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Evaluation of sensitivity and accuracy of maternal serum alpha fetoprotein to the diagnosis of open spina bifida in comparison with sonographic findings of open spina bifida and Chiari II malformation in pregnant women

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Abstract

Background: NTD is one of the most important problems of the nervous system and the second fetal anomaly that is associated with high mortality and morbidity. Therefore, its prenatal diagnosis is very important. AFP has a high false positive, which reduces its diagnostic value, so the discovery of ultrasound findings in OSB is very important and can replace AFP testing.

Results: 4 patients with positive OSB were detected and their diagnosis was confirmed during pathological follow-up (100% diagnostic accuracy) and the rest of the patients with high AFP (51 patients) were negative for OSB. Therefore, the diagnostic accuracy of AFP during statistical analysis was about 7%, which is a very low value.

Conclusion: According to the results of this study, IT, BS, BSOB, BS/BSOB ultrasound criteria in the first screening and decreased BPD and ventriculomegaly in the second screening ultrasound in OSB diagnosis have a higher diagnostic value than the AFP laboratory level. It should pay more attention to MS-AFP results in OSB screening.

Keywords: Serum maternal alpha-fetoprotein, Sonographic markers, Screening, Open spina bifida

Background

An open neural tube defect (ONTD) occurs in 1 per 3000 live births in the United States and results from failure of the posterior neural tube to close during the third and fourth weeks after conception [1]. The clinical consequences of ONTD depend on the site and severity of the defect and any associated motor and sensory neurological deficits, with less than 50% of affected individuals able to live independently as adults [1, 2]. Fetal alpha fetoprotein is synthetized in the fetal liver and diffused in maternal serum across the placenta and the amnion [3, 4]. Alpha fetoprotein is found in cerebrospinal fluid (CSF) in high concentrations [4], and as a result of leakage of CSF through the spinal defect, both amniotic fluid and maternal serum alpha fetoprotein (MSAFP) are usually elevated in pregnant women carrying a fetus with an ONTD. MSAFP is also used to screened other conditions including multiple gestation, fetal abdominal wall

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defects, fetal nephrosis, fetal demise and placental conditions that increase risk of adverse events [5–10].

Mid-trimester MSAFP and sonographic evaluation have been used to screen for spina bifida [2, 11]. However, with the increased popularity of first trimester cell free-DNA screening, and improvements in ultrasonography, the role of MSAFP levels may become redundant [2].

Spina bifida is a congenital malformation belonging to the larger category of neural tube defects with a reported incidence of 1 to 1000 births [12]. It is the most common central nervous system (CNS) malformation compatible with life, represented by the lack of dorsal closure of the vertebrae which lack neural arches and may be located at any level along the spine. These defects can be classified into closed when the spinal defect is skin covered (spina bifida occulta) or open (spina bifida aperta) when the lesion site is not covered by skin and involves abnormalities of the meninges and/or the spinal cord (meningocele/myelomenigocele). Spina bifida aperta is frequently associated with Chiari type IImalformation, which is an abnormality of the posterior fossa characterized by the herniation of the cerebellum and brainstem through the foramen magnum [13]. Also, due to mechanical obstruction, it is often associated with ventriculomegaly [14, 15]. Prenatal ultrasonography (US) represents the gold standard in fetal neural defects evaluation and diagnosis, whereas fetal magnetic resonance imaging (MRI) is used to refine the diagnosis [16].

The overall aim of this study was to compare the diagnostic accuracy between serum AFP levels of maternal blood and open NTD sonographic signs in the detection of OSB in prenatal screening.

Methods

This a cross-sectional study conducted in Besat hospital, Tehran, Iran from April 2018 to April 2019. It is the study of pregnant woman that referred for sonographic detection of fetal anomaly was enrolled. Exclusion criteria were detection of trisomy, dandy walker and other abnormalities other than OSB in the fetus, failure to perform pregnancy AFP test and patient obesity that prevents accurate examination of sonographic markers. In this study, all pregnant women who referred for screening, after taking informed consent, maternal age, co-morbidity, history of abortion, gestational age by LMP, consanguineous marriage, first screening ultrasound report (if seen in second trimester) and AFP level were taken. Then, in the ultrasound examination of the fetus, the symptoms of Chiari II were considered according to the screening stage and the age of the fetus. The presence of IT, the presence of CM, BS diameter, BSOB diameter, BS/BSOB ratio, the presence of ventriculomegaly, BPD and its comparison with fetal age were evaluated and then followed by birth or abortion. For the statistical analysis, the statistical software SPSS version 20.0 for windows (SPSS Inc., Chicago, IL) was used. The results were obtained from the study were analyzed using statistical methods (mean ± standard deviation (SD) for quantitative variables and frequencies and percentages for categorical variables).

This study had been approved by research ethics committee of army university of medical science (IR.AJAUMS.REC.1400.190).

Results

In this study, 55 pregnant women were surveyed, out of 55 people in the research unit, 51 people (93%) did not have OSB and 4 people (7%) had it. According to the AFP variable, all 55 people have it. All OSB-positive patients had high AFP. 2 of these patients were detected in the first screening and 2 in the second pregnancy screening. After legal abortion and sending the fetus to the pathology, these patients were followed up by telephone. The pathology results based on positive OSB were consistent with the sonographic findings and the existence of OSB was confirmed. One of the OSB-positive patients also had triploidism. The values for the rest of the research variable, clinical and sonographic characteristics are listed in Tables 1 and 2.

In this study for rised AFP accuracy and sensitivity was 0.073 and PPV was 1.00. Statistical analysis of sonographic parameters is showed in Table 3. As can be seen, the percentage of diagnostic accuracy of the increased BS 'obliterated IT' Decreased CM 'Decreased BSOB' 'Increased BS/BSOB' in the detection of OSB in the first trimester is 100%, which is a very strong and high value.

Out of 55 patients, 51 patients had negative OSB test results in which the maternal age was 29.229 5 5.259. There were also 4 patients with positive OSB test in whom the mother age was 29.000 6 6.227. Based on the results of independent *t*-test: The relationship between maternal age during pregnancy and OSB in the fetus at 95% confidence level is not significant due to the fact that the significance level of independent

Table 1 Sonographic parameters

Variables	Range (min–max)	Mean	SD
AFP	1.98–5.81	3.0225	.77866
CM	0.5–6.7	4.295	1.3629
BS	2–5.1	2.304	.4247
BSOB	3.5–1.7	3.183	.2744
BS/BSOB	0.6–1.8	.7266	.21557
Maternal age (y)	18–39	29.87	5.278
Fetal age (w)	12–20	17.11	2.492

Table 2 Characteristics of patients and sonographic parameters

	***N* (%)**
OSB	
Positive	4 (7.3%)
Negative	51 (92.7%)
History of abortion	
Positive	13 (23.6%)
Negative	32 (58.2%)
Acid folic use	
Positive	33 (60%)
Negative	3 (5.5%)
Consanguineous marriage	
Positive	1 (1.8%)
Negative	32 (58.2%)
Gestational diabet	
Positive	1 (1.8%)
Negative	54 (98.2%)
Normal IT	
Positive	51 (92.7%)
Negative	4 (7.3%)
Obliterated CM	
Positive	51 (92.7%)
Negative	4 (7.3%)
Increased BS	
Positive	51 (92.7%)
Negative	2 (3.6%)
Decreased BSOB	
Positive	51 (92.7%)
Negative	2 (3.6%)
Increased BS/BSOB	
Positive	51 (92.7%)
Negative	2 (3.6%)
Ventriculomegalia	
Positive	52 (94.5%)
Negative	3 (5.5%)
Decreased BPD	
Positive	0 (0%)
Negative	55 (100%)

t-test is greater than 5% (0.735) and the mean maternal age during pregnancy in both groups Positive and negative OSB test are close to each other and there is no significant difference between them. Therefore, the relationship between maternal age during pregnancy and the incidence of OSB in the fetus is not confirmed ($P > 0.05$). Other relation is showed in Table 4.

Discussion

NTD, including open spina bifida, is one of the most important congenital fetal anomalies that have high morbidity and mortality, so early detection during fetal screening is very important to decide on its future. Choosing the right screening method depends on many factors such as financial cost, time cost, accuracy and sensitivity of the measurement method, availability and safety of the measuring tool, and so on. Laboratory evaluation of maternal blood AFP levels is one of the most common and oldest methods of screening for CNS anomalies, which also has a high number of false positives, and therefore the study of alternative methods is important. Therefore, the study and research on ultrasound symptoms of open spina bifida in embryonic screening, including the symptoms of Chiari II, has recently been studied.

In this study, we examined the significance between high maternal blood AFP and OSB incidence, so the percentage of diagnostic accuracy of maternal blood AFP in OSB detection was 7%, which is a very weak value.

In the study of other variables and their relationship with OSB, the variables obliterated IT, decreased CM, decreased BSOB, increased BS, BS/BSOB increased and decreased BPD, ventriculomegaly have a significant sensitivity 'specifity' PPV NPV and accuracy.

And we showed that acid folic use had statistically significant relationship with OSB, while this was not the case for maternal age, fetal age, gestational diabetes, and consanguineous marriage.

In a study conducted by Wertaschnigg et al. In Australia in 2019 on the ultrasound signs of OSB in the first trimester, 1003 control samples and 27 cases of OSB on sonographic features were studied and it was concluded that MO and BS/BSOB were the best sonographic markers. For the diagnosis of OSB in the first trimester, the significance of the BS/BSOB variable was similar to our study [17].

In another study, Teegala et al. Conducted an OSB in India in 2017 to examine IT as an ultrasonic marker, during which the first and second trimester sonographic findings were evaluated. In this study, 5 IT cases were detected and in all 5 cases, OSB was discovered and it was concluded that the IT view is a reliable criterion in the first trimester for OSB detection [18]. In our study similar to this study, a significant relationship was found between IT and OSB visibility.

In 2017, a study was conducted in Turkey by Kose on 1479 pregnant women to observe post fossa changes for early diagnosis of OSB in the first trimester. In this study, the landmarks of CM, BSOB, IT and BS were examined and mothers were followed up until the birth of the baby. Two cases of OSB were detected in the infants of these mothers. In these two patients, Landmark CM, BS, BSOB were 100% sensitive and in both patients was impaired and IT was impaired in one of the patients and CM had the highest specificity for OSB (99.9%) of these markers,

Table 3 Accuracy, sensitivity, specificity, PPV, NPV of sonographic parameters

	OSB						
	Positive	**Negative**	**Accuracy**	**Sensitivity**	**Specifity**	**PPV**	**NPV**
Rised AFP							
Positive	4	51	0.073	0.073	–	1.00	0.00
Negative	0	0					
Normal IT							
Positive	0	51	1.00	1.00	1.00	1.00	1.00
Negative	4	0					
Decreased CM							
Positive	4	0	1.00	1.00	1.00	1.00	1.00
Negative	0	51					
Increased BS							
Positive	2	0	1.00	1.00	1.00	1.00	1.00
Negative	0	51					
Decreased BSOB							
Positive	2	0	1.00	1.00	1.00	1.00	1.00
Negative	0	51					
Increased BS/BSOB							
Positive	2	0	1.00	1.00	1.00	1.00	1.00
Negative	0	51					
BPD decrease							
Positive	0	0	0.927	–	0.927	0.00	1.00
Negative	4	51					
Ventriculomegalia							
Positive	2	2	0.945	0.667	0.962	0.5	0.98
Negative	1	50					

Table 4 Relation between OSB and qualitative variables

	OSB		
	Negative	**Positive**	***P*-value**
Maternal age	29.94 (± 5.259)	29 (± 6.272)	0.735
Fetal age	17.24 (± 2.43)	15.5 (± 3.109)	0.182
Gestational diabetes			
Positive	1	0	0.77
Negative	50	4	
Abortion			
Positive	12	1	0.86
Negative	30	2	
Acid folic use			
Positive	32	1	0.000
Negative	1	2	
Consanguineous marriage			
Positive	1	0	0.748
Negative	29	3	

which were significant results of BSOB, BS, and CM [19]. this is similar to our study.

A 2016 study by Dr. Pascal et al. In the Department of Neuroscience in Italy examined the accuracy of the IT marker in diagnosing OSB in the first trimester. In this study, the results of 9 separate studies were evaluated, which included 21,070 embryos, and IT was evaluated in all of these embryos. In this study, IT sensitivity of 53.5% and specificity of 99.7% were obtained and it was concluded that due to low sensitivity, IT alone is not a good criterion for diagnosing OSB in the first trimester of pregnancy and more studies are needed to discover the sonographic landmark. It is more appropriate to diagnose OSB in the first trimester [20] but in our study a significant relationship was found between IT visibility and OSB.

In a 2017 study by Moradi et al. at Tehran University of Medical Sciences on the distribution and anomalies associated with NTD by prenatal ultrasound in Iranian fetuses. In this study, the highest risk factor was associated with incomplete consumption of folic acid (45%) and then consanguineous marriage. Accompanying anomalies were detected in 66% of fetuses, most of

which (90%) were in fetuses with spina bifida. Finally, it was important to conclude that ultrasound is the non-invasive and safe selective modality for detecting prenatal NTD with the utmost accuracy. The accuracy of NTD detection with ultrasound also depends on the type of NTD and the age of the fetus at the time of ultrasound. For example, SB detection is 40% in the first trimester and 92% to 95% in the second trimester. The accuracy of ultrasound to detect OSB in this study was 100% [21]. In our study, the accuracy of ultrasound diagnosis in the detection of fetal OSB was similar to this study was 100%.

A 2019 study by Palomaki et al. On laboratory tests for ONTD at the American Society of Medical Genetics found that increased MS-AFP levels at 16 weeks' gestation were 80% more sensitive to OSB and 95% more sensitive to diagnosis. Has anencephaly and stated that determining the level of AFP and acetylcholinesterase in the amniotic fluid followed by targeted ultrasound is the diagnostic method of choice in the detection of ONTD [22].

In the American Journal of Pregnancy and Gynecology in 2014, a page was published by Dr. Spencer that evaluated various studies examining the role of serum AFP levels in OSB screening at weeks 11 to 13 and concluded that few studies supported the study of indexes. Laboratories such as AFP and BHCG are available for OSB screening in the first trimester, and these two indexes cannot compete with OSB sonographic criteria such as fruit sign, IT review, and evidence of BPD reduction and are of lower value [23]. In our study, the diagnostic accuracy of AFP was 7%, which is a very low value.

In a study conducted in 2019 by Sirico A et al. On the BS/BSOB criterion in the diagnosis of OSB in the first trimester, 23 positive OSB cases were detected [24]. In our study, this criterion was seen with high sensitivity and specificity.

Conclusion

In this study, we showed that the AFP has low diagnostic accuracy for diagnosis OSB and many false positive results are seen, and it was also shown that the mentioned ultrasound parameters have high accuracy, sensitivity and specificity in diagnosis OSB. As a result, it should be borne in mind that the mere use of AFP for screening is not useful and causes stress in mother and additional costs.

Abbreviations

MS-AFP: Maternal serum alpha feto-protein; IT: Intracranial translucency; BS: Brain stem; BSOB: Brain stem to occipital bone; MO: Maxillo-occipital line; AOS: Aqueduct to occipital bone diameter.

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Author contributions

Dr RG performed sonographic study on all patients and recorded data related to ultrasound information. Dr TA extracted all non-sonographic information from patients by interview. SB and Dr JK analyzed interpreted the patient data. All authors read and approved the final manuscript.

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Availability of data and materials

The authors declare that they had full access to all of the data in this study and the authors take complete responsibility for the integrity of the data and the accuracy of the data analysis. The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Ethics committee of AJA University of Medical Sciences (IR.AJAUMS.REC.1400.190) approved this descriptive cross-sectional study.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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