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A Review on Techniques for Computer Aided Diagnosis of Soft Markers for Detection of Down Syndrome in Ultrasound Fetal Images

O. JEBA SHINEY[1], J. AMAR PRATAP SINGH[2] and B. PRIESTLY SHAN[3]

[1]Research Scholar, Noorul Islam University, Kumarakoil, Thuckalay, India.
[2]Director (Administration), Noorul Islam University, Kumarakoil, Thuckalay, India
[3]Eranad Knowledge City, Manjeri, Malappuram, Kerala, India.
*Corresponding author E-mail: jebashiney@gmail.com

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ABSTRACT

In this paper, various algorithms and techniques, which aids in development of secondary observer systems for Down syndrome detection in fetus of first and second trimester is being evaluated and presented. 50 papers from 1982 to 2016 has been reviewed and the consolidated study is being presented. The parameters for comparison include Markers for Down Syndrome Detection, Algorithms, Sensitivity, Specificity and accuracy of these algorithms. Markers for study include Nasal Bone Length, Nuchal Translucency Thickness, and Naso Frontal Angle. These markers have been utilized by researchers for design of Secondary Observer systems and have achieved various degrees of accuracies.

Keywords: Down Syndrome, Markers, Secondary Observer Systems, Specificity, Accuracy, Sensitivity, Nasal Bone Length, Nuchal Translucency**.**

INTRODUCTION

Down Syndrome is one of the predominant chromosomal disorder caused by the presence of an extra copy of the 21st chromosome. Usually an individual possess 46 chromosomes, 23 inherited from the father and 23 from the mother. In few cases 47 chromosomes may be present in each cell instead of 46. This condition is termed as Down Syndrome. The British Doctor, John Langdon Down described the syndrome in 1866 and hence the name[1,2].

The prevalence of Down syndrome is approximated to be about 1 in 1000 births worldwide[3]. Earlier it has been 1 in 700[4]. There are three types of Trisomy21 which are complete Trisomy 21, mosaicism and translocation. The most common one which occurs in about 95% of the cases is complete Trisomy 21 in which all the cells possess an extra copy of the chromosome 21. In mosaicism not all the cells will have an extra chromosome and translocation happens when a whole or extra copy of chromosome occurs getting attached to another chromosome[2].

No specific reasons for this disorder has been reported so far other than the maternal age[5]. The likelihood of having a child with Down Syndrome increases with increasing maternal age. Prenatal Screening of Down syndrome involves screening as well as diagnosis tests. Screening is made by noninvasive procedures like 2D/3D ultrasounds and diagnosis involves invasive methods like amniocentesis, chorionic villus sampling (CVS) and percutaneous umbilical blood sampling(PUBS). With invasive procedures there are possibilities for fetal

loss and therefore they are not recommended for prenatal screening. Hence it is worthy to perform diagnosis with noninvasive procedures[6] and the detection rate can be improved by combining these ultrasound findings with maternal serum markers[9,10,11,12].

Two Dimensional ultrasound imaging is more popular in obstetrics and gynecology because it is noninvasive, cost effective, intuitive, convenient and safe. But the problem with ultrasound is the image quality where the original RF signal is subjected to a number of processing steps before being converted into an image as well as the multiplicative speckle noise which reduces the visibility of the image. Therefore the image presented to a physician is such a low quality image which renders it inappropriate for accurate diagnosis[7]. Therefore the ultrasound images require efficient preprocessing algorithms to provide accurate results when they are to be given as inputs to clinical decision support systems.

Down syndrome soft markers

A number of soft markers have been identified for chromosomal aneuploidies. The table below gives a brief picture on the literatures published on the various soft markers identified.

A few soft markers as reported by the Sandiego Perinatal Center have been discussed below:

Nuchal Translucency is the accumulation of hypodermal fluid in the fetal neck between 11.3 and 13.6 weeks of gestation. It has been noted that babies with Down syndrome will have an increased amount of this fluid. The nuchal translucency thickness between 2.2 mm and 2.8 mm during this 10-13 weeks is considered to be normal. The risk increases with increasing translucency thickness. A visible rigid bone at the top of the nose is seen at 15 – 22 weeks of gestation. Absence of this nasal bone is also considered to be an important marker for Down Syndrome. This increases the Down Syndrome risk by a factor between 20 and 60. This can be identified only after 20 – 22 weeks of pregnancy. A linear arrangement of mitral and tricuspid valve in a baby is the symptom for some heart defect in the growing fetus. If the heart functions normal with a linear arrangement of these valves then this increases the risk for Down Syndrome by a factor of 30 to 60.

A ratio between the length of the humerus and the average humerus length is another important marker. If this is far below the expected range, the risk is increased by a factor of 6. Similar to this the femur length will also increase the risk by a factor of 2.2.Echogenic foci and a small amount of extra fluid within the baby's kidneys are also considered to be low level markers for Down Syndrome.

The ratio of biparietal diameter/fronto nasal fold thickness to nasal bone length is also considered as another marker, where the rate of biparietal diameter to nasal bone length according to gestational week is found to be 8.1± 1.4 whereas it is 11.3+2.0 in fetuses with trisomy 21[7,16].

The reference range for detecting these anomalies is being fixed by analyzing a number of measurements taken from different tertiary centres. The ethnicity also plays a major role in finalizing these reference values[25]. These values may vary between different ethnic groups thereby affecting the accuracy of detection which may result in increase of false positive and false negative rates. There is no much reports specifically analyzing a group especially the South Indian population. The table below gives the normal values for few markers in reference to the South Indian population.

Automated diagnosis

Accurate detection of the above markers require skilled sonographers, obstetricians and fetal medicine professionals, since the ultrasound markers can be easily confused with the underlying structures because of the speckle noise. Researchers have been working on automated diagnosis of these soft markers so that observer dependence will be minimized and the detection rate could be improved. If these parameters could be estimated from a B mode image by computer assisted techniques the detection accuracy will be higher and the number of false positive rates or false negative rates could be reduced.

Yenhui Deng *et al* has proposed an ordered structural model for the automated detection of the nuchal translucency region[28]. Anzalone *et al* has proposed a completely automated system for Nuchal Translucency measurement which operates on the image sequence what we get as output

from the ultrasound machine[29]. S. Nirmala and V. Palanisamy have utilized the mean shift analysis and canny operators for segmentation of the nuchal translucency region. The exact thickness of the nuchal translucency region has been estimated using blob analysis. Their results say that the fetus should have a nuchal translucency thickness of 1.85±0.2 mm in the 14th week of gestation[30]. R.Sonia and V. Shanthi[31] propose a computerized method to measure nuchal translucency thickness. Preprocessing is done using Lee filter. Region of Interest is manually extracted. Segmentation is done using morphological operations and otsu thresholding. The Average height and standard deviation of Nuchal Translucency thickness for normal fetus is 1.99 ± 0.62mm and for abnormal fetus is 4.10 ± 9.00 mm respectively. For area it is found to be 37.84 ± 20.28 mm and 126.44 ± 41.80 mm.

Lai K W *et al*[32] have trained the Artificial neural network to locate the region of interest that contains the Nuchal Translucency. The accuracy achieved is 93.33 percentage. The boundary region of the Nuchal Translucency layer is identified using instinctive computerized algorithm. Once the boundary region is located then the optimum thickness of the region is determined. Intensity continuity and edge strength are the local parameters used as biased terms for thickness calculation. Moratalla J *et al*[33] a segmentation algorithm based on minimizing a cost function is proposed. This method is semi-automatic where the region of interest is selected manually. The boundary selection is based on minimization of a cost function. The dynamic programming technique is employed for optimization.

Park JH *et al*[34] has proposed a fully automatic approach for computing Nuchal Translucency (NT) measurement in ultrasound scans of the mid-sagittal plane of a fetal head. The algorithm finds fetal head using discriminative learning-based detectors. The NT region is estimated from the statistical relationship between the fetal head and the NT

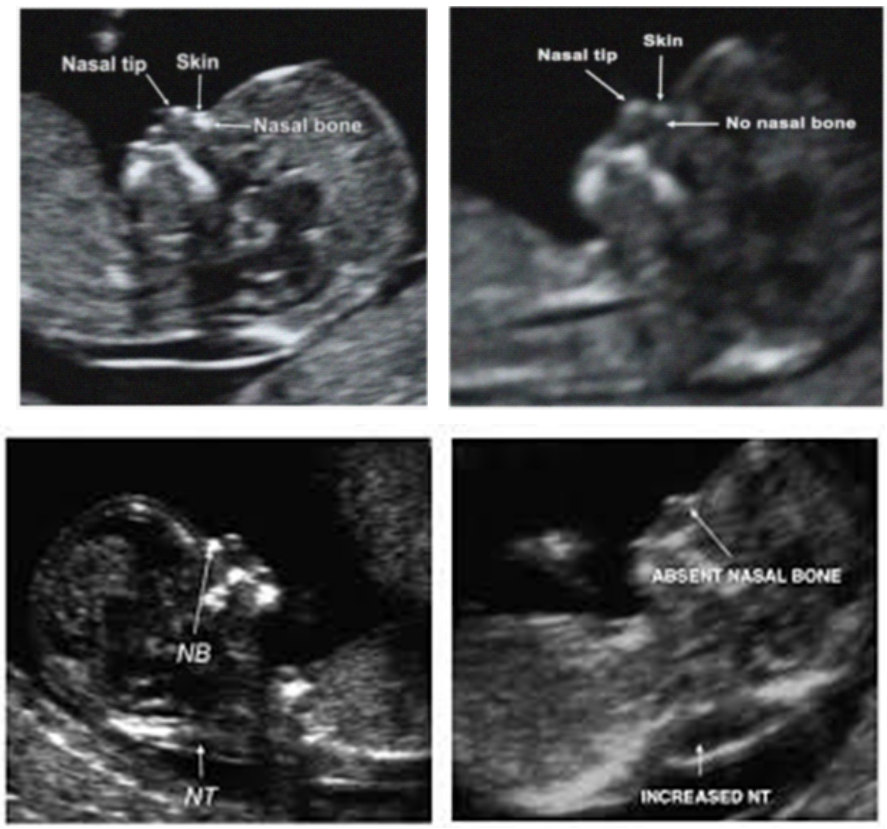

Fig. 1: Normal and affected fetal images

Table : 1 Soft Markers for Down Syndrome

Low maternal serum alpha-fetoprotein.[9] Merkatz IR et.al[1984]	Women suspected of having an affected fetus are subjected to serum screening tests along with normal subjects. It has been noted that those with affected fetus had maternal serum alpha-fetoprotein levels significantly lower than normal subjects.
Femur Length [10] Nyberg et al [1990]	With shortening of femur length as a marker the predictive values are 0.93 and 0.33 for high risk population and low risk population respectively. Therefore it has been concluded that this marker is less effective in screening for down syndrome.
Prenatal ultrasonography [11] Nyberg DA et al [1995]	Analysis of the effectiveness of prenatal ultrasonographic findings in screening for down syndrome when combined with the three biochemical markers--maternal serum alpha-fetoprotein, unconjugated estriol and human chorionic gonadotropin. Unusual results from these examinations reveal the necessity for an invasive screening by amniocentesis.
Maternal age and fetal nuchal translucency [12], Pandya PP et al [1995]	Screening for down syndrome by the combination of maternal age, crown rump length and nuchal translucency screening is proposed.
Free beta-human chorionic gonadotropin and pregnancy -associated plasma protein A [13] Krantz DA et al [1996]	Screening for down syndrome in the first trimester has been proposed which includes testing the levels of pregnancy-associated plasma protein free beta-human chorionic gonadotropin. This method is capable of producing results similar to those produced by the second trimester screening proposed in [10]
Serum screening for Down's syndrome. [14] Wald NJ et al [1996]	Down Syndrome screening using Pregnancy Associated Plasma Protein, Serum free ?-Human Chorionic Gonadotrophin and maternal age at 10 weeks produce better results than the double test mentioned in [11] and the triple test proposed in[13]
Combining ultrasound and biochemistry. [15] Wald NJ et al [1997]	The serum markers are combined with nuchal translucency measurement and the detection rate improved from 62-80 %. The 62% was obtained by combining free ?-Human Chorionic Gonadotrophin and maternal age.
Assessment of risk of trisomy 21[16] Snijders RJ [1998]	Combining maternal age and nuchal translucency thickness at a gestational age of 10 - 14 weeks achieved a detection rate of about 80% of affected pregnancies.
A screening programme for trisomy 21 at 10-14 weeks.[17] Spencer [1999]	89% accuracy with 5% false positive rate can be achieved by the combination of pregnancy associated plasma protein, maternal serum free beta human chorionic gonadotrophin, maternal age and nuchal translucency.
2nd trimester screening for DS [18] Nyberg DA et al [2001]	The following six markers are identified and evaluated: nuchal translucency thickness, shortened femur, hyperechoic bowel, shortened humerus, renal pyelectasis and echogenic intracardiac focus.
Nasal bone hypoplasia [19]	The presence or absence of nasal bone as a useful

Cicero S et al [2003]	marker for down syndrome at 15 - 22 weeks gestation has been identified.
Fetal tricuspid regurgitation [20] Gustavo et al [2006]	The association of tricuspid regurgitation with the presence of chromosomal defects is studied and the likelihood ratios in fetuses with tricuspid regurgitation for trisomy 21 and trisomy 18 are calculated.
Ductus Venosus in the First Trimester [21] Wee L.K et al [2010]	Relationship between an abnormal flow in the ductus venosus and trisomy 21 is studied.
Internal application of soft markers and maternal serum markers.[22] Ghaffari et al [2012]	The efficiency of the first trimester screening can be improved by combining all these markers Nuchal translucency, tricuspid regurgitation, and ductus venosus along with the maternal serum markers thereby reducing the false positive rate from 4.8% to 3.4%
Fronto nasal fold thickness[23] Gonzalez et al [2013]	The FNF/NBL ratio is also identified as a valuable marker in the detection of Trisomy 21.It has been observed that the FNF/NBL ratio remained constant, with a mean value of 0.68, 0.84 in 95th percentile and 0.90 in the 99th percentile.
Fetal Pinna Measurement [24] Rajanna et al [2016]	A study on the Pinna length measurement and its association with chromosomal disorders has been made. There exists a linear relationship between the pinna length and the gestational age. This study is specifically made on south Indian Population and there is no remarkable difference in the values when compared.

Table: 2 Normal Values for soft Markers

Parameters	Normal Values (mm)	Gestation (weeks)
Nuchal Translucency Thickness[28]	<2.12	10-13
Nasal Bone length (Indian population)[26]	3.3	16
Biparietal length/Nasal Bone Diameter[10]	9.9±1.5	No Change
Biparietal Diameter/ Fronto Nasal fold Thickness [27]	8.1±1.4	No Change
Pinna Length(South Indian Population)[24]	8.1-29.5	15 - 28

region. The boundaries of the nuchal translucency region are determined by Dijkstra's shortest path applied on the edge-enhanced image. Finally, these two region edges are used to define foreground and background seeds for accurate graph cut segmentation. The NT measurement is computed from the segmented region.

The significance of neural networks in feature extraction of ultrasound fetal images has been analysed by Neocleous *et al*[35]. A number of artificial neural network schemes, support vector machines and K- nearest neighbour models are developed and tested which revealed that ANN's outperformed the other networks with 0% false negative rate for T21 and identified 96.1% of euploidies with 3.9% false positive rate. Anjit & Rishidas have utilized the backpropagation artificial neural network for the detection of presence or absence of nasal bone. The features are extracted in spatial domain and transform domain using discrete cosine transforms and wavelet transforms and they are provided an inputs to train a BPN. The results obtained shows higher degree of accuracy in transform domain than spatial domain[36].

Table 3: Performance Measures of various computer aided techniques

S. No	Author	Method	No. of subjects	Accuracy (%)	Sensitivity	Specificity	Detection Rate
1	Andreas C Neocleous	Artificial Neural Networks	129	96			
2	Lai Khin Wee	Cross correlation techniques	107	96.26	97	85.77	
3	A. Khashman	Neural Networks	26	92			
4	C.K. Neocleous	Neural Networks	71		80.3	98.6	78.9
5	Anjit T. A	Neural Networks	50(with nasal bone				86
			50(without nasal bone)				88
6	Eko Supriyanto	Neural Networks	100	93.3			

Table : 4 Segmentation Algorithms for DS markers

Kalpathi R.Subramanian et al [43]	Segmentation by region growing as well as split and merge algorithms with slight variant applied are explored and the results show that upto 50 images can be segmented in 5-6 minutes.
Shazia Anjum et al [44]	Multilevel thresholding and multilevel thresholding with smoothing are compared. The experimental results show that the later one performs better.
Vibhakar Shrimali et al [45]	The femur is separated from the background using morphological operators to obtain a single pixel wide skeleton of the femur. The observed results are consistent and in good agreement with conventional manual method of measurement.
Lalit Gupta et al [46]	The low quality of US images are taken into consideration and therefore the intensity variations of different tissues along with their shape priors are utilized in the optimization function.
Sonia Dahdouh et al [47]	B-spline two dimensional wavelet transform is utilized. Feature vectors are generated for each pixel with the following parameters gray level, moments and texture. These parameters are given as input for fuzzy C means clustering.
Nourhan Zayed et al [48]	The Nuchal translucency region is extracted by region growing segmentation technique based on threshold boundary computation.
Siqing Nie et al [49]	The presence of fetal head in ultrasound images is detected by training a network, the deep belief network and the position as well as size is measured by the use of modified circle detection method.
Angee Paola et al [50]	A hierarchial segmentation technique is adopted, where initially the fetal nose is identified and then the three lines in the nasal region. The presence of nose is recognized using the combination of regional maxima and high eccentricity detection algorithms. The nasal lines using morphological operators and k means clustering algorithms.

Lai KW *et al*[37] has worked out a mathematical model which combines three maternal serum markers using trivariate log normal distribution and automatically calculates the likelihood of having a fetus with down syndrome have been introduced. A semiautomatic measurement of fetal nuchal translucency has been proposed with the development of a software package by Bernardino *et al*[38]. An enhancing diffusion filter has been applied to enhance the border and reduce noise in[39]. The NT is detected by minimization of a cost function that combines intensity, edge strength and continuity using dynamic programming. Fully automatic measurement of biparietal diameter (BPD), abdominal circumference, head circumference (HC), humerus length, femur length and crown rump length has been proposed in[40]. The nuchal translucency thickness varies with gestational age as well as crown rump length. These discrepancies should also be taken into consideration while obtaining normative values for anomaly detection[41] presents a reference value for nuchal translucency thickness with respect to gestational age and crown rump length.

Automated detection of nasal bone has not been much reported so far. Lai Khin Wee *et al* have presented a method to recognize and detect the fetal nasal bone based on 2D ultrasound images using cross correlation techniques. The threshold is set 0.35 for classifying the presence or absence of nasal bone. The accuracy achieved by this technique is 96.26[42].

An important step in feature extraction from ultrasound images is extraction of the region of interest. A number of approaches have been proposed in literatures for efficient segmentation of the underlying region of interest. Table below gives a review of few algorithms proposed for segmentation of ultrasound fetal images.

CONCLUSION

A review on the various soft markers identified for the detection of down syndrome from the first and second trimester ultrasound fetal images has been made. The normal and abnormal values for these markers has been studied. It could be noted from literatures that the diagnostic accuracy can be improved by the combinational analysis of two or more soft markers rather than relying on a single marker alone. A brief survey on few segmentation schemes on ultrasound images has been made.

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