Quest Journals
Journal of Medical and Dental Science Research
Volume 11~ Issue 7 (2024) pp: 12-18
ISSN(Online) : 2394-076X ISSN (Print):2394-0751
www.questjournals.org

Research Paper

Short term outcome of pregnancies with one or more soft markers in second trimester- a prospective observational study

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Abstract
Background: Soft markers of pregnancy are usually normal variants. A single soft marker is usually not of much significance. However multiple or some single soft markers are a pointer towards presence of aneuploidy.
Methods: Prospective observational study done on 571 women presenting to out-patient and in-patient department of MCCH Anantnag which is an associated hospital of Government Medical College Anantnag. Fetuses with any soft marker like intra-cardiac echogenic focus (ICEF), ventriculomegaly(VM), choroid plexus cysts (CPC), pyelectasis and thickened nuchal folds(TNF) were included in the study. Data was analyzed using SPSS for windows (ver. 22). A p value of <0.05 was considered significant
Results: Out of 571 women screened for presence of soft markers, 63 women were identified with positive one or more soft markers. Most common soft marker was an intra-cardiac echogenic focus(ICEF) followed by choroid plexus cysts (CPC), pyelectasis (PL), echogenic bowel (EB) ,ventriculomegaly (VM),mega cistern magna (MCM) and thickened nuchal folds (TNF) in that order.Mean maternal age was 28.6 ±4.2 years. 32 mothers were primi-gravidae (50%), 39% (25) were G2 and 6 (9.5%) mothers were G3. Six patients had a history of preterm delivery (9.52%) and the rest 57 (90.48 %) had a term delivery. 30 patients were male (47.62%) and 33 babies were female (52.38%). About 55 babies were appropriate for gestational age, AGA (87.3%) 5 babies were small for gestational age, SGA (7.94%) and 3 babies were large for gestational age, LGA (4.77%). Only 7 babies needed NICU support at birth (11.11%).
Conclusion: The outcomes of pregnancy with isolated soft markers are usually favorable except in conditions where the markers occur in combination. Reassurance of mothers forms mainstay of management
Keywords: *ICEF, VM, pyelectasis, CPC, MCM TNF,SGA,LGA,AGA*

***R**eceived 26 June, 2024; **R**evised 03 July, 2024; **A**ccepted 05 July, 2024 © The author(s) 2024.*
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I. Introduction

During the second trimester women are routinely screened for the presence of soft markers of aneuploidy. The risk of a woman having aneuploidy is determined by the presence of one or more markers in isolation or in combination. The risk of aneuploidy in a pregnancy can be determined either by presence of structural anomalies or soft markers. Acombination of multiple parameters like maternal age, prenatal ultrasonography, biochemical tests and some invasive tests like amniocentesis is used for assessing the risk of aneuploidy in an individual patient. An early sonographic examination done at 16-20 weeks is the most comprehensive test to detect presence of soft markers[1]. Although majority of soft markers are eventually found to be normal variants but soft markers can be a pointer towards chromosomal anomalies especially if the occur in combination[2, 3]. Isolated presence of soft markers is usually not of major concern and it can occur in 11-17% of normal pregnancies. Most commonly used soft markers in mid trimester ultrasonography include intra cardiac echogenic focus (ICEF, n=18), choroid plexus cysts (CPC ,n=17) , echogenic bowel (EB ,n=10), short femur (SF, n=8), short humerus (SH, n=7) , ventriculomegaly (VM ,n=3), pyelectasis etc[5] .Basically these markers have been studied in the past to estimate risk of Down syndrome in the patient but with time presence of certain specific markers is known to associated with non-aneuploidy related conditions like pathological placental conditions and structural anomalies.[6]

II. Material And Methods

This was a prospective observational studyconducted in the department of Obstetrics and Gynecology GMC Anantnag over a period of one year from March 2022 to March 2023. Fetuses with CPC, MP, VM, increased nuchal fold thickness, ICEF, EB were included in the study.

Method of calculation: For nuchal fold thickness calculation we obtained a transverse section of head at the level of septum cavum pellucidum and thalamus directed posteriorly. Measurement of ≥6mm between 15 to 23 weeks was considered as a thickened nuchal fold.

ICEF was defined by an area which was echogenically bright in the fetal heart and moves synchronically to the atrio-ventricular valves

Mild pyelectasis was suggested by renal APPD≥4 mm and<10mm in the second trimester ultrasound.

A CPC was suggested by a lucent cyst like area within choroid plexus of lateral ventricle

Echogenic bowel was defined by increased echogenicity of fetal bowel noted on ultrasound more simply exemplified by a hyper echoic area in the lower abdomen of the fetus.

Mild ventriculomegaly was defined by a transverse diameter of <10 mm at any gestational age.

We collected data of maternal age, parity, gender of the child, results of aneuploidy screening and status of infant at birth and entered results in a predesigned proforma. Infants were assessed for short term outcomes after birth and results assessed.

III. Results

571 women were screened for 2nd trimester screening by ultrasound during the study period. About 63 women with soft markers were identified. We found the following frequency of soft markers in study population. ICEF was the most common soft marker observed in our study as shown below.

Soft marker	Number	Percentage
ICEF	18	28.57 %
CPC	17	26.98%
Pyelectasis	10	15.87%
Echogenic bowel	8	12.70%
Ventriculomegaly	5	7.93%
TNF	3	4.76%
MCM	2	3.17%
Total	63	

Table 1= Table showing number and percentage of soft markers obtained in the second trimester ultrasound

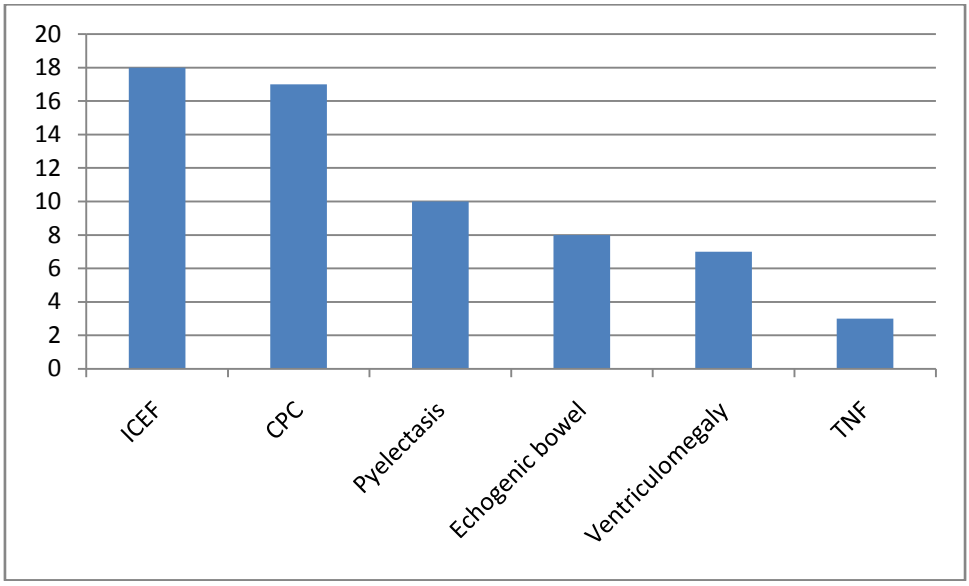

Figure 1=Bar chart showing frequency of soft markers encountered in the study population

Majority of women in our study were primi-gravidae as tabulated below

Parity	Number	Percentage
Primi	32	50%
G1	25	32%
G2	6	9.5%

Table 2=Table showing parity of study population

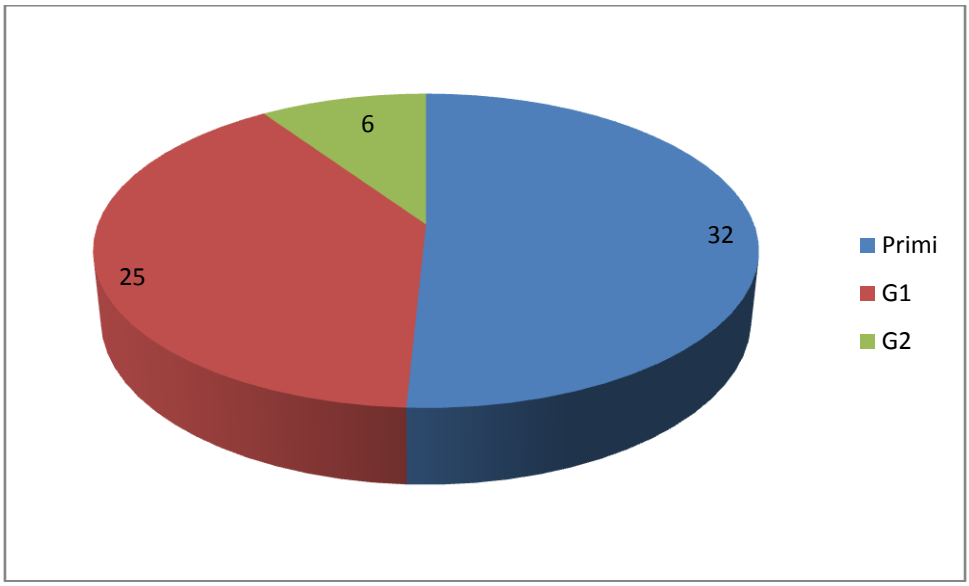

Figure 2=Pie chart showing parity of study population

Majority of babies were born by spontaneous conception.

Spontaneous conception	60
Assisted conception	3
Total	63

Table 3 = Mode of conception

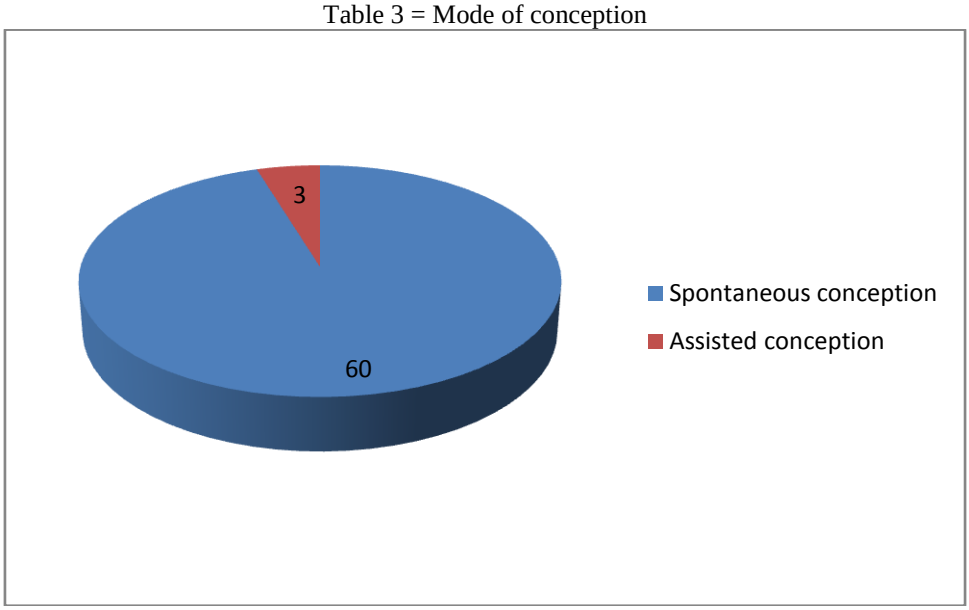

Figure 3=Pie chart showing mode of conception

More females had a positive soft marker of aneuploidy as compared to males.

Gender	Number	Percentage
Male	30	47.62%
Female	33	52.38%

Table 4 = Table showing gender distribution of study population

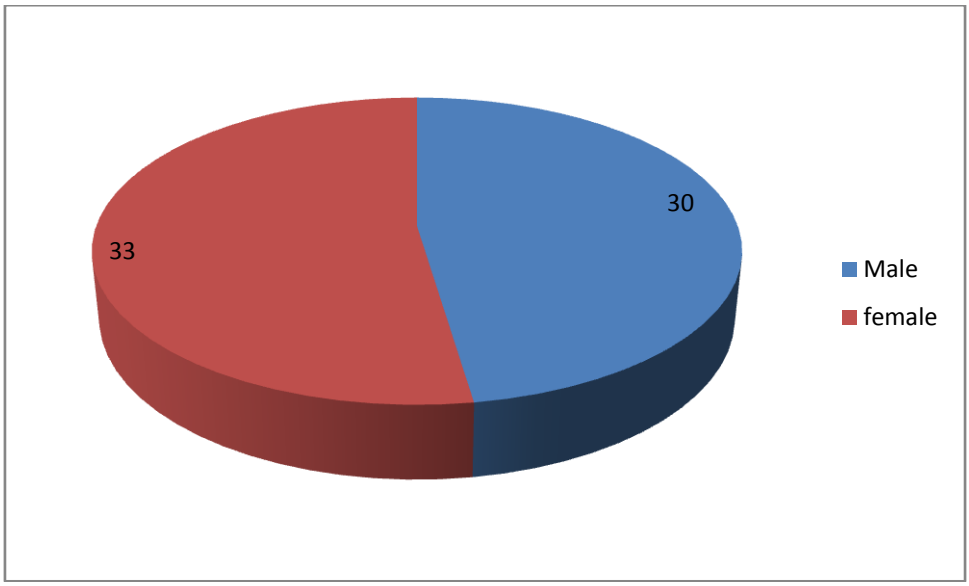

Figure 4 =Pie chart showing gender distribution of study population

Majority of babies were born appropriate for gestational age.

Gestation	Number	Percentage
SGA	5	7.94%
AGA	55	87.3%
LGA	3	4.77%

Table 5=Table showing gestation of study population

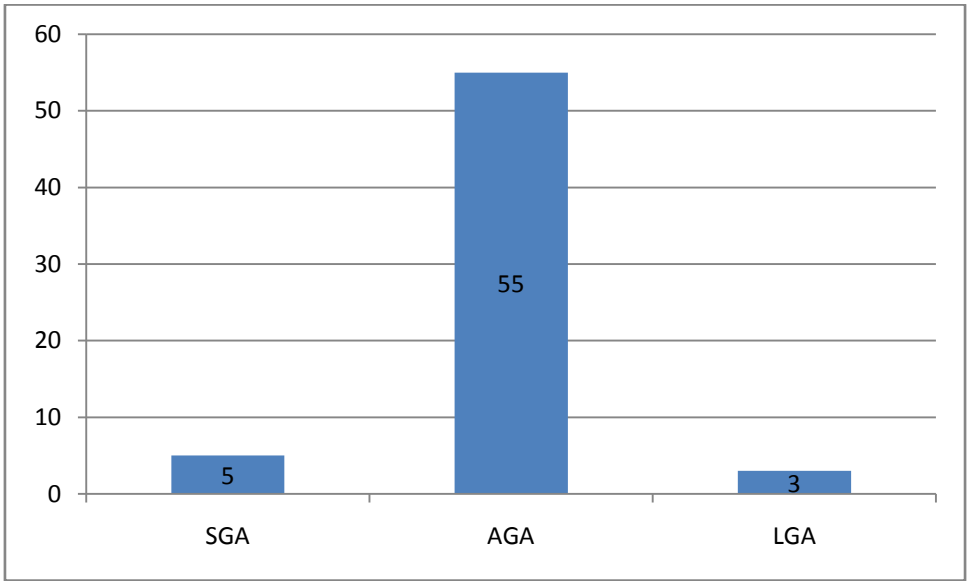

Figure 5=Histogram showing gestation of study population

The overall mean maternal age was 28.6 ±4.2 years. 32 mothers were primi-gravidae (50%), 25 (32%) mothers were G2 and 6 (9.5%) mothers were G3.60 mothers had a history of spontaneous conception and 3 had a history of assisted reproductive technique (IVF). Risk assessment of mother was performed by Nuchal Translucency (NT) and biochemical tests both of which were performed in the Ist trimester. Patients were classified into low risk group, intermediate risk group and high risk groups. Six patients had a history of preterm delivery (9.52%) and the rest 57 (90.48 %) had a term delivery. 30 patients were male(47.62%) and 33 babies were female (52.38%). About 55 babies were appropriate for gestational age, AGA (87.3%) 5 babies were SGA (7.94%) and 3 babies were LGA (4.77%). Only 7 babies needed NICU support at birth (11.11%).

Of 18 patients with ICEF, majority of patients had a normal outcome i.e., n=17. Post natal echocardiogram was done in all cases .One patient had a small muscular VSD which resolved on serial scans. There was no intrauterine or post natal demise in any patient. There was a favorable perinatal course in all

patients. About 14 patients had an ICEF in the left ventricle and the rest had an ICEF in the right ventricle. There was no neonatal death in the study group under consideration. 3 patients required NICU care due to unrelated complications like sepsis and congenital pneumonia.

Of 17 patients with isolated CPCs, risk assessment was done by NT and biochemical tests in the second trimester All fetuses underwent fetal echocardiography but no anomalies were found on fetal echo. All the patients with choroid plexus cysts had a normal phenotype at birth. No case of abortion was noted. No structural abnormalities were found in patients with CPCs. However 2patients required ICU care due to complications of prematurity. These patients were admitted for complications of early onset sepsis.

Of the 10 patients diagnosed with antenatal pyelectasis,patients were classified into mild moderate and severe pyelectasis depending upon the gestation age at presentation and antero-posterior pelvic diameter (APPD). Mild pyelectasis was identified in 5 patients, moderatepyelectasis in 3 and severe pyelectasis in 2 patients. In the mild pyelectasis group, all the patients fared well with no adverse perinatal outcome. In the moderate pyelectasisgroup, 1 patient required NICU care due to oliguria and neonatal AKI at birth. In the severe pyelectasis group, one patient required NICU care because of UTI due to vesico-ureteral reflux.

Of the 5 patients with echogenic bowel majority of patients fared well. One patient presented with delayed passage of meconium with meconiumileus. Pilocarpine iontophoresis performed at 3 weeks of age was suggestive of cystic fibrosis which was confirmed later by mutational analysis. Rest of the patients didn't require any specialized care or NICU admission. There was no evidence of any vertically transmitted infections in the EB group. There was no incidence of chromosomal anomalies in the EB group.

Of the patients with antenatally diagnosed ventriculomegaly it was noted that mild isolated ventriculomegaly doesn't lead to any adverse perinatal outcome. There was no adverse perinatal or immediate neonatal event in the VM group in all subjects. However, based on data extrapolated from previous studies, it is prudent to follow these children for long term and asses their development by various scores like Baileys Mental Development Index, Baileys' psychomotor development index, Trivendrum test, Baroda Screening Test etc as these children are prone to developmental delay especially if VM is severe i.e, >10 mm. Because of the potential of developmental delay in patients with isolated mild ventriculomegaly, screening in this group of population is also warranted.

Both patients with MCM fared well. Both were discharged in stable condition with no adverse perinatal or immediate neonatal event.

Babies with thickened nuchal folds also fared well. Only one of these babies was found to have a positive quadruple screen and amniocentesis confirmed Down syndrome. The baby however died due to congestive cardiac failure (CHF) from massive endocardial cushion defect in the immediate neonatal period. Rest of the babies didn't require additional testing or NICU care.

Marker	number	Adverse perinatal event	Survived	Died	Cause of morbidity/ Death
ICEF	18	3	18	0	Early onset sepsis, n=2 Congenital pneumonia ,n=1
CPC	17	2	17	0	Prematurity, n=1 Early onset sepsis, n=1
PL	10	1	10	0	Sepsis due to vesico-ureteral reflux, n=1
EB	08	1	8	0	Nil
VM	05	0	5	0	Nil
MCM	03	0	3	0	Nil
TNF	02	0	1	1	Death, n=1 due to congenital congestive cardiac failure

IV. Discussion

We studied the prevalence of soft markers of aneuploidy in pregnancy and the relevance of such markers in terms of immediate neonatal outcomes during the first 28 days of life. The prevalence of intra-cardiac echogenic focus in 2nd trimester sonograms has been found to be 0.5 – 20 %[7]. It is more common in Asian than non Asian population. Long term follow-up of patients with isolated single or multiple ICEFs has shown that the risk of aneuploidy is not increased. Neither is the risk of adverse cardiac outcomes increased. Even a screening fetal echo is not required if there is no evidence of cardiac dysfunction provided 2nd trimester scan is normal[8].

Choroid plexus cysts are found in 0.18 to 3.6% of 2nd trimester sonograms. The natural course of these CPCs is that these involute on serial second trimester scans.[9]Current studies and guidelines suggest that isolated CPCs do not affect neurological outcomes and are not associated with higher risk of aneuploidy. Furthermore, they don't require long term sonographic follow up.[10-13]

The incidence of fetal pyelectasis was 1-3% in fetuses during 2nd trimester scans in recent meta-analyses of RCTs. The risk of aneuploidies has been found to be increasedin fetuses with USG documented

2nd trimester pyelectasisbut the presence of fetal pyelectasis in isolation is not a risk factor for aneuploidies[13, 14, 15] However, the presence of fetal pyelectasis merits further evaluation by follow up examinations [16].

The incidence of echogenic bowel (EB) in 2nd trimester pregnancy scans ranges from 0.2-1.8%. Two studies with contrasting results have been conducted to study the risk of chromosomal abnormalities in patients with echogenic bowel on 2nd trimester ultrasound. Firstly E Kin et al [18] found that the risk of chromosomal abnormalities in isolated echogenic bowel cases was 6.7% with no significant increase in risk when additional soft markers were present. However, Buiter et al[19] found that although presence of two soft markers was not associated with increased risk of chromosomal abnormalities, but the presence of three or more soft markers was associated with increased risk of chromosomal anomalies. Serial sonographic evaluation for presence of echogenic bowel is indicated even in the absence of other abnormal findings.

The prevalence of ventriculomegaly in 2nd trimester scans is roughly 0.7%.[21]. Rate of chromosomal anomaly is in the range of 4-5% for pregnancies with isolated VM and up to 18 % of pregnancies with VM will have other soft markers[22, 23]. It is recommended to screen mother for CMV and toxoplasmosis during evaluation of isolated VM[24] .Meta analyses of randomised controlled trials have shown that mild ventriculomegaly (<12 mm) is not associated withsevere developmental delay on follow up scans. However, mild developmental delay can be obswerved[25].

V. Conclusion

Most of isolated soft markers are not predictive of adverse neonatal and perinatal outcomes. However in the presence of certain soft markers follow up and evaluation are recommended even if present in isolation. Presence of multiple soft markers should prompt more comprehensive evaluation for aneuploidy.

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