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Correlation Between Fetal Central Nervous System Anomalies With Increased Lateral Ventricle Size

Lateral Ventrikül Boyutundaki Artış İle Fetal Merkezi Sinir Sistemi Anormallikleri Arasındaki Korelasyon

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Abstract

Introduction: Ultrasonographic evaluation of the width of the lateral cerebral ventricles during the routine anomaly scan is recommended. The purpose of this study is to establish the correlation between lateral ventricle size and central nervous system(CNS) anomalies at 16-28 weeks of gestation.

Methods: 1875 pregnant women at 16–28 gestation weeks who have admitted to our clinic between 2015–2016 were involved in this retrospective study. Fetal lateral ventricles were measured bilaterally at the level of the choroid plexus glomus. The widths of the left and right ventricles were compared with gestational age, maternal age and presence of CNS anomalies. The relationship between ventricular asymmetry, isolation and other ultrasonographic anomalies was also analyzed.

Results: There was no statistically significant difference between maternal age, gestational age and fetal sex with CNS anomalies and ventricular width ($p>0.05$). The presence of CNS anomalies appeared to be strongly related to the size of the lateral ventricle ($p<0.001$). In the ROC curve analysis, cut-off values of the right and left ventricular widths for detecting CNS anomalies were found to be 9.25 mm (61% sensitivity and 98.7% specificity) and 9.15 mm (68.3% sensitivity and 97.4% specificity), respectively. 37.5% (n=15) of cases with ventriculomegaly were diagnosed with isolated ventriculomegaly and 42.5% (n=17) of ventriculomegaly cases were found to be asymmetric. 2.1 %(n=41) of all cases had other ultrasonographic abnormalities coexisting with CNS anomalies.

Conclusion: Ventriculomegaly can be a prognostic indicator for CNS abnormalities. Pregnancy follow-up examinations should involve the width of the both lateral cerebral ventricles. Further investigations to determine the cut-off value of the lateral ventricle size should involve the postpartum period as well..

Keywords: Central nervous system abnormalities, fe-

tal cerebral ventriculomegaly; prenatal ultrasonography.

Öz

Giriş: Rutin anomali taraması sırasında lateral serebral ventriküllerin genişliğinin ultrasonla değerlendirilmesi önerilmektedir. Bu çalışmada 16-28 gebelik haftasında lateral ventrikül boyutları ile merkezi sinir sistemi (MSS) anormallikleri arasındaki ilişkinin saptanması amaçlanmıştır. Yöntem: Bu retropektif çalışmaya 2015-2016 yılları arasında kliniğimize ileri tetkik için başvuran 16-28 gebelik haftasındaki 1875 kadın dahil edildi. Fetal lateral ventriküller koroid pleksus glomus seviyesinde bilateral olarak ölçüldü. Ventriküllerin genişliği gestasyonel yaş, anne yaşı ve MSS anomalilerinin varlığı ile karşılaştırıldı. Ventriküler asimetrisite, izolasyon ve diğer ultrasonografik anomalilerle olan ilişki de analiz edildi. **Bulgular:** Anne yaşı, gestasyonel yaş ve fetal cinsiyet ile MSS anomalileri ve ventrikül genişliği arasında istatistiksel olarak anlamlı farklılık bulunmadı. (p>0.05). MSS anomalilerinin varlığı ile lateral ventrikülün büyüklüğü arasında kuvvetli bir ilişki saptandı (p<0.001). ROC eğrisi analizinde MSS anomalilerini saptamada anlamlı sağ ve sol ventrikül genişliğinin cut-off değerleri sırasıyla 9,25 mm (sensitivite % 61 ve spesifite % 98,7) ve 9,15 mm (sensitivite % 68,3 ve spesifite % 97,4) bulundu. Ventrikülomegali olan olguların %37.5'inde(n=15) izole ventrikülomegali ve %42,5'ünde(n=17) asimetrik ventrikülomegali saptandı. Tüm vakaların %2,1'inde(n=41) MSS anomalileri ile birlikte diğer ultrasonografik anormallikler saptandı. **Sonuç:** Ventrikülomegali MSS anomalileri için prognostik bir gösterge olabilir. Gebelik takibi sırasındaki kontrol muayenelerde her iki lateral serebral ventrikül genişliği de ölçülmelidir. Lateral ventrikül büyüklüğü cut-off değerinin belirlenmesi için ileri araştırmalara postpartum dönemi de dahil edilmelidir.

Anahtar Kelimeler: Fetal serebralventrikülomegali, merkezi sinir sistemi anormallikleri, prenatal ultrasonografi.

Introduction

Central nervous system (CNS) anomalies are frequently seen among the congenital malformations. Evaluation of the atrial width of the lateral cerebral ventricles is recommended during routine anomaly scan with ultrasonography (1). Ventricle diameter remains stable throughout the 14-38th weeks of pregnancy with a mean of 5.4 to 8.2 mm (2). Fetal ventriculomegaly (VM) is defined as a dilation of cerebral ventricles and it can be diagnosed at the time of second trimester ultrasound evaluations (3). VM is classified as mild (10-11.9mm), moderate (12-14.9 mm) and severe ventriculomegaly (≥15mm) (1). In some studies 'borderline ventriculomegaly' is used as synonym with 'mild VM'. VM is called isolated if there is no concomittant malformations or markers of aneuploidy at the time of diagnosis (2,4,5). Isolated VMs mostly have a better prognosis (6). VM may also be associated with chromosomal abnormalities, congenital infections and other fetal cerebral and extra cerebral anomalies. It may also have long-term neurodevelopmental consequences (2). The incidence of VM identified on sonography is less than 2%, varying between 0.3 and 22 per 1000 births (7). It can be isolated or associated with fetal central nervous system anomalies. The prognosis of ventricular dilation varies and depends on the degree of dilation and the presence of associated cerebral or extracerebral abnormalities (8). The sonographic assessment of the cerebral ventricles has been the object of many studies and several different approaches to the definition and diagnosis of fetal ventriculomegaly have been proposed. It is aimed to investigate the association between both lateral ventricular diameters and central nervous system anomalies in this study.

Materials and Methods

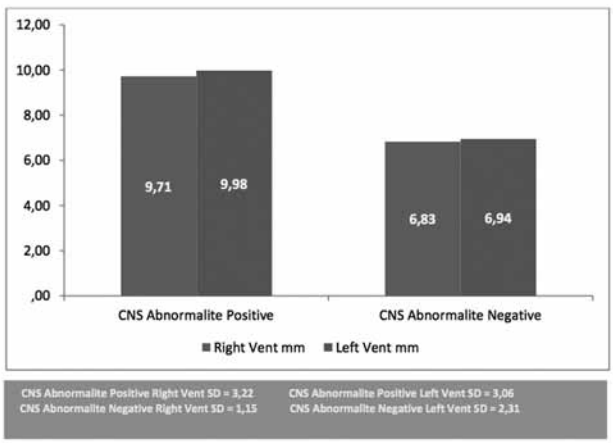
Medical records of 1875 eligible pregnant women at 16-28 gestational weeks without any known risk factors for fetal CNS anomalies and lateral ventricul diameters were analyzed. All ultrasonography evaluations have been performed by a single operator in a single tertiary center between 2015 and 2016 for routine prenatal management. Approval from the local ethics committee and informed consent from all patients were obtained. Gestational week, maternal age and fetal sex were recorded in all patients and ultrasonographic datas were recorded. Patients who had positive serological results for TORCH infections were excluded. Both lateral ventricles of all fetuses were measured transabdominally with a multifrequency (4- to 12-MHz) probe of the Voluson S-8 (GE Medical Systems, Zipf, Austria) sonography.For each fetus, both lateral ventricles were measured in axial plane, at the level of the frontal horns and cavum septi pellucidi with the calipers positioned at the level of the internal margin of the medial and lateral wall of the atria, at the level of the glomus of the choroid plexus, on an axis perpendicular to the long axis of the lateral ventricle as recommended by the guidelines for sonographic examination of the fetal central nervous system (1).Ventriculomegaly was considered as

mild at 10–11.9 mm, moderate at 12–14.9 mm and severe if measurement was ≥ 15 mm. Asymmetry was defined with a difference of 2 mm or more between the two lateral ventricles. The width of the measured ventricles and CNS anomalies was compared and statistically analyzed by using the Statistical Package for the Social Sciences software, Version 17.0. Correlation analysis was used to examine the relationship among ventricle width and CNS findings.

Results

This study is carried out on 1875 pregnancies in any weeks of gestation. The ventricular sizes of patients with and without fetal CNS abnormalities were compared. The statistical analyses showed that ventricular diameter is higher in patients with CNS anomalies (Graph 1).

Graph 1: Association of lateral ventricle width with CNS abnormalities



The median gestational age at ultrasonographic examination was 21 weeks (SD:2.45). The maternal age ranged from 16 to 52 with the mean age of 30 years (SD:4.8). There was no statistically significant difference between ventricle width in terms of maternal age (p=0.310), gestational age (p=0.674) and fetal sex (p=0.510) and they were not found to be associated with CNS anomalies. Mean size of ventricle for the rigth ventricle was 6.88±1.3 mm, and for the left ventricle it was 7.00±2.36 mm. Right and left ventricular sizes are shown in two separate charts with nomograms at 5th, 50th and 95th percentiles correlated with gestational age (Table 1, Table 2).

Table 1: Mean and percentile values for left ventricle at different gestational ages

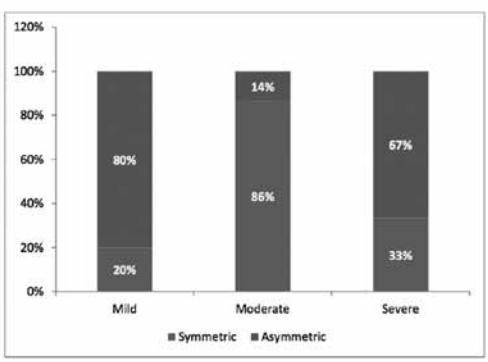
Gestational age	Left Vent mm		Percentiles		
	Mean	Standard Deviation	5	50	95
16	6.34	1.05	4.8000	6.3000	.
17	6.57	1.29	5.0250	6.5000	8.6000
18	7.25	4.63	4.9000	6.8000	9.2400
19	6.97	1.31	5.3000	6.8000	8.9000
20	7.15	4.34	5.3000	6.8000	8.6000
21	7.03	1.25	5.4000	7.0000	8.8050
22	6.95	1.10	5.3000	6.9000	8.7000
23	6.92	1.25	5.3000	6.8000	8.9000
24	6.88	1.17	5.0000	6.9000	9.0950
25	7.47	2.17	4.7100	7.3000	10.2300
26	7.21	1.57	4.9750	6.8500	9.8000
27	6.92	2.00	4.5800	6.3000	12.6500
28	6.99	1.77	4.3200	6.9500	10.6650
Total	7.01	2.37			

Table 2: Mean and percentile values for right ventricle at different gestational ages

Gestational age	Right Vent mm		Percentiles		
	Mean	Standard Deviation	5	50	95
16	6.28	1.10	4.3000	6.2000	.
17	6.51	1.25	5.0250	6.4000	8.7000
18	6.85	1.39	4.8600	6.8000	8.5700
19	6.97	1.31	5.1000	6.9000	8.8000
20	6.92	.98	5.5000	6.8000	8.6000
21	6.98	1.38	5.2000	6.9000	8.9000
22	6.85	1.11	5.3000	6.8000	8.5650
23	6.82	1.15	5.1000	6.8000	8.7000
24	6.86	1.10	5.2000	6.7500	8.7000
25	7.26	2.38	4.5000	7.0500	11.3600
26	7.13	1.59	4.9000	6.9500	9.5250
27	6.78	1.56	4.6000	6.4500	10.5250
28	6.68	1.65	4.1150	6.9000	9.2950
Total	6.89	1.30			

37.5% (n=15) cases were diagnosed with isolated ventriculomegaly. 42.5%(n=17) of ventriculomegaly cases were found to be asymmetric. Among cases with lateral ventricle size 10-11.9 mm (mild VM), the prevalence of CNS abnormalities was significantly higher in asymmetric ventriculomegaly compared with symmetric ventriculomegaly. The prevelance of CNS abnormalities was higher in symmetric ventriculomegaly compared to asymmetric ventriculomegaly when ventricle size is 12-14.9 mm (moderate VM) (Graph 2).

Graph 2: Association of CNS anomalies with mild-modarete-severe VM in terms of symmetricity. Because there were 4 patients with severe VM, the statistical analysis is not valuable for clinical practice.



2.1 % (n=41) of all cases were in association with other ultrasonographic abnormalities of CNS anomalies. Among those, hydrocephalus was the most common CNS abnormality. Distribution of CNS anomalies according to ventriculomegaly severity is shown by Table 3.

Table 3: Distribution of CNS anomalies according to ventriculomegaly severity

CNS	Ventriculomegaly			
	Normal (n%)	Mild (n%)	Moderate (n%)	Several (n%)
Anencephaly	.0%	.0%	5.3%	.0%
Arnold Chiari Malformation - Cerebellar Pathologies	.0%	12.5%	5.3%	.0%
Choroid Plexus Cyst	82%	12.5%	10.5%	.0%
Dandy walker	.0%	.0%	.0%	.0%
Encephalocele	2.2%	.0%	.0%	.0%
Hydrocephalus	5.6%	62.5%	42.1%	.0%
Cystic hygroma	2.2%	.0%	.0%	.0%
Mega Sisterna Magna	2.2%	.0%	.0%	.0%
Meningocele meningomyolocele	1.1%	,0%	15.8%	.0%
spina bifida	4.5%	12.5%	21.1%	100%
Total	100%	100%	100%	100%

There was statistically significant relationship between ventriculomegaly and CNS abnormalities (P < 0.001). The percentages of CNS anomalies of mild, moderate, and severe VM were 17.1%, 41.5%, and 2.4%, respectively. Cut-off value for right ventricle was 9.25 mm with 61% sensitivity and 98.7% specificity (p<0.001) and 9.15 mm for left ventricle with 68.3% sensitivity and 97.4% specificity, respectively (Table 4) .

Table 4: Cut-off values of right and left ventricles to discriminate CNS anomalies

	Cut-off value (mm)	Sensitivity	Specificity	AUC±SE.	%95 CI (min-max)	P Value
Right ventricle	9.25	61%	98.7%	0.752±0.057	0.640-0,864	<0.001
Left ventricle	9.15	68.3%	97.3%	0.780±0.058	0.666-0,893	<0.001

AUC: Area under curve SE: Standard Error

Discussion

A large number of detailed anomaly scan with ultrasonography at any week of gestation revealed that the presence of CNS anomalies are strongly related with both lateral ventricle size (p<0.001) as in our study. This study suggests the cut-off lateral ventricle diameters that may be correlated with CNS anomalies to be 9.25 mm for right and 9.15 mm for the left lateral ventricle. This study presents also the percentile values (5th, 50th and 95th) of lateral ventricles with regard to the gestational age in a very large sample. Our relatively low sensitivity may be explained by heterogeneous distribution of the number of the cases for different gestational ages and low amount of CNS anomalies.

Perinatal mortality and morbidity increases with the presence of VM. Early diagnosis allows identification of additional pathologies and enables the pregnancy termination option (9).Cerebral malformations can be seen concomitant with ventriculomegaly, particularly with severe VMs. Tatlı et al found a 9% of additional anomaly incidence if the ventricular width was 10-15 mm (10). An MRI-based study found that the anomaly risk of CNS findings is strongly related to the width of the ventricle and have demonstrated that the width of both ventricles were positively associated with an increased number of CNS anomalies (11).Current study showed that the presence of CNS anomalies is closely related to the width of the lateral ventricle. The association between CNS anomalies and ventricul diameter stresses the importance of investigation of fetal ventriculomegaly. In a study of Barzilay et al therewerenoanystatisticallysignificantdifferencebetween maternal age, fetal sex, gestational age and ventriculomegaly and CNS anomalies. Its was also found that symmetric ventriculomegaly was associated with CNS findings more than asymmetric ventriculomegaly. This difference was apparent in mild and moderate ventriculomegaly, while the rates of minor and major CNS findings were similar between symmetric and asymmetric severe ventriculomegaly (11).Maternal age did not differ significantly between cases with or without ventricle asymmetry or among cases of mild, moderate, and severe ventriculomegaly. Similarly, maternal age and VM and CNS abnormalities were not statistically significant in our study (p=0.074). There was no difference in terms of median gestational age and fetal sex between cases with or without ventricle asymmetry or among cases of mild, moderate, and severe ventriculomegaly as its in our study (p<0.005). We also found similar results for severe VMs.

Several studies demonstrated 10-20% of infection positivity in severe VMs and 1-5% in mild VMs (6,12). There are many studies in the literature that recommend evaluation of infection for all cases diagnosed with VM (5,13).Because of the difficulty of detecting abnormalities in early USG examination maternal serum CMV and toxoplasma evaluation should be considered in the future studies.

Poor assosication of severe VM and CNS anomaly is probably because of few number of severe VM cases detected in our study. Our datas demonstrated that when ventricle diameter increases, the presence of CNS anomalies increase as well. CNS malformations

can be seen as an additional abnormality in ventriculomegalies. Breeze et al indicated that particular severe VM is commonly accompanied by corpus callosum agenesis and spina bifida (14,15).Similarly severe VM is most frequently accompanied by spina bifida, whereas mild and modare VMs are commonly seen with hydrocephalus.

MRI and transvaginal USG examination have been shown to be useful in identifying additional anomalies that are not detected by abdominal USG (15). Although it is understood that MR examination as a diagnostic method is better than USG, USG is widely used as first choice in gynecology. Analysis of gyration screening is an advantage of fetal brain MRI and may be useful for perinatal therapy when termination of pregnancy is unfavorable and can be a guide to end up family concerns (6,15-18). Some authors suggest routine use of MRI for all fetuses with mild VM, but some suggest if only there is inadequate USG examination or suspect of associated brain abnormality (16).Although MRI was not used in this study, we think that our results are reasonable as our physician who performed all USG examinations is an experienced perinatologist, yet we are aware that more research is needed.

Melchiorre et al evaluated the neurological outcome of children who have diagnosed with mild ventriculomegaly in the prenatal period and authors found that there was a wide variation in the incidence of neurodevelopmental delay, together with a combined data it was approximately 11% (2). The lack of postpartum follow-up data on present anomalies, neurodevelopmental outcume of children were the limitations of the study, however, patients' ongoing follow-up will be presented in later periods.The cross-sectional assessments are another main limitation although we believe that very large cohort may reduce bias. Longitudinal evaluation is needed to confirm the lateral ventricle width percentiles. The main advantage of this study includes containing both lateral ventricle size measurements and very large number of cases.

Conclusion

This study highlights the mean lateral ventricle size widths for right and left ventricles seperately with percentiles in a large Turkish population and also cut-off values related with CNS anomalies. Longitudinal researches including postpartum period are needed in order to reconsider the limits. Control examinations during follow-up should involve the width of the both lateral cerebral ventricles.

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