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Role of Second-Trimester Soft Markers for Screening of Down Syndrome

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Abstract

Down syndrome is clinically characterized by mental retardation, birth defects, and specific physical features that are identifiable at birth. Mental retardation ranges from mild to severe with most cases showing a moderate level, to evaluate the effectiveness the second-trimester soft marker sonography combined with biochemical quadriple test screening for prenatal diagnosis of triosmy 21 in patient with risk factor for down syndrome, this is a prospective cohort study that was conducted at Department of obstetrics & Gynecology ,at Benha university hospital, and carried on 80 patients ,Ultrasound was done by voluson 2d and 3d searching for a number of soft markers, that there is high significant correlation between down syndrome and Hyper echogenic fetal bowel, Nasal bone hypoplasia, Mild ventriculomegally and Enlarged cysterna magna. Also there is significant correlation between Down syndrome and Choroid plexus cyst, Intra-cardiac echogenic foci, Single umbilical artery and Mild hydronephrosis, Second-trimester soft markers, especially a thickened nuchal fold, remain important observations in the detection of Down syndrome by sonography among fetuses who have had first-trimester sonographic screening for aneuploidy.

Keywords: Benha, Cohort Down Syndrome, Second-Trimester and Soft Markers,.

1. Introduction

Screening tests are generally evaluated in terms of detection rate [sensitivity], false-positive rate, and odds of being affected given a positive result [OAPR]. These performance-based measures are frequently used to justify particular protocols. However, maximizing options for individual patients must be paramount. Timely transfer of information together with a respect for patients' ethical values, sensitivities, and decision options at every step in the prenatal testing pathway are some of the most important aspects of screening and diagnosis of Down syndrome [1].

Ultrasonography was first used in 1958 by Dr Ian Donald for obstetric imaging. Over the course of the last 50 years, it has become increasingly essential in the practice of prenatal diagnosis and standard practice to recommend to patients that they undergo a screening sonogram between 18 and 22 weeks of gestation [2].

Chromosomal abnormalities occur in 0.1–0.2% of live births. Trisomy 21 [Down's syndrome] is the most common chromosomal abnormality in live-born infants [1 per 800 live births]. Sonographic findings in fetuses with Down's syndrome include both structural and nonstructural markers. However, other aneuploidies like trisomy 13, trisomy 18, monosomy X, and triploidy can also be detected by ultrasound [3].

Many methods have been used to identify women at risk of carrying a fetus with aneuploidy, including maternal age, biochemical markers, prenatal ultrasound and amniocentesis, however, there is a 0.5–1.0% fetal mortality associated with this invasive procedure [4].

A second-trimester ultrasound scan is usually done at 16– 20 weeks. Two types of sonographic markers suggestive of aneuploidy can be observed in the second trimester. Major fetal structural abnormalities and soft markers of aneuploidy are less-defined; less significant and often transient although these markers are not pathognomonic because they may be seen in the normal fetus but they have been used to screen for Down's syndrome and other aneuploidies. Thus, prenatal ultrasonography during the second trimester provides a ''genetic sonogram'' that is used to identify structural features of fetal Down's syndrome [5].

More recently, theoretical models incorporating highly discriminatory soft markers [nuchal-fold thickness, nasal bone length and prenasal thickness] have predicted even higher detection rates [81% for a 5% false-positive rate]. However, correlations between these second- and first-trimester markers have not been described, precluding their incorporation into sequential screening protocols [6].

2. Patients and methods

Type of study: Prospective cohort study. Depaetment of obstetrics & Gynecology, at Benha university hospital. Number of patients is 80 patients were included.

2.1 Inclusion criteria

At risk for down syndrome: any criteria Maternal age > 35 years, Previous child with down syndrome, Family history of down syndrome, Consanguinity, Exposure of parents to toxic chemicals [Suttur S and Nallur B ,2007] 16 -22 weeks gestation.

2.2 Exclusion criteria

Fetus known to have congenital anomalies and multiple pregnancies.

2.3 Methods

Every patient was subjected to Complete history taking with special attention to the personal history [age, consanguinity or special habits], obstetric history [previous trisomy 21], past history [exposed to irradiation or chemicals], menstrual history [gestational age] and family history [previous trisomy 21], Complete general examination and Estimation of quadriple test: Serum human chorionic gonadotropin,

Serum alpha fetoprotein, Serum unconjugated estiol and Serum inhibin-A.

3. Results and discussion

3.1 Results

This table shows that mean maternal age is 42±6.1 with range of [35-48], mean maternal height is 160.9±5.7 with range of [155-172] and mean maternal weight is 70.2±4.2 with range of [62-88] Table [1].

This table showed that Down syndrome represented 18.75% of cases in comparison to 81.25% normal fetusesTable [2]

This table shos that there is significant relation between Down syndrome and Family history of down syndrome, Consanguinity and Previous child with down. Also there is high significant difference between Down syndrome and Maternal age, while there is no significant relation between down syndrome and Exposure of parents to toxic materials Table [3].

This table shows that there is high significant correlation between Down syndrome and Hyperechogenic fetal bowel, Nasal bone hypoplasia, Mild ventriculomegally and Enlarged cysterna magna. Also there is significant correlation between Down syndrome and Choroid plexus cyst, Intracardiac echogenic foci, Single umbilical artery and Mild hydronephrosisTable [4].

This table shows that the greater the number of markers abnormality present, the higher the chance of Down syndrome Table [5].

This table shows that abnormality in More than 2 soft markers is 14 to 15 times more likely to occur in Down syndrome. Also abnormality in Quadriple test is 15 to 16 times more likely to occur in Down syndromeTable [6].

Table (1) Maternal characteristics of the studied cases.

Variable	
Age [Years]:	
Mean ± SD	42±6.1
Range	35-48
Maternal height :	
Mean ± SD	160.9±5.7
Range	155-172
Maternal weight:	
Mean ± SD	70.2±4.2
Range	62-88

Table (2) Frequency of Down syndrome among the studied cases.

Variable		
	N	%
Down syndrome	15	18.75
Normal	65	81.25

Table (3) Distribution of different risk factors on down syndrome and normal cases.

Variable	**Down syndrome N=15**		**Normal cases N=65**		**T test**	**P value**
Maternal age:						
Mean ± SD	44.2±3.2		39.7±2.3		6.32	**<0.001 [HS]**
	No.	**%**	**No.**	**%**	χ^2	
Family history of down syndrome:						
Yes	5	33.3	2	3.1	Fisher test	<0.05
No	10	66.7	63	96.9		[S]
Consanguinity :						
Yes	7	46.7	9	13.8	8.2	<0.05
No	8	53.3	56	86.2		[S]
Previous child with down :						
Yes	6	40.0	10	15.4	4.6	<0.05
No	9	60.0	55	84.6		[S]
Exposure of parents to toxic materials:						
Yes	3	20.0	8	12.3	0.33	0.423
No	12	80.0	57	87.7		

Table (4) Correlation between ultrasound markers and Down syndrome.

Variable	R	P
Choroid plexus cyst	0.48	<0.05 [S]
Intracardiac echogenic foci	0.44	<0.05 [S]
Hyperechogenic fetal bowel	0.64	<0.001 [HS]
Mild hydronephrosis	0.427	<0.05 [S]
Long bone biometry	0.075	0.12
Nasal bone hypoplasia	0.56	<0.001 [HS]
Single umbilical artery	0.245	<0.05 [S]
Mild ventriculomegally	0.513	<0.001 [HS]
Enlarged cysterna magna	0.634	<0.001 [HS]

Table (5) Odds ratio between the number of ultrasound markers and Down syndrome.

Variable	Odds ratio	[95% CI]	p-value
0	0.1	0.0-0.2	0.998
1	10.5	4.2-22.4	<0.05 [S]
≥2	14.3	4-46.7	<0.001 [HS]

Table (6) Logistic regression analysis for prediction of Down syndrome.

	B	Wald	Sig	Exp[B]	95% CI for EXP [B]	
					Lower	upper
More than 2 soft markers	5.76	4.12	<0.001 [HS]	14.3	4	46.7
Quadriple test	6.53	2.33	<0.001 [HS]	15.1	5	51.8

Table (7) The validity of different soft markers in the detection of down syndrome

Variable	Sensitivity%	Specificity %	PVP%	PVN%
Choroid plexus cyst	93.2	91.3	92.1	92.9
Intracardiac echogenic foci	94.1	95.2	94.5	93.1
Long bone biometry	61.2	74.1	70.1	65.2
Hyperechogenic fetal bowel	86.1	85.0	83.1	84.1
Mild hydronephrosis	88.1	89.2	87.2	88.2
Nasal bone hypoplasia	87.3	89.1	88.9	86.8
Single umbilical artery	93.1	92.2	91.1	92.3
Mild ventriculomegally	94.4	95.2	94.9	93.2
Enlarged cysterna magna	95.2	94.1	93.8	94.5

3.2 Discussion

Down syndrome screening has shifted from the second to the first trimester in recent years. First-trimester combined screening offers both better performance and the advantages of providing earlier reassurance or a safer termination of pregnancy, if requiredNevertheless, first-trimester sonography has not obviated the need for a second-trimester scan to exclude major structural defects and other recognizable complications of pregnancy [7].

A second-trimester ultrasound scan is usually done at 18 to 22 weeks. Two types of sonographic markers suggestive of aneuploidy can be observed in the second trimester. Major fetal structural

abnormalities comprise the first type. There are many other, less-defined features that have been given less significance as "possible markers" of aneuploidy, and these are collectively called "soft markers" of aneuploidy. Although not pathologic themselves, these markers have been used to screen for, or adjust the risk for, Down syndrome and other aneuploidies [8].

Soft markers may be seen in the normal fetus but have an increased incidence in infants with chromosomal abnormalities. These markers are nonspecific, often transient, and can be readily detected during the second-trimester ultrasound. Thus, prenatal ultrasonography during the second trimester provides a "genetic sonogram" that is used to identify morphologic features of fetal Down syndrome [3].

This is why the study was selected to be conducted to study the role of second trimester soft markers for screening of Down syndrome on patients admitted to Obstetrics & Gynecology department. Banha University.

The study was prospective cohort study included 80 patients admitted to Obstetrics & Gynecology department. Banha University. The duration of the study had been from 6 to 12 months. The patients are at risk of Down syndrome, maternal age more than 35 years, has previous Down baby, family history of Down syndrome, consanguinity and exposure of parents to toxic chemicals.

The main results of the study were as following:

The mean maternal age is 42±6.1 with range of [35-48], mean maternal heigh is 160.9±5.7 with range of [155-172] and mean maternal weight is 70.2±4.2 with range of [62-88].

L. Li et al., [7] reported that the median age of the pregnant women in our study was 29 [range 12–41] years old, and the procedure was performed at a median of 24 [range 16–35] weeks.

M. Kjersti Aagaard-Tilleryet al., [9] reported that the mean [±SD] maternal age in the study was 30.6±6.1 years, consistent with recent U.S. estimates on the mean maternal age distribution approximating 28 years. Compares the patient characteristics of those who had a genetic sonogram at one of the 13 participating FASTER centers compared with those who were not scanned there. The cohort who received a genetic sonogram at a FASTER center did not differ from the index study population by virtue of mean maternal age [30.6±6.1 compared with 30.1±5.8 years], advanced maternal age, body mass index [25.1±5.2 compared with 25.1±5.3 kg/m2], or obesity [body mass index 30 kg/m2 or greater] .

[10] reported that reported that in the group of euploid fetuses, the 95th percentile for the PT/NB ratio was 0.82. So, we determined the cut-off for a pathologic PT/NB ratio for ratios >0.8. Of the initial 148 fetuses with trisomy 21, 9 had no evaluable profile pictures [6.1%]. In the remaining 139 fetuses, the median gestational age at ultrasound assessment was 21.0 weeks of gestation [range, 14.1–32.6] and the median maternal age was 37.0 years [range, 14–45].

our results show that down syndrome represented 18.75% of cases in comparison to 81.25% normal fetuses.

[11] reported that There were 42 fetuses [0.4% [1/230]] with trisomy 21 identified in the study cohort. Down syndrome was suspected based on sonographic findings at the time of the NT scan in 28 fetuses [67%] and at the second-trimester anatomy scan in 14 [33%].

Our results show that the sensitivity of Choroid plexus cyst is 93.2%, specificity of 91.3%, PVP of 92.1% and PVN of 92.9%, the sensitivity of Intracardiac echogenic foci is 94.1%, specificity of 95.2%, PVP of 94.5% and PVN of 93.1%, the sensitivity of Long bone biometry is 61.2%, specificity of 74.1%, PVP of 70.1and PVN of 65.2%, the sensitivity of Hyperechogenic fetal bowel is 86.1%, specificity of 85%, PVP of 83.1%and PVN of 84.1%, the sensitivity of Mild hydronephrosis is 88.1%, specificity of 89.2%, PVP of 87.2%and PVN of 88.2%, the sensitivity of Nasal bone hypoplasia is 87.3%, specificity of 89.1%, PVP of 88.9%and PVN of 86.8%, the sensitivity of Single umbilical artery is 93.1%, specificity of 92.2%, PVP of 91.1%and PVN of 92.3%, the sensitivity of Single umbilical artery is 93.1%, specificity of 92.2%, PVP of 91.1%and PVN of 92.3%, the sensitivity of Mild ventriculomegally is 94.4%, specificity of 95.2%, PVP of 94.9%and PVN of 93.2%, the sensitivity of Mild ventriculomegally is 95.2%, specificity of 94.1%, PVP of 93.8%and PVN of 94.5%.

[10] reported that among DS [Down syndrome] fetuses the median PT/NB [prenasal skin thickness-to-nasal bone length] ratio was 1.06 [IQR 0.729] and was significantly higher compared to normal fetuses with 0.62 [IQR 0.148], [$p<0.001$]. Gestational age had no influence on the PT/NB ratio. A PT/NB ratio >0.8 had the highest prevalence of all markers with 89.2% in the group of DS fetuses, 3 cases were negative for all markers and 3 cases were positive only for PT/NB ratio >0.8. Marker-specific comparison between prevalences of a suspicious PT/NB ratio with respect to the presence or absence of other markers was statistically significant for hypoplastic NB and major anomalies [$p<0.05$]. Utilization of at least one of the following five markers was sufficient for detecting 136 out of 139 fetuses with trisomy 21: suspicious PT/NB ratio, hypoplastic NB, nuchal fold thickness, white spot, shortened femur.

[12] reported that femur and humerus length MoM values were highly correlated in the 25 Down syndrome pregnancies with both measurements [r0.57] and the 3,777 unaffected pregnancies [r0.76]. For this reason and because humerus length was not recorded in approximately half the pregnancies, only the femur length MoMs were used in the calculation of risk. The means and log10 standard deviations of femur length were 0.94 and 0.034 MoM in Down

syndrome and 1.00 and 0.030 MoM in unaffected pregnancies. The detection rates of the genetic sonogram alone, for a fixed 1– 8% false-positive rate, were 39% [23/59], 49% [29/59], 59% [35/59], 66% [39/59], 69% [41/59], 75% [44/59], 80% [47/59], and 83% [49/59]. The detection and false-positive rates for a 1 in 270 midtrimester risk cutoff were 83% [49/59] and 12% [922/7,783].

[13] reported that among the 1913 patients, an ARSA [aberrant right subclavian artery] was detected in 20 fetuses [1.04%], all with a normal karyotype. Thirteen of 20 fetuses had an isolated ARSA, and 7 of them were nonisolated. Associated abnormal sonographic findings were an intracardiac echogenic focus [n = 3], a choroid plexus cyst [n = 1], pyelectasis [n = 1] and tetralogy of Fallot [n = 2]. One of the cases of tetralogy of Fallot was also associated with a persistent left superior vena cava, a persistent right umbilical vein, hydrocephalus, rhombencephalosynapsis, and unilateral renal agenesis. There were only 2 fetuses with Down syndrome in this group, and both of them had a normal origin of the right subclavian artery.

Our results show that there is high significant correlation between Down syndrome and Hyperechogenic fetal bowel, Nasal bone hypoplasia, Mild ventriculomegally and Enlarged cysterna magna. Also there is significant correlation between down syndrome and Choroid plexus cyst, Intracardiac echogenic foci, Single umbilical artery and Mild hydronephrosis.

A. Hagen et al. [10] reported that in 52 fetuses [37.4%], we found major anomalies. In 50 cases we detected heart defects, partially in combination with other structural abnormalities. In the group of heart defects, 29 fetuses [58.0%] had an atrioventricular septal defect. In all cases with PT/NB ratio >0.8, pyelectasis and echogenic bowel did not increase the detection rate and gave no further information.

J. Miguelez et al., [12] reported that second-trimester scan was performed from 18 to 19 + 6 weeks in 20.9%, from 20 to 21 + 6 weeks in 71.2% and from 22 to 22 + 6 weeks in 7.9% of cases. All MoM-converted continuous-variable medians [nasal bone length, femur length, humerus length, largest renal pelvis, prenasal thickness and nuchal-fold thickness] were close to 1.0 and fitted a log-normal distribution as assessed by histograms and QQ plots. A statistically significant correlation between log NT-MoMs and all second-trimester continuous variables was found. The Pearson correlation coefficient was then calculated for each variable. This was low in all cases ,the highest being that of nuchal-fold thickness [r = 0.10].

TK. Lau et al., [14] argued that second-trimester sonographic screening programs should focus on the evaluation of a few strong markers. Most soft markers are too weak or subjective to be useful in the post first-trimester screening era. **[9]** reported that a total of 7,842 pregnancies were studied, including 59 with Down syndrome. Major malformations and 8 of the 18 soft markers evaluated were highly significant. The detection rate for a 5% false-positive rate for the genetic sonogram alone was 69%; the detection rate increased from 81% to 90% with the combined test, from 81% to 90% with the quadruple test, from 93% to 98% with the integrated test, from 97% to 98% with the stepwise test, and from 95% to 97% with the contingent test. The stepwise and contingent use of the genetic sonogram after first-trimester screening both yielded a 90% detection rate.

The results from this study suggest that modifying first-trimester Down-syndrome risk by using fixed likelihood ratios derived from the second-trimester genetic sonogram findings may lead to inaccurate estimates. This calculation depends critically on the assumption that the first-trimester markers and the anomaly scan results are independent predictors of risk. The fact that the presence of soft markers was twice as common in cases with increased NT implies that this assumption is incorrect [12].

The second-trimester anatomic scan in conjunction with the identification of soft markers is a routine part of obstetric care and until recently was the primary method of risk assessment for aneuploidy [7] .

Our results show that abnormality in More than 2 soft markers is 14 to 15 times more likely to occur in Down syndrome. Also, abnormality in Quadriple test is 15 to 16 times more likely to occur in Down syndrome.

In conclusion, Second-trimester soft markers, especially a thickened nuchal fold, remain important observations in the detection of Down syndrome by sonography among fetuses that have had first-trimester sonographic screening for aneuploidy.

4. Conclusion

Second- trimester soft markers, especially a thickened nuchal fold, remain important observations in the detection of Down syndrome by sonography among fetuses who have had first- trimester sonographic screening for aneuploidy.

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