray) which confirmed trisomy 18.

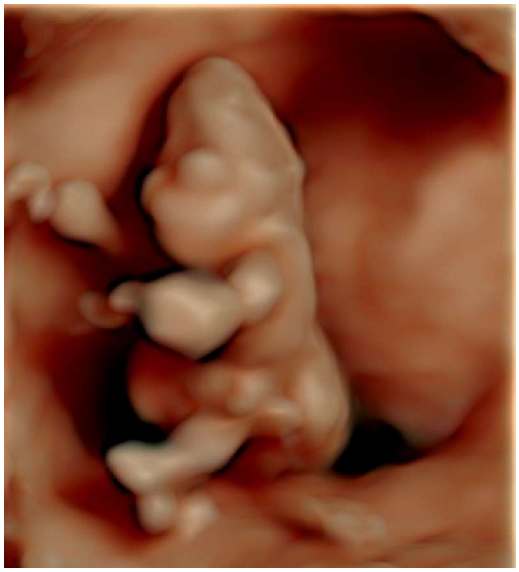

Figure1: 3D Ultrasound showing misshapen conical appearing fetal head due to acrania and an anterior abdominal wall mass due to omphalocele

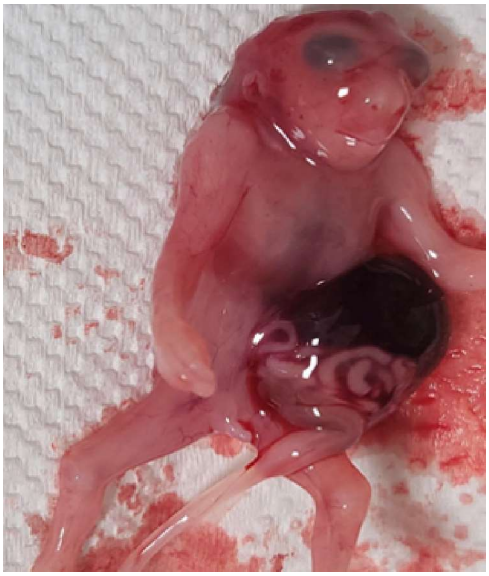

Figure 2 : Abortus confirming acrania and omphalocele

DISCUSSION: The finding of a fetal structural anomaly increases the possibility of a chromosomal abnormality or genetic defect and should prompt further evaluation into genetic etiologies. The frequency of a chromosomal abnormality depends on several factors: the specific anomaly, the number of anomalies, and the combination of anomalies identified.[1] Chromosomal abnormalities have been reported in 18–35% of fetuses with multiple structural defects detected on prenatal ultrasound examination.[2,3] The most common chromosomal abnormalities in newborns are trisomies 21,18,13, monosomy X and other sex-chromosome aneuploidies, accounting for up to 95% of the cases. With the knowledge of patterns of abnormalities seen with individual syndromes, first trimester identification of these anomalies can lead to early definitive diagnostic genetic testing, which can help counseling the parents regarding the current and future pregnancies.

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JUST IMAGES

MANY MOODS

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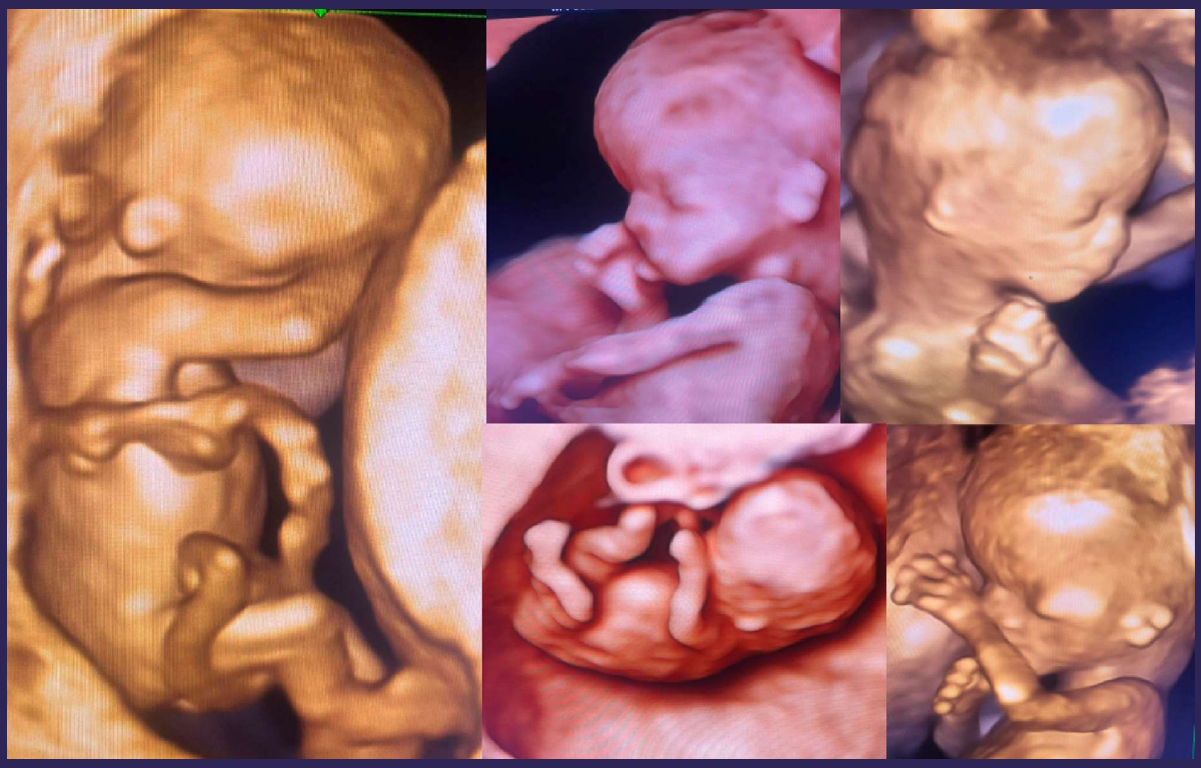

'NEVER MISS' ANOMALIES OF THE FIRST TRIMESTER

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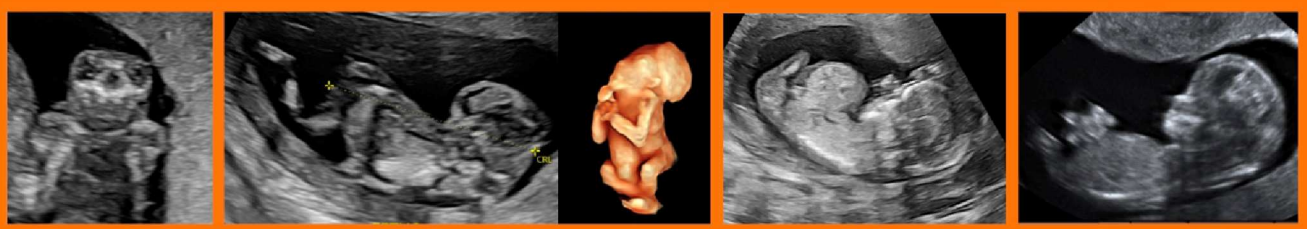

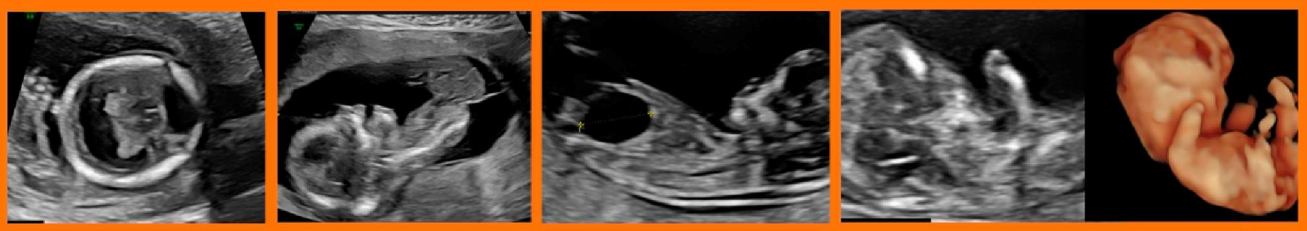

JUST IMAGES

FIRST TRIMESTER SEMILOBAR HOLOPROSCENCEPHALY

Dr. Shivani Gupta (Senior Resident), Dr. Nidhish Sharma (Senior Consultant)
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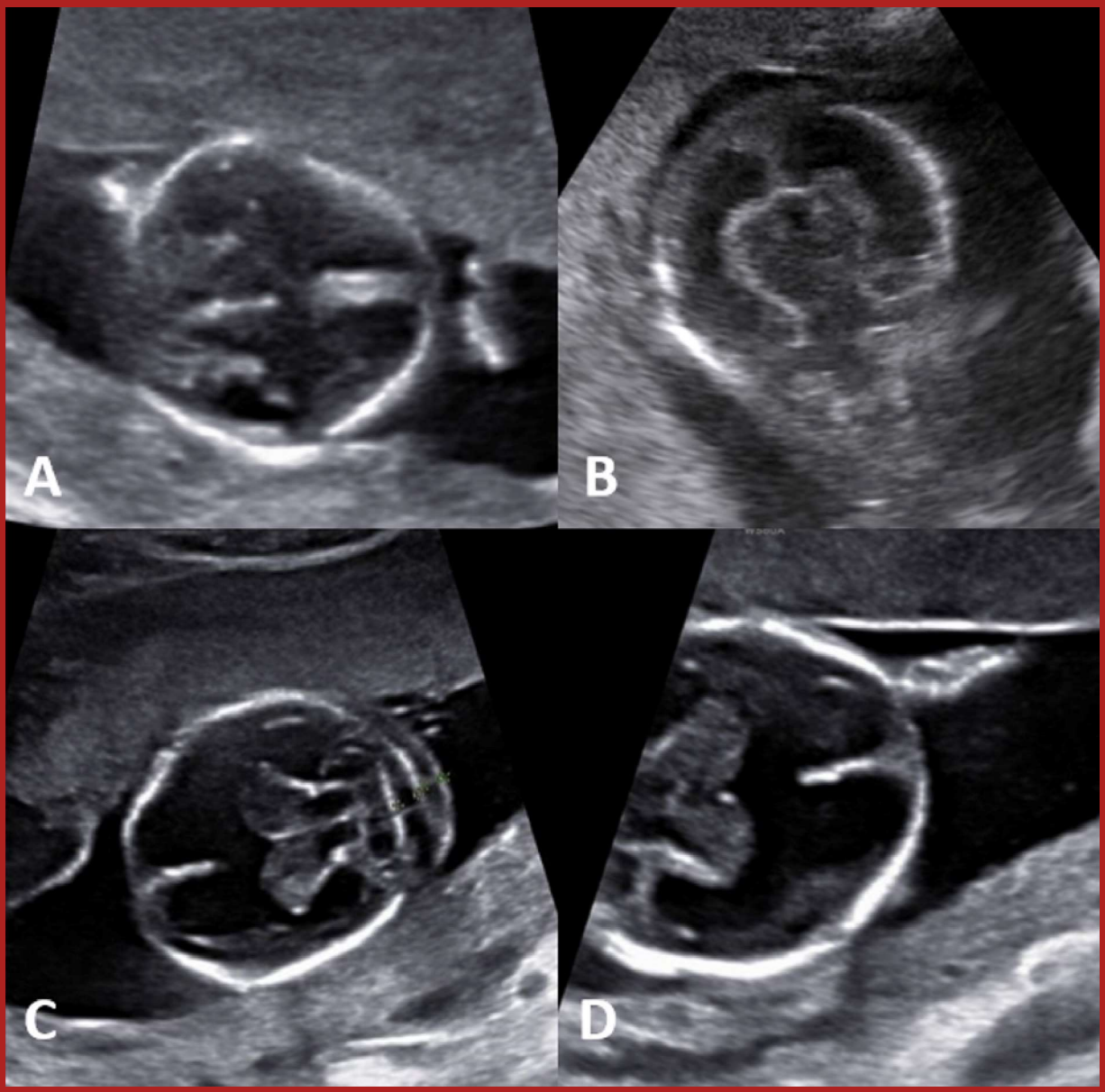


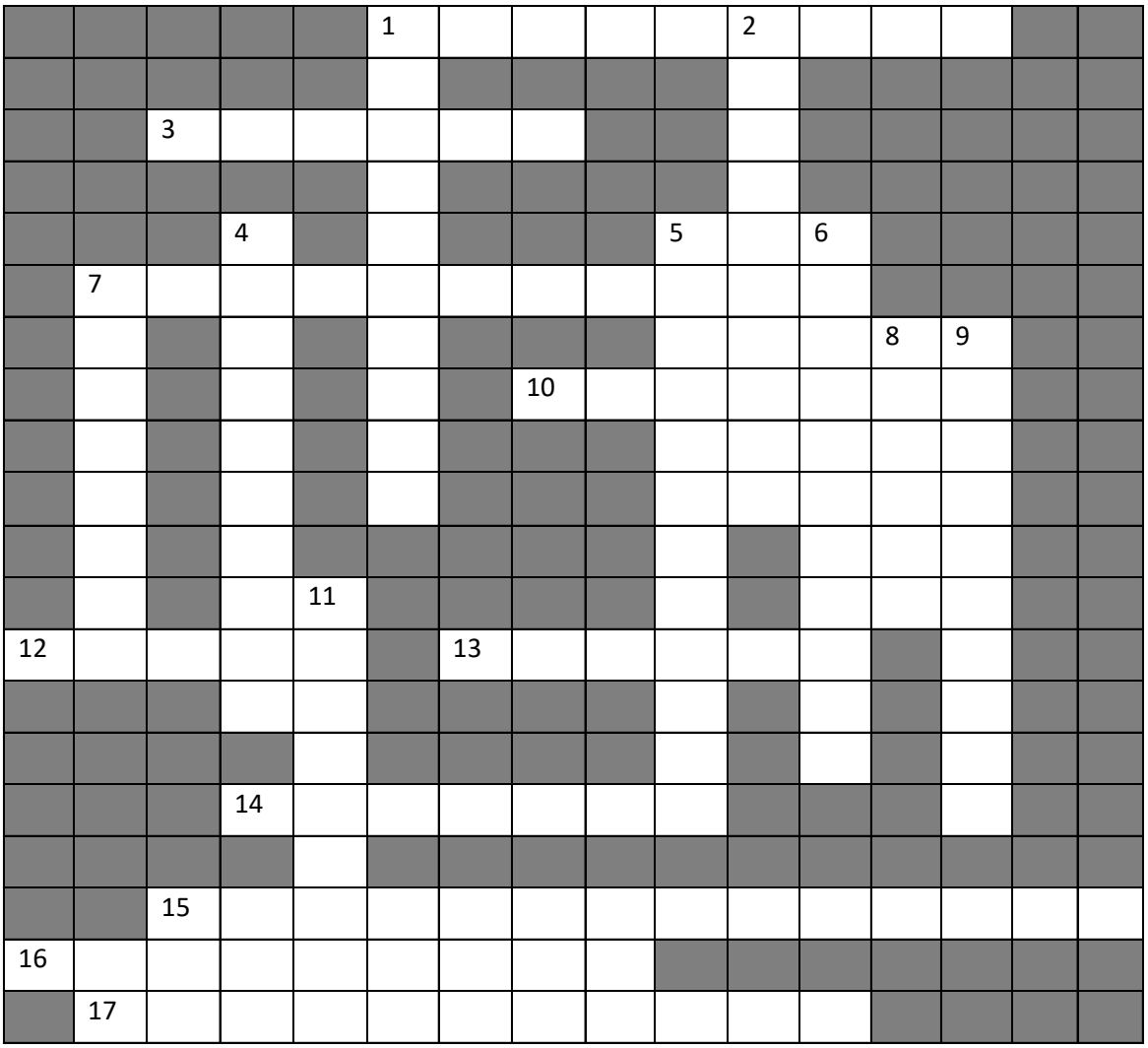
A: 12 Weeks fetus. Axial scan of the fetal brain showing interrupted midline falx.

B: Coronal section of the fetal brain in the same fetus showing fused thalami.

C & D: Follow up at 15 Weeks. Axial sections of the fetal brain showing interrupted falx, dilated lateral ventricles communicating with each other, and fused thalami.

CROSSWORD PUZZLE

Dr Alok Varshney



ANOMALIES AND DEFECTS

ACROSS

1. Unibrow
3. Abnormal protrusion
7. Narrowing of a vessel
10. Absent skull
12. Swollen vein
13. Ear loss
14. No lens
15. Contraction of the skull
16. Abnormal development
17. Extra digit

DOWN

1. Fingers united
2. Wrong assembly of organs
4. Smooth brain
5. Undersized chin
6. Missing brain
7. Abnormal eye hole
8. Split spine
9. Bent limb
11. Exposed brain

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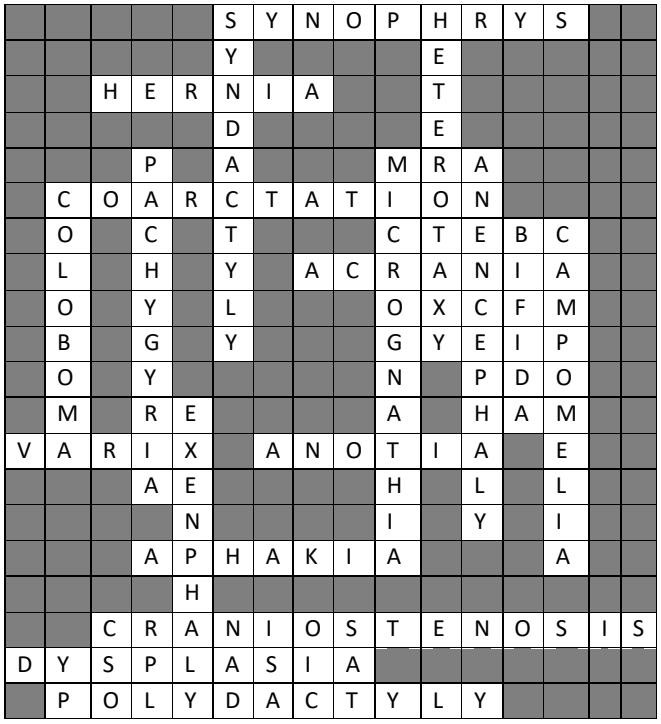
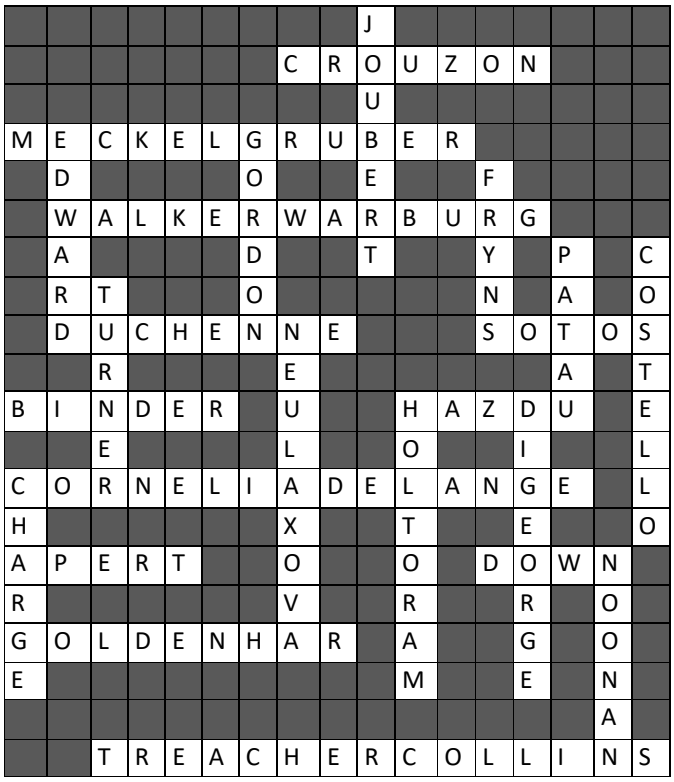
Dr Ratna Puri

CROSSWORD PUZZLE

ANSWER TO CROSSWORD PUZZLE (VOL.2)



ANSWER TO CROSSWORD PUZZLE (VOL.1)



Glimpses from SFM Delhi Meets

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George Bernard Shaw

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