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# CLINICAL SIGNIFACNCE OF ISOLATED FETAL SOFT MARKERS DETECTED ON PRENATAL ULTRASOUND AND THEIR ASSOCIATION WITH PERINATAL OUTCOMES: A PROSPECTIVE OBSERVATIONAL STUDY

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**ABSTRACT**

**Background:** Fetal soft markers observed during prenatal ultrasounds are transient sonographic findings that may raise concerns due to their potential association with chromosomal abnormalities and adverse perinatal outcomes. Their clinical significance remains debated, necessitating further research to confirm their validity.

**Objectives:** To assess the outcomes following the detection of ultrasound soft markers, their associations, and clinical significance, and to determine if any markers should be routinely screened

**Method:** This prospective cross-sectional study was conducted at the Department of Radiodiagnosis, MMCRI, Mysore, from September 2024 to March 2026. A total of 300 pregnant women undergoing routine second-trimester ultrasounds were enrolled. All participants underwent a follow-up scan between 32–36 weeks, and neonatal assessments were performed post-delivery.

**Results:** Soft markers were found in 16% of participants, with intra-cardiac echogenic focus and single umbilical artery being the most common. A significant association was found between soft markers and previous history of fetal anomalies. However, no significant association was observed between soft markers and maternal age or consanguinity. Neonatal outcomes were generally favorable, with no significant congenital anomalies detected.

**Conclusion:** Most fetal soft markers are benign and transient. Isolated markers, particularly in low-risk pregnancies, are not predictive of adverse neonatal outcomes and should be interpreted within a broader clinical context

**Contribution:** This study contributes to prenatal diagnostics by affirming the benign nature of isolated fetal soft markers, promoting judicious clinical decision-making, minimizing unwarranted interventions, and supporting evidence-based counseling through structured follow-up assessments.

**KEYWORDS**: Fetal soft markers, Prenatal ultrasound, Fetal anomalies, Chromosomal abnormalities, Echogenic intracardiac focus

## INTRODUCTION

With the advent of technology, the analysis of fetal anatomy by ultrasound has become easier and thus we are able to identify slight deviations from normal. During the second trimester scan in the pregnancy (anomaly scan), the soft markers are often looked for. However, the significance of these markers remains contentious and needs further research to confirm their validity. Abdelmonsef et al. mention the need for thorough assessment when soft markers are noted [1].

Soft markers are transient sonographic findings observed on ultrasound that have recently gained significance for assessing risks of chromosomal and other adverse outcomes. Some of these markers are echogenic intracardiac focus (EIF), choroid plexus cysts (CPC), mild pyelectasis, nuchal fold thickening, echogenic bowel and single umbilical artery and are usually seen on the second-trimester anomaly scan. Many of these markers resolve spontaneously and can be considered as normal variants. However, they can raise anxiety in the parents and further workup may be suggested. Most fetuses with the presence of isolated soft markers are found to have no chromosomal abnormality. Thus, it is important that these markers are interpreted in proper clinical context and parents counselled accordingly. A key area of understanding foetal soft markers is resolving the distinction between isolated versus multiple findings (congenital anomalies). Isolated soft markers are likely to be at a reduced risk for chromosomal anomalies than other cases with multiple markers or major anomalies [2].

Recent research has focused on improving risk assessment by including items like maternal age, past screening results and the presence of multiple markers, to avoid unnecessary invasive testing procedures .It is important they vary so the appropriate patient counselling and management can be done to prevent undue anxiety and invasive investigation in low pre-test probability of aneuploidy pregnancy. If there are many soft markers, then a more intensive workup is needed, which may include genetic counselling and consideration of invasive testing, such as amniocentesis or chorionic villus

sampling [3]. The invention of chromosomal microarray examination (CMA) has also complicated the evaluation of these soft markers. CMA can find smaller chromosomal problems that might contribute to developmental issues or other health conditions, unlike conventional karyotyping which can only detect bigger issues and chromosomal problems such as trisomy [4].

A meta-analysis has evaluated the clinical importance of CMA in pregnancies with isolated ultrasound soft markers and a normal foetal karyotype. The portion of isolated ultrasonographic soft markers with normal karyotype foetuses which detected pathogenic or likely pathogenic copy number variants (CNVs), as they found CNVs in 2.0% of foetuses with such findings. It's still up for debate whether all cases of isolated soft markers should use CMA due to clinical significance of certain CNVs uncertain and there's cost-effectiveness of widespread screening [5].

It has been found that some of the foetal soft markers can be associated with abnormal placentation and increased perinatal mortality and therefore importance of looking for specific soft markers on routine ultrasound has increased [6].

**Aim:** This prospective study aims to assess the outcome following the detection of ultrasound soft markers along with studying their associations and clinical significance and to assess whether any soft markers should be looked for routinely as a part of screening ultrasound.

## MATERIAL AND METHODS

This is a hospital based cross sectional observational prospective study conducted at Mysore medical college and research institute(MMCRI), Mysore, under the Department of Radiodiagnosis, MMCRI.The study was performed in 300 pregnant women from Cheluvamba hospital, who have been sent for routine second trimester anomaly scan at the department of Radiodiagnosis, MMCRI during the period of september 2024 to march 2026.Clinical and physical examination findings of pregnant women who met the inclusion criteria were entered in the structured case proforma after obtaining the informed consent. After that each pregnant woman got subjected to two ultrasound examinations. First trans-abdominal ultrasound done at the time of 16-24 weeks of gestation (Fetal anomaly scan) and second examination done at 32-36 weeks of gestation for confirmation of the presence or absence of the soft marker. Patients were followed up till delivery and the newborns were examined by neonatologists carefully for confirm the final diagnosis.

## RESEARCH METHODS AND DESIGN

### Study Design

This is a hospital based cross sectional observational prospective study

### Setting

The study was conducted at Mysore medical college and research institute (MMCRI), Mysore. This is a tertiary care hospital providing obstetric ultrasound scans for pregnant women sent from Cheluvamba hospital (part of MMCRI).

### Study Population and Sampling Strategy

Study Population:The study included all the pregnant women who fulfilled the inclusion criteria and reported to the Radiodiagnosis Department, MMCRI, for obstetric scans

### Inclusion Criteria:

1.Pregnant women between 16–24 weeks of gestation undergoing routine second-trimester ultrasound.
2.Singleton pregnancies with no evidence of major congenital anomalies detected on the initial scan.
3.Pregnant women who agree to have a follow-up ultrasound between 32 and 36 weeks of pregnancy, as well as a postnatal assessment.

### Exclusion Criteria:

1.Multiple pregnancies.
2.Fetuses diagnosed with evidence of major congenital anomalies on initial ultrasound.
3.Pregnant women with known chromosomal abnormalities or pre-existing genetic conditions.

### Sample Size and Calculation:

A minimum of 300 patients were enrolled in the study. The sample size was calculated with the help of a statistical formula for estimating proportions, considering an expected prevalence of fetal soft markers of 10%, a 95% confidence interval, and a margin of error of 5%. This calculation provided sufficient statistical power for the study.

### Sampling Strategy:

A purposive sampling technique was used to recruit patients who met the inclusion criteria over eighteenmonths, from September 2024 to March 2026.

### Data Collection

### Ultrasound imaging analysis and interpretation

Two obstetric ultrasound examinations were performed for all the study participant pregnant women in Philips Affinity 70 , Mindray D C 80 and GE Voluson E6 ultrasound machines –First scandone between 16 – 24 weeks of gestation (Mid trimester scan) and the follow up scan done between 32-36 weeks of gestation

**Mid-Trimester Ultrasound Examination -assessed two main components**

1.Estimation of gestational age of the fetus with the help of biometric measurements such as the femur length, biparietal diameter and abdominal circumference.

2.Fetal anatomical survey using a checklist

The features listed below are checked to confirm normal fetal development.

i.Head shape and internal structures

ii.Cavum septum pellucidum, cerebellum, cisterna magna and atrial width of the lateral ventricles to rule out its dilatation (Normal < 10mm).

iii.Orbits, lips and nasal bones.

iv.Heart (Position,axis, four chamberview ,three vessel view and outflow tracts)

v.Lungs and diaphragm

vi.Spine examined in both longitudinal and transverse views

vii.Shape and contents of the abdomen at the levels of stomach,kidneys and umbilicus

viii.Renal pelvis (anteroposterior diameter <4 mm) and urinary bladder.

ix.The visualization of bones of upper limbs and lower limbs with counting of fingers and toes

x.Umbilical cord for number of vessels and site of insertion

**Fetal soft markers include:**

(1) Choroid plexus cyst. (2) Mild ventriculomegaly. (3) Nasal bone hypoplasia. (4) Increased nuchal fold thickness. (5) Echogenic cardiac focus. (6) Single umbilical artery. (7) Pyelectasis. (8) Echogenic bowel

**Ultrasound characteristics of each soft marker**

1)Choroid Plexus Cyst: Choroid cysts are created due to accumulation of fluid within the choroidal villi situated in the choroid plexus. Ultrasonography will show these cysts as little fluid-filled cavities (≥3 mm) located within the lateral ventricles.

2)Mild Ventriculomegaly: Defined as an atrial diameter greater than 10 mm in the lateral ventricles measured in an axial plane.

3)Nasal Bone Hypoplasia: To assess the nasal bone, utilize a zoomed mid-sagittal view of the fetal head and upper chest. A proper image shows three lines: skin line, thick more echogenic nasal bone, and the nasal tip.

4)Nuchal Fold Thickness (NFT): It denotes the thickness of the skin and soft tissue located at the back of the fetal neck. The measurement is carried out in an axial section of the fetal head, at the level where the thalami, cavum septipellucidi, and cerebellar hemispheres are visualized. NFT more than 6mm is considered abnormal .NFT usually assessed between 16 to 24 weeks of gestation

5)Echogenic Cardiac Focus (ECF): They are bright and echogenic spots in the ventricles, usually near the papillary muscles or chordae tendineae. They move in concert with the cardiac valves.

6)Single Umbilical Artery (SUA): Refers to the absence of one umbilical artery and can be assessed at the site of insertion to fetal abdomen or on either side of the fetal urinary bladder as they arise from iliac arteries.

7)Renal Pyelectasis: Denotes dilation of the anteroposterior diameter of renal pelvis, defined as ≥4 mm (15–20 weeks). ≥5 mm (20–30 weeks). ≥7 mm (30–40 weeks).

8)Echogenic Bowel: When the fetal bowel is echogenic, it appears as bright or brighter than adjacent bone with a homogeneous pattern.

Patient demographic data, clinical and ultrasound findings were recorded using a structured case proforma. Statistical analysis was performed using IBM SPSS software version 30.0 (IBM Corporation, Armonk, NY, USA).Quantitative data were expressed as mean and standard deviation and were compared by Student t-test. Nominal data expressed as frequency (percentage) and Chi square test was used for such data. Level of confidence was kept at 95% and hence, p-value was considered significant if <0.05.

**Ethical Considerations**

- Ethical approval was obtained from the Institutional Ethics Committee of MMCRI, Mysore.
- The study adhered to the Declaration of Helsinki guidelines.
- Written informed consent was obtained from all patients prior to participation.

**RESULTS**

Baseline features of the study group: Most of the women (34%) who participated in our study were between 20 and 25 years old. Thus 90 women (30%) were between 30 to 35 years old, and 80 women (26.7%) were between 25-30 years of age. Only 28 women (9.3%) were above 35 years of age. 132 women (44%) gave positive history of consanguinity .Previous history of fetal anomalies were noted in 36 (12%) women (14cases had ventricular septal defect, 12 cases had cleft lip, 6 had omphalocele and4 had renal agenesis ) .All the women had their first ultrasound between 16 and 24 weeks of gestation for the detection of soft markers. Some of the soft markers such asechogenic bowel, increased nuchal fold thickness and nasal bone hypoplasiawere not found in any of the study participants.

**Table 1: Sociodemographic and obstetric characteristics of the study participants (n = 300)**

| Study variable | Frequency, n (%) |
|---|---|
| **Maternal age group** | |

| | |
|---|---|
| 20–24 years | 102 (34.0%) |
| 25–29 years | 80 (26.7%) |
| 30–34 years | 90 (30.0%) |
| ≥35 years | 28 (9.3%) |
| **History of consanguinity** | |
| Yes | 132 (44.0%) |
| No | 168 (56.0%) |
| **Previous history of fetal anomalies** | |
| Yes | 36 (12.0%) |
| No | 264 (88.0%) |

Out of the study (after mid trimester scan), 48 (16%) women were found to have soft tissue markers; 42 (14%) women had isolated soft tissue markers and only 6 (2%) women had multiple soft tissue markers. The most frequent soft tissue markers were intra cardiac echogenic focus (6%) and single umbilical artery (4.7%). Renal pyelectasis was seen in 12 women (4%) and 8 women (2.7%) had choroid plexus cyst (Figure 1).

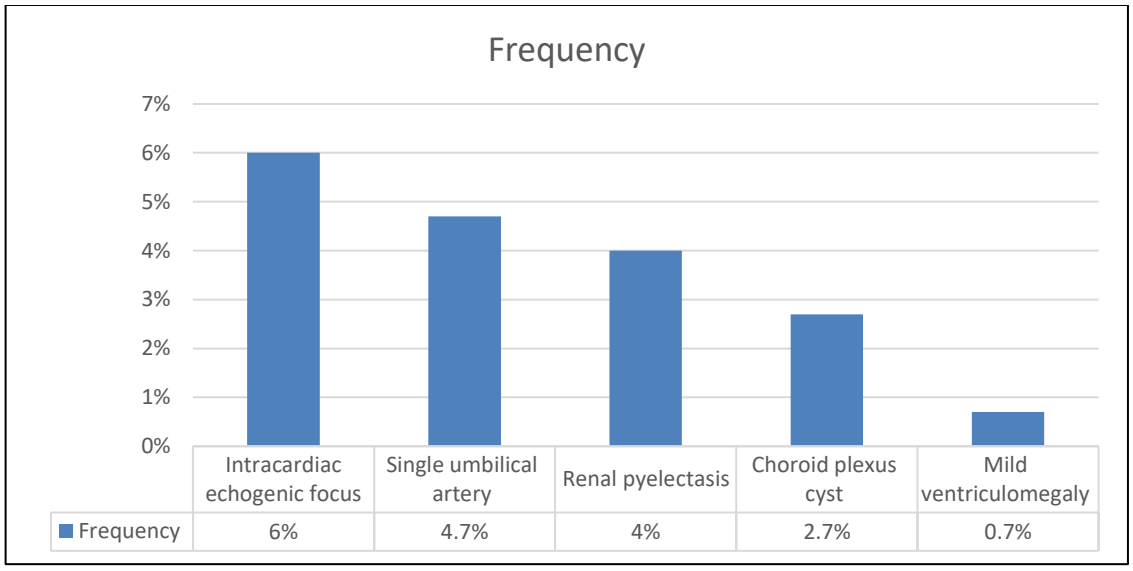


**Figure1: Distribution of fetal soft markers detected on prenatal ultrasound**

Statistically significant association of moderate strength was found between the presence of fetal soft markers and previous history of fetal anomalies ($p < 0.001$), suggesting that individuals with a history of fetal anomalies are more likely to exhibit soft markers during prenatal screening.

Soft tissue markers observed during the first scan (mid trimester scan) in the study group showed no statistical association ($P > 0.05$) with maternal age or positive history of consanguinity; the occurrence or absence of each soft tissue marker was not influenced by the age of the mother or positive history of consanguinity.

A second ultrasound examination was performed on all 300 participants between 32- and 36-weeks of gestation to assess fetal growth and to look for persistence of soft markers if any. It has been found that frequency of some of the soft markers such as intra cardiac echogenic focus (5.35%), renalpyelectasis (2.7%) and choroid plexus cyst (2%) decreased whereas some soft markers such as single umbilical artery (4.7%) and mild ventriculomegaly (0.7%) persisted (Figure 2).

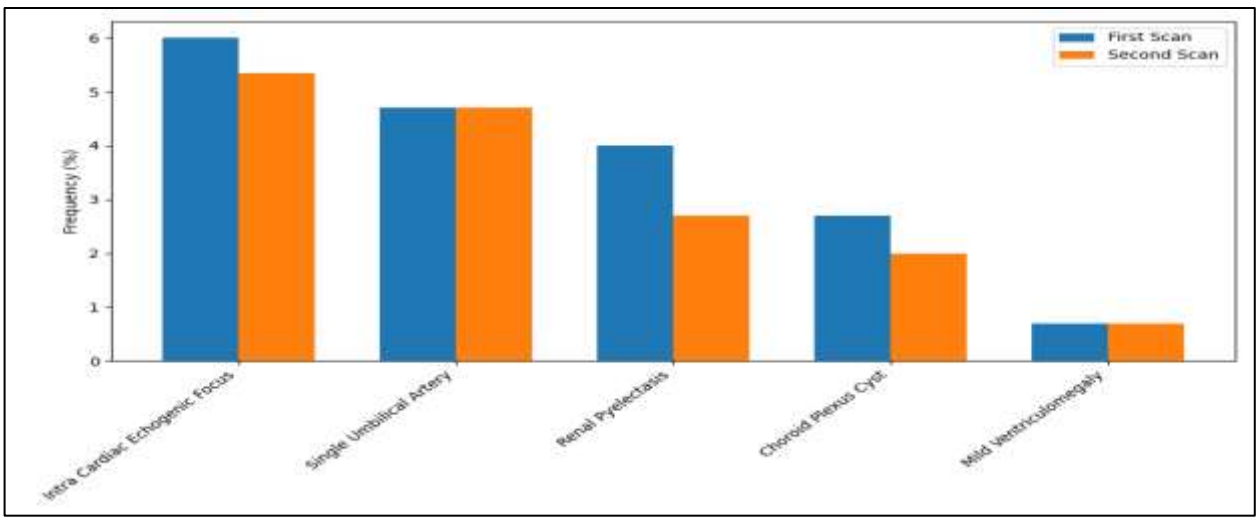


**Figure 2: Distribution of fetal soft markers at the initial and follow-up ultrasound examinations**

In the studied population of 300 women, the average Apgar score was 8.54 with a standard deviation of 0.47, and the mean birth weight was 2926.46 ± 287.52 grams. A total of 30 neonates required NICU admission. All newborns were found to be free of any congenital anomalies. Neonatal outcome had no significant statistical association with presence of soft markers($P>0.05$).

## DISCUSSION

The present study aimed to evaluate the prevalence and implications of fetal soft markers detected during mid-trimester ultrasound scans and their association with maternal and neonatal outcomes. Our findings contribute to the growing body of literature on prenatal screening and its predictive value for fetal anomalies.

### Maternal Age and Consanguinity

In our study, the majority of participants were between 20 and 25 years old, consistent with demographic trends observed in similar studies [7]. The lack of association between maternal age and the presence of soft markers aligns with previous research indicating that age alone is not a significant predictor of soft marker occurrence [8]. This suggests that while maternal age is a known risk factor for chromosomal abnormalities, it may not directly influence the presence of soft markers, which are often benign and transient.

Similarly, the absence of a significant relationship between consanguinity and soft markers suggests that genetic factors may not play a predominant role in the manifestation of these markers. This finding corroborates the work of Rosén and Werkö, who found that consanguinity did not significantly increase the risk of soft markers, although it is a known risk factor for certain genetic disorders [9]. This highlights the complexity of genetic and environmental interactions in prenatal development, suggesting that other factors may be more influential in the development of soft markers.

### Prevalence of Soft Markers

The prevalence of soft markers in our study was 16%, with intra-cardiac echogenic focus and single umbilical artery being the most common. This prevalence is in line with rates reported in other studies, which range from 10% to 20% [10].

The presence of these markers can often cause anxiety for expectant parents, but it is important to note that many soft markers are transient and may resolve as gestation progresses. For instance, the decrease in frequency of intracardiac echogenic focus ,renalpyelectasis and choroid plexus cysts upon follow-up supports the notion that these markers often do not persist [11].

The clinical significance of these markers has been debated, with some studies suggesting that they may be associated with chromosomal abnormalities such as Down syndrome. However, the majority of soft markers are considered benign and do not result in adverse outcomes. This is supported by the work of Anderson and Jyoti, who found that isolated fetal intracardiac echogenic focus is not significantly associated with adverse outcomes in younger women [12]. This finding is crucial for clinical practice, as it helps in counseling expectant parents about the potential implications of these markers.

### Association with Previous Fetal Anomalies

A significant association was found between the presence of soft markers and previous history of fetal anomalies, suggesting that women with such histories are at increased risk for soft markers in subsequent pregnancies. This finding is supported by the work of Nyberg and Souter, who reported similar associations, emphasizing the importance of detailed prenatal screening in this population [13]. The presence of soft markers in these cases may warrant further investigation to rule out underlying anomalies.

The role of advanced techniques, such as chromosomal microarray analysis, has been highlighted in recent studies as a means to improve diagnostic accuracy in cases where soft markers are detected [14]. This approach allows for a more comprehensive assessment of potential genetic abnormalities, providing valuable information for clinical decision-making. Additionally, the integration of non-invasive prenatal testing (NIPT) could further enhance the accuracy of detecting chromosomal abnormalities, offering a safer alternative to invasive procedures like amniocentesis. These advancements in prenatal screening technology represent a significant step forward in the early detection and management of potential fetal anomalies.

### Neonatal Outcomes

Despite the presence of soft markers, neonatal outcomes in our study were generally favorable, with an average Apgar score of 8.54 and no significant congenital anomalies detected. This aligns with the findings of Arda et al., who reported that isolated soft markers often do not correlate with adverse neonatal outcomes [14]. The lack of significant association between soft markers and NICU admissions further supports the notion that these markers, in isolation, may not be indicative of severe fetal compromise [15].

The findings of Carriço et al. also support this conclusion, as their study on isolated fetal choroid plexus cysts found no significant impact on neonatal outcomes [15]. This reinforces the idea that while soft markers may warrant further investigation, they should not be used in isolation to predict adverse outcomes. It is crucial for healthcare providers to communicate effectively with expectant parents, providing reassurance and clear information about the implications of soft markers. This communication is essential to alleviate anxiety and support informed decision-making, ensuring that parents are well-prepared and confident in their understanding of the situation.

Lorente et al. conducted a meta-analysis on the validity of echogenic intracardiac foci for calculating the risk of Down syndrome, emphasizing the need for a nuanced approach in interpreting these markers [16]. Their findings support the integration of multiple screening modalities to enhance diagnostic accuracy.

**Clinical Implications**

The study emphasizes a comprehensive approach to managing soft markers in prenatal care, advocating for strategic scheduling of follow-up ultrasounds to monitor their evolution. This practice helps distinguish between markers likely to resolve and those requiring further investigation. Integrating genetic counseling into the care plan, especially when there is a history of fetal anomalies, provides parents with a clearer understanding of potential genetic risks and available options. A holistic risk assessment approach is crucial, considering factors such as maternal age, family history, and previous pregnancy outcomes to guide clinical decisions. The study reassures that soft markers often do not lead to adverse neonatal outcomes, offering comfort to parents and clinicians and alleviating concerns about these markers. Additionally, the advancement of prenatal screening techniques, such as chromosomal microarray analysis (CMA) and non-invasive prenatal testing (NIPT), enhances the detection and understanding of genetic abnormalities, leading to more accurate diagnoses and better-informed clinical management. Overall, the study highlights the importance of interpreting soft markers within the broader clinical context, emphasizing that many are benign and transient, and underscores the need for clear, reassuring communication to parents.

## CONCLUSION

The conclusion of the study is that while fetal soft markers detected during mid-trimester ultrasound scans can initially cause concern for expectant parents, many of these markers are benign and transient, not correlating with adverse neonatal outcomes. The study underscores the importance of a comprehensive approach to prenatal care, which includes strategic follow-up scans, integration of genetic counseling, and a holistic risk assessment that considers maternal and family history. Advanced prenatal screening techniques, such as chromosomal microarray analysis (CMA) and non-invasive prenatal testing (NIPT), are valuable tools for enhancing diagnostic accuracy and guiding clinical management. Effective communication and counseling are essential to reassure parents and support informed decision-making, ultimately reducing anxiety and ensuring appropriate care.

**Limitations**

Despite the promising findings, the study has several limitations:
1)Relatively small sample size, which may affect generalizability.
2)Single-Center Study: Conducted at a single institution, the study's findings
may be influenced by local practices, technology, and expertise, which could differ from other centers, affecting the generalizability of the results.
3)Limited Follow-Up: The study follows participants only until delivery, which may not capture long-term outcomes related to the presence of soft markers, such as developmental issues that could arise later in childhood.
4)Confounding Factors: The study may not fully account for all potential confounding factors, such as environmental influences or other maternal health conditions, which could impact the presence and significance of soft markers
Future studies should focus on larger cohorts, multi-center validation with longer follow up periods and more comprehensive genetic testing, to better understand the implications of fetal soft markers.

**Acknowledgements**

**Competing interests**

The authors declare that they have no financial or personal relationships that may have inappropriately influenced them in writing this article.

**Authors' contributions**

Dr Manasa M R contributed to the study design, data collection , review of literature , interpretation & article creation. Dr Sujedlal Kattungaland Dr Pradeep Kumar C N were involved in the conceptualization of the initial idea, as well as the study design, data collection, analysis, interpretation and article preparation. Dr Vaishnavi, Dr Abhilasha S and Dr Aravind A assisted with the study design, data collection and article creation.

**Funding information**

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

**Data availability**

The data that support the findings of this study are available from the corresponding author,Dr Sujedlal Kattungal, upon request.

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**REPRESENTATIVE IMAGES OF FEW ULTRASOUND FETAL SOFT MARKERs**

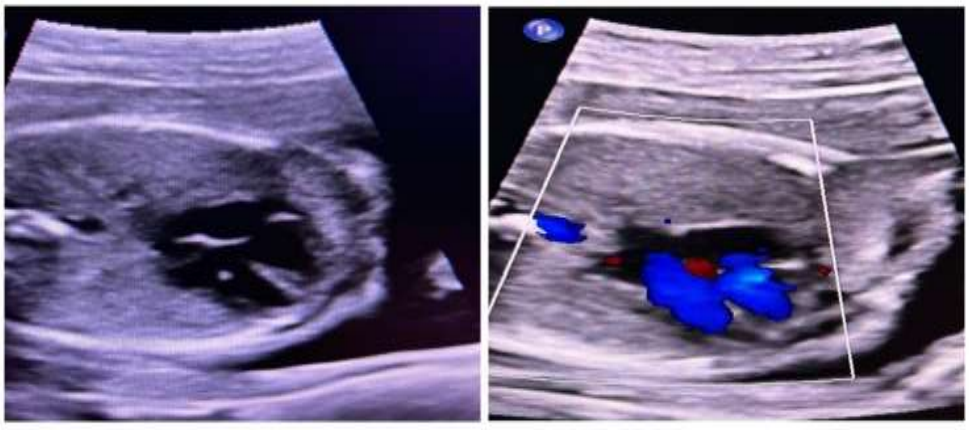

**Figure 3: Intracardiac echogenic focus in left ventricle**

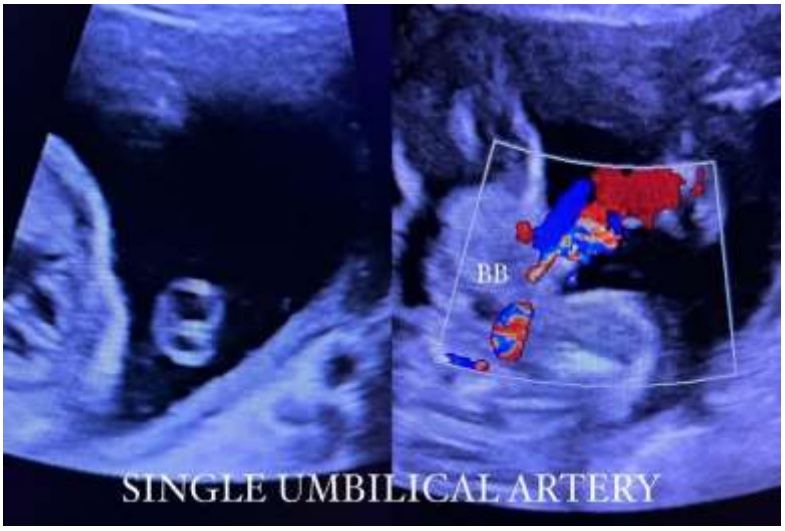


**Figure 4: Single umbilical artery**

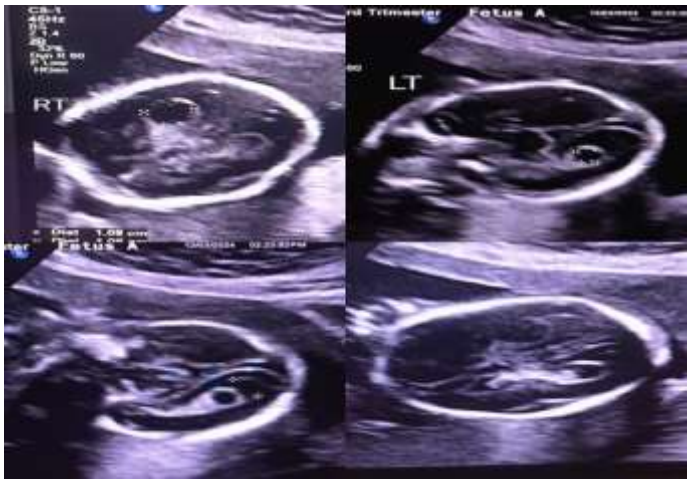


**Figure 5: Choroid plexus cysts in bilateral lateral ventricles**

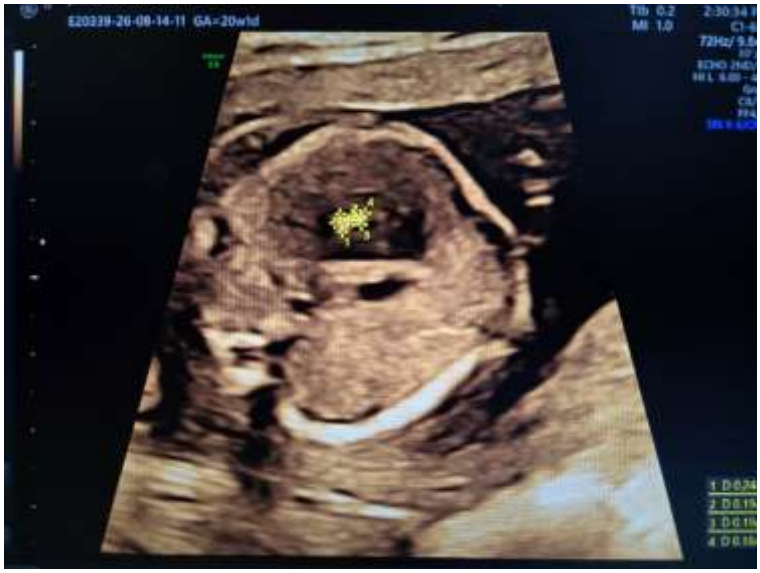

**Figure 6: Intracardiac echogenic focus in left ventricle**

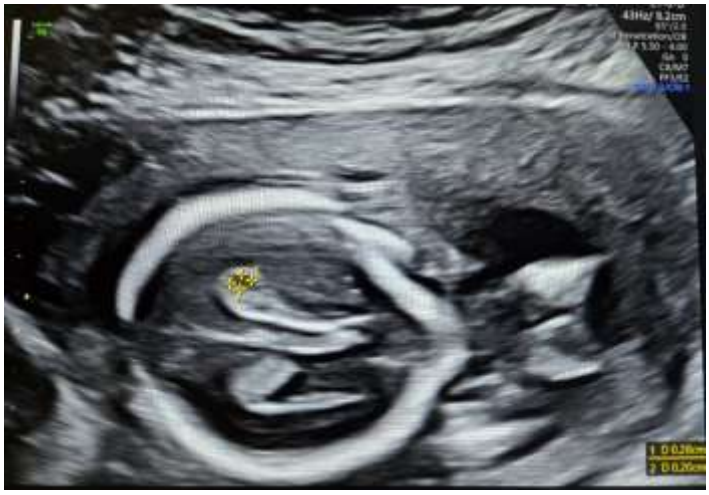

**Figure 7: Choroid plexus cyst in left lateral ventricle**