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CONTENTS

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Original Articles

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Original Article

The results of karyotype analysis and 22q11.2 (DiGeorge Syndrome critical region) deletion investigation in fetal cardiac system anomalies

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ABSTRACT

Objective: We aimed to determine the presence of accompanying chromosomal anomalies and 22q11.2 deletion in patients with cardiac system anomalies.

Material and Methods: In our retrospective and cross-sectional study, 99 fetuses born with cardiac anomalies were evaluated in terms of chromosomal anomalies. 36 fetuses were evaluated for 22q11.2 deletion. Fetuses who were diagnosed with prenatal congenital heart defect and underwent invasive prenatal diagnostic tests for fetal karyotyping between 01.01.2010 and 30.06.2017 at a tertiary cancer center were included in the study.

Results: Of 99 cases, 48 (48.4%) had only cardiac anomalies and 51 (51.5%) had non-cardiac anomalies. Chromosomal anomalies were found in 37 (37.4%) of the cases. Autosomal trisomy 18(43.2%) and autosomal trisomy 21(32.4%) were the most common chromosomal anomalies. The study results support the strong association of chromosomal changes and cardiac malformation, especially in septal defects, atrioventricular septal defects, and conotruncal malformations. Deletion was detected in one (2.8%) of 36 cases evaluated for 22q11.2 deletion. The fetus with this deletion had isolated tetralogy of fallot and had no extracardiac anomaly.

Conclusion: In cases with cardiac anomalies, isolated or accompanied by extracardiac anomalies, investigations should be made in terms of underlying chromosomal diseases in the perinatal evaluation. In addition, the investigation of 22q11.2 deletion in fetuses with conotruncal cardiac anomalies should be included in prenatal genetic examination.

Keywords: DiGeorge Syndrome; fetal anomalies; karyotype, trisomy, 22q11.2 Deletion Syndrome

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Introduction

Congenital heart disease (CHD) is the most common congenital structural malformation and causes significant prenatal and postnatal morbidity and mortality [1–3]. Although its incidence varies with different studies, it is 12-14 species per 1000 live births. This rate is higher in intrauterine fetal death [4,5]. Congenital heart diseases are associated with other structural anomalies and chromosomal anomalies [3]. Aneuploidies and microdeletion syndromes may accompany cardiac anomalies. Cardiac anomalies are most frequently accompanied by trisomy 21, 13, 18 and Turner syndrome [2,3,6]. 22q11.2 deletion syndrome, also known as DiGeorge Syndrome, which is the most common microdeletion syndrome, is often associated with cardiac anomalies [7]. Conotruncal anomalies are the main type of these cardiac anomalies [8,9].

Prenatal diagnosis has been shown to improve postnatal outcomes in [10–12]. In utero surgery can also be performed on [13]. In addition, prenatal diagnosis provides planned delivery in tertiary centers [11,14]. Diagnosing a prenatal heart defect, determining the severity of the disease, and determining the presence of chromosomal anomaly with prenatal genetic diagnosis help to offer the termination option to the family within ethical limits [1,2,15].

Karyotyping is the main method of identifying associated chromosomal abnormalities and many obstetricians recommend genetic screening for 22q11.2 deletion by Fluorescent in Situ Hybridization (FISH) for prenatally diagnosed heart diseases [16,17]. In the previous studies, a significant difference was found in terms of termination in patients with chromosomal anomaly and multiple malformations [15]. Determining the absence of karyotype anomaly is as important as determining the presence of karyotype anomaly in order to decide on the continuation of pregnancy in fetuses with isolated cardiac defects that can be treated with cardiac surgical methods.

In our study, we aimed to determine the effect of fetal cardiac system anomalies on the karyotype result and the presence of 22q11.2 deletion.

Material and methods

At a tertiary cancer center, between 01.01.2010 and 30.06.2017, 99 cases with fetal cardiac system anomaly detected during fetal anomaly screening or routine obstetric ultrasound (US) examination or fetal echocardiography were evaluated retrospectively. The study was approved by the institutional ethics committee. All patients were basically evaluated in terms of the compatibility of the anomaly with life and pregnancy prognosis in the perinatology council, which included a

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perinatologist, obstetrician, pediatrician, medical geneticist, pediatric cardiologist, cardiovascular surgeon, pediatric surgeon, and radiologist. Information about maternal age, gravida, parity, number of abortions, gestational week at diagnosis, type of anomaly, presence of accompanying anomaly, chromosome analysis results and council decisions were collected from the medical records of all patients. Karyotyping was performed with invasive diagnostic methods according to the gestational weeks of all cases. Each family who would undergo invasive procedure for fetal karyotyping was given extensive information about genetic counseling, the technique of the procedure, and complications before the procedure. Invasive fetal karyotyping was performed with written consent. Amniocentesis was performed in 79 cases between 16-22 weeks of gestation, cordocentesis in 15 cases between 20-30 weeks of gestation, and chorionic villus biopsy (CVS) in 3 cases between 11-14 weeks of gestation by five different experienced operators working in the perinatology prenatal diagnosis and treatment unit. 22q11.2 deletion was also investigated in 36 of these cases. Of the cases whose 22q11.2 deletion was investigated; amniocentesis was applied to 22 of them and cordocentesis was applied to 14 of them. The obtained materials were sent to the genetics laboratory of our hospital, and the chromosomes of the fetuses were obtained by undergoing a series of processes and culturing. Giemsa banding technique was used while performing traditional karyotyping. In FISH analysis, 22q11.2 locus was studied using TUPLE1 AND N25 probes (Cyctosel Aquarusin probes). Karyotyping and FISH analyzes were performed according to the manufacturer's instructions.

Statistical analysis

Statistical analyzes were done in SPSS 20.0 statistical package program. Numerical variables were presented as mean, standard deviation, minimum and maximum values, and categorical variables were presented as frequency and percentage (%). The relationship between the variables and the karyotype results was analyzed with the chi-square test. Significance level was accepted as $p<0.05$.

Results

The study group consisted of 99 pregnant women whose fetuses were found to have cardiac anomaly and underwent karyotyping. The clinical characteristics of the study group are shown in Table 1.

Table 1. The demographic data of the pregnant women who participated in the study.

Maternal age (Mean±SD)	29,24±6,71
Gravida (Median min-max)	2(1-6)
Parity (Median min-max)	1(0-3)
Abortion (Median min-max)	0(0-3)
Neonatal Death (n)	3
Stillbirths (n)	0
Diagnosis week at pregnancy (Mean±SD)	21,77±2,95
Cardiac Anomaly (n)	99
1 anomaly, n (%)	70 (70,7)
2 anomaly, n (%)	16 (16,2)
3 anomaly, n (%)	9 (9,1)
4 anomaly, n (%)	2 (2,0)
5 anomaly, n (%)	2(2,0)
Echogenic intracardiac focus, n (%)	11 (11,1)
Arrhythmia, n (%)	4 (4)
Oligohydramnios, n (%)	2 (2)
Abnormal Karyotype, n (%)	37 (27,3)
Gestational Termination, n (%)	54 (54,5)

Mean maternal age was 29.2±6.7, gravida 2(1-6), parity 1.3±0.5, abortion 0(0-3). The mean gestational week at which fetal cardiac anomaly was diagnosed was 21.7±2.9. Of 99 fetuses with cardiac anomaly; only one cardiac anomaly in 70 (70.7%), two cardiac anomalies in 16 (16.2%), three cardiac anomalies in 9 (9.2%), four cardiac anomalies in 2 (2%) and five cardiac anomalies in 2 (2%) was present at the same time.

Table 2. Fetal cardiac anomalies and karyotype results.

	Normal Karyotype n (%)	Abnormal Karyotype n (%)	Anomaly, n (%)	p value
Cardiac septal defects	68 (46.2)	32 (47)	T18, 14 (43.7) T21, 10 (31.2) T13, 4 (12.5) Turner Syndrome, 1(3.1) T16, 1 (3.1) Familial perisentric inversion carrier, 1 (3.1)	0
Atrial septal defects	10 (6.8)	3 (30)	T18, 2 (66.6) T13, 1 (33.3)	0,615
Ventricular septal defects	37 (25.2)	15 (40.5)	T18, 7 (46.7) T21, 4 (26.7) T13, 1 (6.7) Turner Syndrome, 1(6.7) T16, 1 (6.7) Familial perisentric inv carrier, 1 (6.7)	0,611
AVSD	21 (14.3)	14(66.7)	T18, 6 (42.9) T21, 6 (42.9) T13, 2 (14.3)	0,002
HLHS	7 (4.8)	1 (14.3)	T 13, 1 (100)	0,190
Pulmonary stenosis	3 (2.0)	-	-	0,174
Pulmonary	5 (3.4)	2 (40)	T18, 1 (50) Turner S, 1 (50)	0,982
Aortic stenosis	4 (2.7)	-		0,115
Aortic coarctation	4 (2.7)	1 (25)	Turner Sydrome, 1 (100)	0,602
Conotruncal Malformation	32 (21.7)	9 (28.1)	T18, 3 (33.3) T21, 1 (11.1) T13, 1 (11.1) Familial perisentric inv carrier, 1 (11.1)	0,039
Transposition of the great artery	10 (6.8)	4 (40)	T18, 2 (50) T21, 1 (25) Familial perisentric inv carrier, 1 (25)	0,856
Tetralogy of Fallot	9 (6.1)	-	-	0,093
DORV	9 (6.1)	4 (44.4)	T18, 3 (75) T13, 1 (25)	0,646
Truncus arteriosus	4 (2.7)	1(25)	T 18, 1 (100)	0,602
Cardiomyopathy	8 (5.4)	-	T21, 1 (100)	0,023
HRHS	1 (0.7)	-	T21, 1 (100)	0,437
Tricuspid Atresia	3 (2.0)	-	T18, 1 (100)	0,174
Single ventricle	2 (1.4)	1 (50)	T18, 19 (44.1)	0,709
Ebstein's anomaly	3 (2.0)	1 (33.3)	T21, 13(30,2)	0,883
Dextrocardia	7 (4.8)	1 (14.3)	T13, 6(13,9)	0,190
Total	147 (100)*	43(29.2)**	T16, 1(2,3) Familial perisentric inv carrier, 2(4,6)	

AVSD: atrioventricular septal defect, HLHS: hypoplastic left heart syndrome, DORV: double outlet right ventricle, HRHS: hypoplastic right heart syndrome, T21: trisomy 21, T18: trisomy 18, T13: trisomy 13, T16: trisomy 16, inv: inversion *n=147 because more than one cardiac anomaly can be found in one case (total number of cases is 99).** Calculated over 147 percent.

Abnormal karyotype was present in 37(37.4%) fetuses. 54(54.5%) of the pregnancies were terminated depending on the decision of the council.

Fetal cardiac anomalies and karyotype results are presented in Table 2. Septal defects and conotruncal malformations were common among fetal cardiac anomalies. Among these, ventricular septal defect (VSD), atrioventricular septal defect (AVSD), atrial septal defect (ASD), transposition of the great arteries (TGA), tetralogy of fallot (TOF), double outlet right ventricle (DORV) were observed most frequently. Abnormal karyotype results were found in 40.5% of those with VSD, 30% of those with ASD, and 66.7% of those with AVSD. Abnormal karyotype results were observed more frequently in septal defects. The frequency of septal defect (p=0.001), AVSD (p=0.002) and conoturuncal malformation (p=0.039) was statistically significantly higher in patients with abnormal karyotype results compared to those with normal results.

Table 3. Cardiac anomalies according to cases

	n (%)
VSD	22 (22,2)
AVSD	19 (19.1)
TOF	9 (9,1)
Dextrocardia	7 (7,1)
ASD	3 (3)
Ebstein's anomaly	3 (3)
HLHS	3 (3)
VSD and ASD	3 (3)
AS and CMP	2 (2)
CoA	2 (2)
CMP	2 (2)
VSD and PA	2 (2)
AVSD and TGA	1 (1)
AVSD, TGA and DORV	1 (1)
AVSD, DORV and CMP	1 (1)
AVSD and HLHS	1 (1)
AVSD, PS, TGA, DORV ve CMP	1 (1)
TGA	1 (1)
TGA and Single ventricle	1 (1)
CoA ve DORV	1 (1)
HLHS ve TGA	1 (1)
HLHS ve DORV	1 (1)
PA, AS ve Single ventricle	1 (1)
PA, TGA ve DORV	1 (1)
PS and TGA	1 (1)
Tricuspid Atresia	1 (1)
Truncus arteriosus	1 (1)
VSD, AS and CMP	1 (1)
VSD, ASD and TGA	1 (1)
VSD, ASD, HLHS, PS and Tricuspid Atresia	1 (1)
VSD, ASD, HRHS and CMP	1 (1)
VSD, ASD and Truncus Arteriosus	1 (1)
VSD and TGA	1 (1)
VSD, CoA and Truncus arteriosus	1 (1)
VSD and DORV	1 (1)
VSD, DORV and Truncus arteriosus	1 (1)
VSD, PA, DORV and Tricuspid Atresia	1 (1)
Total	99 (100)

VSD: Ventricular septal defects, AVSD: atrioventricular septal defect, TOF: Tetralogy of Fallot, ASD: atrial septal defects, AS: Aortic stenosis, CMP: cardiomyopathy, CoA: Aortic coarctation, PA: Pulmonary atresia, TGA: Transposition of the great artery, DORV: double outlet right ventricle, HLHS: hypoplastic left heart syndrome, DORV: double outlet right ventricle, PS: Pulmonary stenosis, HRHS: hypoplastic right heart syndrome

The largest part of the cases with abnormal karyotype was trisomy 18 with 16 (43.2%) cases, and trisomy 21 with 12 (32.4%) cases with the second frequency.

The frequencies of fetal cardiac anomalies are shown in Table 3 on the basis of cases. The most common cardiac anomaly was isolated VSD, followed by AVSD, TOF, and Dextrocardia.

A total of 99 cases; 48 had isolated cardiac anomaly and 51 had extracardiac anomaly. Of 48 cases with isolated cardiac anomaly; the karyotype result was normal in 32 (66.6%) and abnormal in 16 (33.4%). Of 51 cases with extracardiac anomaly; the karyotype results were normal in 30 (58.8%) and abnormal in 21 (41.2%). There was no statistically significant difference in the karyotype result according to the presence of isolated anomaly and additional anomaly (p=0.533).

The accompanying extracardiac anomalies and karyotype distribution are shown in Table 4. Central nervous system, urogenital system and extremity anomalies were observed most frequently in the cases. Chromosomal anomaly had a statistically significant relationship only with facial anomaly and extremity anomaly (p=0.022, p=0.024, respectively). There was no statistically significant relationship between the presence of accompanying extracardiac anomaly (except for facial and extremity anomalies) and the karyotype result (p>0.05).

Table 4. Extracardiac anomalies accompanying to fetal cardiac anomalies and their effects on karyotype results.

		Normal Karyotype, n (%)	Abnormal Karyotype, n (%)	p value
Extracardiac anomalies	Absent	32 (51.7)	16 (43.2)	0,533
	Present	30 (48.3)	21 (56.8)	
Central nervous system	Absent	47 (75.8)	24 (64.9)	0,242
	Present	15 (24.2)	13 (35.1)	
Genitourinary system	Absent	54 (87.1)	29 (78.4)	0,264
	Present	8 (12.9)	8 (21.6)	
Fasial	Absent	60 (96.8)	31 (88.3)	0,022
	Present	2 (3.2)	6 (16.2)	
Abdominal wall defects	Absent	61 (98.4)	35 (94.6)	0,287
	Present	1 (1.6)	2 (5.4)	
Skeletal	Absent	59 (95.2)	30 (81.1)	0,024
	Present	3 (4.8)	7 (18.9)	
Hyperechoic bowel syndrome	Absent	56 (90.3)	34 (91.9)	0,793
	Present	6 (9.7)	3 (8.1)	
Cystic Hygroma	Absent	60 (96.8)	35 (94.6)	0,628
	Present	2 (3.2)	2 (3.2)	
Situs inversus totalis	Absent	59 (95.2)	37 (100)	0,174
	Present	3 (4.8)	0 (0)	

22q11.2 deletion was investigated in 36 of 99 cases. Deletion was detected in one (2.8%) case. Fetus with deletion had isolated TOF. In the case with deletion, the maternal age was 23 and it was the first pregnancy. The fetus was diagnosed TOF at 21st gestational week. Cordocentesis was used as the method of karyotyping. Termination decision was taken at the council of perinatology for the fetus whose karyotype result was found to be normal.

Discussion

CHD is the most common fetal structural malformation, with high morbidity and mortality[5]. Chromosomal anomalies have been suggested as the major cause of CHD[18].

In this study, we evaluated aneuploidies and 22q11.2 deletion in fetuses with cardiac system anomaly in a single center.

In large case reports, the rate of aneuploidy in fetal cardiac anomaly cases varies between 28% and 43.7%[2,3,19–23]. Consistent with the literature, the rate of aneuploidy was found to be 37% in our study. In our study, extracardiac anomalies were detected in 51% of the fetuses and chromosomal anomalies were detected in 41.2% of the fetuses with extracardiac anomalies with the conventional method. The most common aneuploidy was trisomy 18 and followed by trisomy 21.

The incidence of aneuploidy is very high in fetuses with heart defects. However, the presence of 22q11.2 microdeletion has been reported in fetuses with isolated conotruncal heart defects.

The study results support the strong association of chromosomal changes and cardiac malformation, especially in septal defects, atrioventricular septal defects, and conotruncal malformations.

In many previous studies, it has been reported that trisomy 21 most frequently accompanies cardiac anomalies. In these studies, the frequency of extracardiac anomalies in fetuses ranged from 29% to 36.9%[2,22,23]. Sheng Mau et al. found that extracardiac anomaly in 25% of fetuses with cardiac anomaly[18]. In the same study, the most common karyotype anomaly was trisomy 21 (28.3%), while the number of fetuses with trisomy 18 and trisomy 13 was reported equally. There are also studies in which trisomy 18 was detected most frequently in fetuses with cardiac anomalies. Of these studies, Luo et al. found extracardiac anomalies in 54.2% of fetuses, while Boldt et al. reported extra cardiac anomaly in 40% of fetuses [19,21]. Trisomy 18 is a syndrome with multiple anomalies [24]. Therefore, the reason that trisomy 18 was the most common karyotype anomaly in our study may be related to the high rate of fetuses with extracardiac anomalies. Other reasons include the fact that our hospital is a referral center for prenatal diagnosis and that patients accept invasive karyotyping in the presence of multiple anomalies rather than isolated anomalies. Unlike our study, in the study of Tennstedt et al., although the rate of extracardiac anomaly was high (66%), the most common karyotype anomaly was trisomy 21 [3].

The most common fetal cardiac anomaly in the literature was septal defects. While AVSD was the most frequently detected cardiac anomaly in some studies VSD was the most common cardiac anomaly in many other studies, similar to our study[20,25–27] In our study, abnormal karyotype was also detected in 40.5% of 37 fetuses with VSD. Varying rates have been reported regarding the relationship between VSD and chromosomal anomalies. In studies investigating karyotypes in fetuses with VSD, Paladini et al. found abnormal karyotype in 46.8% of fetuses and Boldt et al. found abnormal karyotype in 56% of fetuses[21,28]. In both studies, the most common chromosomal abnormality was trisomy 18, followed by trisomy 21. In the study of Axt-Fliedner et al., 23.9% of fetuses with VSD had extracardiac anomalies and 32.9% had aneuploidies. In the same study, the most common aneuploidy was trisomy 18 (28%), while trisomy 21 (20%) and trisomy13 (20%) were the second most common at the same rate [29]. Consistent with these studies, the most common aneuploidy in our cases with VSD was found to be trisomy 18 (46.7%). On the other hand, in the study of Çağlı et al. it was reported that trisomy 21 was the most common aneuploidy in fetuses with VSD[30]. In our study, 48.3% of fetuses with normal karyotype and 83.7% of fetuses with abnormal karyotype results had septal defects. The frequency of septal defect was statistically significantly higher in fetuses with abnormal karyotype results compared to fetuses with normal karyotype results (p=0.002). Similarly, the incidence of AVSD and conotruncal anomaly was significantly higher in fetuses with abnormal karyotype results (p=0.02 and p=0.03). Similar to our study, Mone et al. also showed no significant difference in the incidence of aneuploidy in fetal cardiac anomalies other than septal defects[23].

It is known that there is a strong relationship between AVSD and fetal aneuploidy. In studies, it has been reported that the rate of abnormal karyotype in fetuses with AVSD diagnosed prenatally is between 54%-80%[20,22,31]. In the necropsy study of Tenndest et al., the most common heart defect associated with chromosomal anomaly was found to be AVSD[3]. In the study of Song et al. the most common association with chromosomal anomaly was truncus arteriosus and AVSD without accompanying heterotaxy[2]. In the literature, AVSD was most frequently associated with trisomy 21 [8,20,31,32]. In our study, the rate of chromosomal anomaly in fetuses with AVSD was 66.7%, and the number of fetuses with trisomy 21 and trisomy 18 was equal.

In our study, the rate of chromosomal anomaly was higher in fetuses with extracardiac anomaly than in fetuses without (41.2% vs. 33.4%). This rate was not statistically significant (p=0.533). Similar to our study, in the study of Respondek et al. the number of fetuses with extracardiac anomaly and the number of fetuses with isolated CHD were equal in the abnormal karyotype group[33]. However, recently Qiu et al. reported that abnormal karyotype increased significantly when cardiac anomalies were associated with extracardiac anomalies[34]. In our study, the frequency of facial anomaly (p=0.022) and extremity anomaly (p=0.024) was statistically significantly higher in patients with abnormal karyotype results. This finding shows that care should be taken in terms of chromosomal anomaly in fetuses with cardiac anomaly accompanied by facial or extremity anomalies.

In previous studies, it has been shown that the rate of concomitant CHD is high in fetuses with 22q11.2 deletion. CHD was reported in 55% of fetuses with 22q11.2 deletion by Zhao et al. and in 75% of fetuses with 22q11.2 deletion by Ryan et al[35,36]. Considering the types of CHD, it is seen that conotruncal malformations are the most common group in fetuses with 22q11.2 deletion. Similarly, Kong et al. detected 22q11.2 deletion in 5.4% of fetuses with conotruncal defect, but they did not detect 22q11.2 deletion in any of the fetuses with non-conotruncal heart defect[9]. In a study investigating 1137 fetuses with cardiac defects in Korea, 22q11.2 deletion was reported in 4.7% of fetuses and the most common CHD in these fetuses was TOF (n=24, 45%), followed by interrupted aortic arch, VSD, DORV, and aortic coarctation (ACoA) [8]. In other studies, in fetuses with TOF; the presence of 22q11.2 deletion was shown between 4.1% and 16.3%[37,38]. In our study, 22q11.2 deletion was found in one fetus (2.8%) with TOF findings. The karyotype analysis of this fetus, which did not have any extracardiac anomaly, was also normal. There was 22q11 deletion in one (5%) of 20 fetuses with conotruncal deformity and in one (14.2%) of 7 fetuses with TOF. Although the number of our cases is lower compared to the literature, the incidence of 22q11.2 deletion seems to be consistent with the literature. On the other hand, although there are studies showing the relationship between VSD and 22q11.2 deletion, 22q11.2 deletion was not found in any of the 8 fetuses with VSD in our study. In another words, in our study, 22q11 deletion was shown to be associated only with conotruncal defects.

As a conlusion in the antenatal period, a wide spectrum of diagnoses can be made with ultrasonography, from

relatively simple anomalies such as isolated VSD to complex anomalies incompatible with life. In order to determine the association of diagnosed fetal cardiac anomalies with structural anomalies, the fetus should be evaluated systemically. In cases with isolated cardiac anomaly or with cardiac anomalies accompanied by extracardiac anomalies, investigations should be made in terms of underlying chromosomal diseases.

Disclosure

Authors have no potential conflicts of interest to disclose.

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Original Article

Impact of the type of ductus venosus agenesis and the presence of associated anomalies on prognosis

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ABSTRACT

Objective: The Ductus Venosus (DV) connects the umbilical vein to the inferior vena cava. With a portocaval pressure gradient, the well-oxygenated blood in the ductus venosus accelerates towards the left sidewall of the inferior vena cava, directing the blood preferentially towards cephalic and coronary circulation through the foramen ovale (1). DV serves as a shunt, expanding to protect the heart and brain in hypoxic conditions. Ductus Venosus Agenesis (DVA) is a rare congenital abnormality with a prevalence of 0.03-0.07%. The type of DVA, along with any additional anatomical or chromosomal anomalies in fetuses with DVA, significantly affects the postnatal prognosis. Some fetuses with DVA develop normally, while others may experience growth retardation, heart defects, or other complications. In this study, we aimed to evaluate the frequency of associated anomalies in DVA cases, examine the impact of each type of DVA (intrahepatic and extrahepatic venous drainage) on prognosis, and contribute to the literature on this rare disease.

Materials and Methods; We conducted a retrospective study of all cases diagnosed prenatally with DVA at a tertiary center between 2016-2019. Our study reviewed obstetric data, associated anomalies, other systemic anomalies, type of DVA, chromosomal or genetic anomalies, and perinatal and postnatal outcomes. Postnatal infants were followed up to the 6th month.

Results; We identified 16 cases with ductus venosus agenesis. The type of DVA (intrahepatic-extrahepatic shunt), presence of chromosomal anomalies, accompanying ultrasonographic findings, and perinatal outcomes were recorded. Generally, in 7 out of the 16 cases, the umbilical vein drained into the portal system (44% - intrahepatic), and in 9 cases, it drained into the systemic venous system.

Conclusion; DVA is a rare congenital abnormality with potentially significant implications for affected fetuses and infants. Early diagnosis, careful monitoring, and appropriate management strategies are crucial to optimize outcomes for these patients. There's a need for future research to better understand the underlying etiology and pathophysiology of DVA and to develop more effective treatment options for affected individuals.

Keywords: ductus venosus agenesis; extrahepatic; intrahepatic; chromosomal anomaly; neonatal outcomes

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Introduction

The fetal ductus venosus (DV) is a pivotal structure connecting the umbilical vein to the inferior vena cava at the heart's entrance. The portocaval pressure gradient facilitates acceleration of well-oxygenated blood in the DV towards the left sidewall of the inferior vena cava, ensuring blood preferentially flows cephalad and to the coronary circulation via the foramen ovale [1]. Acting as a shunt, the DV expands to protect the heart and brain under hypoxic conditions. 20-30% of well-oxygenated blood from the umbilical vein is delivered to the left atrium via the DV, inferior vena cava (IVC), and foramen ovale [2]. Under normal circumstances, two-thirds of umbilical venous flow nourishes the liver, while the remaining third passes through the DV. In hypoxic situations, there's an increase in the DV shunt, ensuring vital organs, notably the heart and brain, receive adequate oxygen and glucose [3]. Ductus Venosus Agenesis (DVA) is a rare congenital abnormality with a prevalence of 0.03-0.07%, characterized by the absence of the DV during fetal development, responsible for transporting oxygen-rich blood from the umbilical vein to the inferior vena cava [3,4]. In fetuses with DVA, the umbilical venous return occurs through two distinct pathways: extrahepatic and intrahepatic.

Extrahepatic; Drainage from the umbilical vein bypasses the liver (connecting directly to the iliac vein, inferior vena cava, renal vein, right atrium, or, rarely, the left atrium or coronary sinus).

Intrahepatic; The umbilical vein drains into the liver (connecting to the portal sinus as usual) [5].

Fetuses with DVA may exhibit a range of clinical manifestations, including cardiac and non-cardiac anomalies, intrauterine growth restriction (IUGR], and even fetal death in severe cases [6]. The etiology of DVA remains unclear, but genetic factors and environmental influences may play a role [7]. Prenatal diagnosis is typically made during the first trimester ultrasound examination [8].

Management of DVA is contingent on the severity of the condition, presence of associated anomalies, and the gestational age at diagnosis. Postnatal management of infants with DVA is determined by the severity of the condition and the presence of associated anomalies [9]. Given the elevated risk of IUGR and other complications in fetuses with DVA, it is crucial to closely monitor fetal growth and well-being [10]. In certain situations, such as hydrops fetalis or significant cardiac dysfunction, intrauterine intervention may be considered [11].

The prognosis in fetuses with DVA varies depending on the presence of associated anomalies and alternative venous shunts. While some fetuses with DVA develop normally, others may experience growth retardation, heart defects, or other complications. In this study, we aimed to evaluate the frequency of associated anomalies in DVA cases and, in the context of the literature, to explore the impact of

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each type of DVA with intrahepatic and extrahepatic venous drainage on prognosis.

Material and methods

Between 2016 and 2019, we conducted a retrospective study of all cases diagnosed with prenatal DVA at the Istanbul Kanuni Sultan Suleyman Training and Research Hospital. The study was approved by the local ethics committee. Transabdominal ultrasound examinations were performed using a Voluson E6 (GE Healthcare Ultrasound, Milwaukee, WI, USA) ultrasound machine equipped with an RAB 6D (2-7 MHz) probe.

During all ultrasound examinations, general anatomical evaluations, fetal echocardiography, and Doppler studies of the ductus venosus were conducted. A diagnosis of DVA was established when the blood flow between the portal vein and the inferior vena cava couldn't be demonstrated using color Doppler in optimal scanning planes. The connection of the umbilical vein to the portal venous system was classified as intrahepatic, and to the systemic venous system was classified as extrahepatic shunt.

Cases were classified as either isolated or associated with other abnormalities. Genetic counseling was recommended for all cases. Cases with additional anomalies were recommended for karyotype analysis and scheduled accordingly.

In our study, we reviewed obstetric data, associated anomalies, other systemic abnormalities, type of DVA, chromosomal or genetic anomalies, and perinatal and postnatal outcomes. Postnatal infants were followed up until the 6th month. Patients who dropped out of follow-up at any stage of pregnancy and gave birth at another center were excluded from the study.

Results

In our study, we identified 16 cases with ductus venosus agenesis. The type of DVA (intrahepatic-extrahepatic shunt), presence of chromosomal anomalies, accompanying ultrasonographic findings, and perinatal outcomes were recorded (Table-1). One case was observed in a twin pregnancy in a single fetus, while all other pregnancies were singleton.

Overall, of the 16 cases, the umbilical vein connected to the portal system in 7 cases (44% - intrahepatic) and to the systemic venous system in 9 cases (56% - extrahepatic). All three identified chromosomal anomalies (trisomy 21, Turner syndrome, phenylketonuria) were in the extrahepatic drainage group. All pregnancies in the extrahepatic shunt group were either terminated or lost post-delivery. In the intrahepatic drainage group, one baby was lost post-delivery (n:1 - 14%), while the others survived. 25% of the cases (n:4) were isolated, and all isolated cases belonged to the intrahepatic drainage group and resulted in live births. Among ultrasonographic findings, a single umbilical artery was the most frequently observed (n:4 - 25%). Other common findings included signs of cardiac overload, such as cystic hygroma, hydrops, and cardiomegaly.

Discussion

In recent years, studies concerning ductus venosus anomalies have gained momentum. The management of DVA depends on the type of agenesis, the presence of associated anomalies, and the gestational age at diagnosis. When DVA is diagnosed prenatally, due to the elevated risk of IUGR and other complications in these fetuses, it is vital to closely monitor fetal growth and well-being [10].

Postnatal management of infants with DVA is determined by the severity of the condition and the presence of associated anomalies. In cases with portosystemic shunts, surgical intervention may be required to prevent complications like liver dysfunction and pulmonary hypertension [9,11].

Table 1. Classification, concomitant anomalies and prognosis of fetuses in DVA patients

Case	DVA Type	Chromosome	Additional Sonographic Findings	Outcome
1	IHE	Normal	One of the twins dva	Live birth at term
2	EH	Normal	Cystıc hygroma Omphalocele Single umbilikal artery	Termination at 16 weeks
3	EH	Unknown	Cystic hygroma Bilateral talipes	Termination at 18 weeks
4	IH	Normal	Single umbilikal artery Cardiomegaly Blake pouch cyst	Live birt at 36 weeks 21 days NICU-Lives
5	IH	Normal	Ventricular septal defect	Live birt at 32 weeks Postpartum died
6	EH	Phenylketonuria	Cardiac hyperechoic focus	Live birt at term 6 months NICU-Died
7	EH	Unknown	Cleft palate	Live birt at 36 weeks 3 days NICU-Died
8	IH	Unknown	None	Live birth at term 1 month NICU-Lives
9	EH	Unknown	IUGR Umbilical vein varicose	Live birth at 32 weeks Postpartum died
10	EH	Normal	Ventriculomegaly Diaphragmatic hernia	Termination at 28 weeks
11	EH	Turner	Hydrops fetalis Cystic hygroma Single umblical artery	Termination at 19 weeks
12	IH	Unknown	None	Live birth at term
13	EH	Trisomy 21	Increased nb Hyperechoic bowel	Termination at 22 weeks
14	EH	Normal	IUGR, Bilateral uterine artery notch, Single umbilikal artery, Cardiothoracic index increased Shortness of long bones	Live birth at 30weeks 6 months NICU-Died
15	IH	Unknown	Hydrocephalus Shift of the heart axis to the left	Live birt at term 15 days NICU-Lives
16	IH	Normal	None	Live birth at term

In other cases, conservative treatment with regular follow-up to monitor potential complications might be appropriate [12]. Previous studies in the literature have explored the outcomes and effects of DVA in fetuses. Moaddab et al. (2016) found 46.7% normal outcomes, 34.4% chromosomal abnormalities, and 18.9% structural

abnormalities in 259 DVA cases, while Pacheco et al. (2018) identified isolated DVA in 44.6% of the cases and associated anomalies in 55.4%. Maruotti et al. (2018) reported 42.1% normal outcomes, 31.6% chromosomal abnormalities, and 26.3% structural abnormalities in 19 DVA cases [5].

Similarly, Strizek et al. (2019) found 47.9% normal outcomes, 29.2% chromosomal abnormalities, and 22.9% structural abnormalities in 48 cases, while McBrien et al. (2021) reported 44% normal outcomes, 30% chromosomal abnormalities, and 26% structural abnormalities. These studies demonstrate that DVA is associated with diverse outcomes and effects in fetuses (4,11,13].

In our study, of the 16 cases with DVA, the umbilical vein connected to the portal system in 7 cases (44% - intrahepatic) and to the systemic venous system in 9 cases (56% - extrahepatic). The three identifiable chromosomal anomalies were similarly in the extrahepatic drainage group in line with the literature. All pregnancies in the extrahepatic shunt group were either terminated or lost post-delivery. In the intrahepatic drainage group, one baby was lost post-delivery (n:1 - 14%), while the others survived. 25% of the cases (n:4) were isolated, and all isolated cases were in the intrahepatic drainage group and resulted in live births.

The absence of the DV is a rare condition with outcomes varying based on associated factors such as other congenital anomalies, fetal growth restriction, and the presence of portosystemic shunts. Some studies suggest that the prognosis can be positive in cases where no other significant anomaly is present [10, 14]. However, the existence of concomitant malformations or chromosomal abnormalities can significantly worsen the prognosis [4, 11, 13]. Prenatal characteristics and the diameter of portosystemic shunts can also influence outcomes [15,16]. We must bear in mind that the absence of the DV might not always be an isolated finding and can be accompanied by congenital heart disease [17,18], growth retardation, and chromosomal abnormalities [19].

As mentioned in the studies referenced above, research in the literature indicates that while approximately 40-50% of DVA cases do not coexist with another anomaly, the rest are associated with structural or chromosomal abnormalities. A better prognosis is expected in cases without associated anomalies and those without extrahepatic venous drainage.

While studies have clearly demonstrated the incidence of congestive heart failure in DV agenesis with extrahepatic venous drainage, there is limited information regarding the intrahepatic venous drainage portion of DV agenesis [4,19].

In conclusion, DVA is a rare congenital abnormality with potentially significant implications for affected fetuses and infants. Early diagnosis, careful monitoring, and appropriate management strategies are essential to optimize outcomes for these patients. Further research is required to better understand the underlying etiology and pathophysiology of DVA and to develop more effective treatment options for those affected.

Disclosure

Authors have no potential conflicts of interest to disclose.

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Original Article

The effect of anti-phospholipid syndrome on pregnancy outcomes in patients with habitual abortus

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ABSTRACT

Objective: The aim of this study was to research the pregnancy outcomes of women with anti-beta2 glycoprotein 1 and anti-cardiolipin antibody positivity and to determine the association with pregnancy morbidity.

Materials and methods: This retrospective study contained pregnant women with anti-beta2 glycoprotein 1 and anti-cardiolipin antibody positivity and a control group without these antibodies. Totally 190 sera sent from Obstetrics and Gynecology clinics between January 2019 and January 2023 were analyzed in the medical microbiology laboratory of xx.

Results: In a patient population separated into antibody-positive and antibody-negative groups, the gravida was found to be 3.8±0.1 and 3.5±0.3 respectively (p=0.333). Parity was 1.1±0.1 and 0.8±0.1 (p=0.071), abortion rates were 2.3±0.1 and 2.5±0.2 (p=0.659), and gestational age was 35.7±0.8 and 34±1.5 (p=0.047). Intrauterine fetal death was found to be higher in the antibody-positive group compared to the antibody-negative group (p=0.03). There was no statistically significant difference between the two groups regarding additional pregnancy complications such as intrauterine growth restriction, oligohydramnios, gestational diabetes, and gestational hypertension (respectively p=0.623, 0.074, 0.312, 0.626). However, smoking was significantly higher in the antibody-positive group (p=0.049).

Conclusion: Antiphospholipid syndrome adversely affects pregnancy outcomes. During the initial visit, a thorough patient history should be obtained, and in pregnant women with a history of poor obstetric outcomes or habitual abortions, this syndrome should be considered.

Keywords: antiphospholipid syndrome; pregnancy complication; pregnancy outcome

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Introduction

Among various antiphospholipid antibodies, especially anticardiolipin (aCA) and anti-B2-glycoprotein 1 (aβ2GP1) antibodies have been associated with poor pregnancy outcomes [1]. These antibodies identify many phospholipids and phospholipid-binding proteins during pregnancy and cause antiphospholipid syndrome characterized by hypercoagulopathy during pregnancy [2]. Antiphospholipid syndrome (APS) stands as an autoimmune disorder defined by non-inflammatory mechanisms, which can clinically present as both venous and arterial thrombosis, thrombocytopenia, and adverse outcomes during pregnancy, including fetal loss [3]. The occurrence of APS is approximated to be 5 instances per 100,000 individuals annually for incidence and 40-50 cases per 100,000 population annually for prevalence [4]. While the complete understanding of APS's pathogenesis remains elusive, the defining features of this condition involve the existence of antiphospholipid antibodies like lupus anticoagulant (LA), aCA antibodies, and aβ2GP1 antibodies [5]. These autoantibodies are thought to affect haemostasis and complement activation to promote thrombosis, although the underlying mechanisms are not yet clear [6].

Obstetrical issues associated with APS encompass repetitive early miscarriages, fetal demise, and later pregnancy complications like pre-eclampsia and fetal growth restriction (FGR) [7]. There's a proposition that these obstetrical issues arise from inadequate placental function triggered by the hindrance of trophoblast growth in the initial trimester, alongside compromised invasion/proliferation of extravillous trophoblasts and the occurrence of placental thrombosis [8].

Diligent obstetric surveillance and preventive measures involving low-dose aspirin (LDA) and low molecular weight heparin (LMWH) can yield favorable obstetric results in the majority of APS cases; however, complications still manifest in approximately 20-30% of pregnancies [9].

Several studies in the literature have described obstetric complications of APS [10,11]. Moreover, numerous investigations have recognized potential factors that could contribute to adverse obstetric results among women with AFS. These encompass a past record of thrombosis and pregnancy-related complications, the existence of other autoimmune disorders, positive testing for multiple antiphospholipid antibodies, reduced levels of complement proteins C3 and C4, and atypical readings from umbilical artery Doppler velocimetry during the 23-26 weeks of gestation [12,13]. Nevertheless, information regarding risk elements associated with pregnancy-related complications in APS-afflicted women is currently restricted.

The aim of this study was to evaluate the potential impact of positive Anti-Beta-2 Glycoprotein (aβ2GP1) and Anti-Cardiolipin antibodies on obstetric complications and pregnancy outcomes.

Material and methods

Study Centre and Participants

The study was conducted in the Medical Microbiology and Gynaecology Clinic of Tepecik Education and Research Hospital, between January 2019 and January 2023. Blood samples of patients with habitual abortus were collected for

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measurement of antiphospholipid antibodies. Patients with antibody positivity were assigned to study group and patients with antibody negativity were assigned to control group. During pregnancy follow-up, blood sera were obtained from 190 patients, including 133 patients who exceeded the 20th gestational week and developed complications during pregnancy and 57 control group. Patients with uterine anomalies and genetic disorders were excluded. aCA and aβ2GP1 antibody levels were analyzed. The study was approved by the Ethics Committee of Tepecik Education and Research Hospital (ethics approval number: 2023/03-05, date: 05.04.2023). The diagnosis of intrauterine growth retardation was made when the ultrasound estimated fetal weight was <10 per cent or the birth weight was <5% or the birth weight was < -2SD units.

Immunological Analysis

aCA and aβ2GP1 were analysed according to the manufacturer's instructions by enzyme-linked immunosorbent assay (ELISA) (Alegria®; ORGENTEC Diagnostika, Mainz, Germany). aCA IgG and aβ2GPI IgG were measured by using a random-access analyser (Alegria®; ORGENTEC Diagnostika). The cut-off value was performed for aCA IgG and aβ2GPI IgG was >10 GPL and >8 GPL, respectively.

Statistical Analysis

Data analysis was performed using the Statistical Package for the Social Sciences (SPSS), version 25.0 (SPSS Inc., Chicago, IL). Kolmogorov-Smirnov test was used to evaluate normal distribution. When comparing two groups with positive or negative marker results, T-Test was used for normally distributed parameters and Mann-Whitney U test was used for non-normally distributed parameters. Quantitative data analysis results were presented as mean±standard deviation and median, and categorical data were presented as frequency (percentage). p value below 0.05 was considered statistically significant in all tests.

Results

A total of 190 patients participated in the study. Maternal age in the study population was 34.2±6.05 years. Table 1 shows the evaluation of continuous variables according to antibody status. There was no statistically significant difference between gravida, parity, number of living children and number of abortions (p=0.333, 0.071, 0.059 and 0.659, respectively). When antibody-positive pregnant women were compared with antibody-negative pregnant women, the level of intrauterine excitus was found to be higher in the antibody-positive group (p=0.03). Gestational age was higher in antibody-positive pregnant women (p=0.047). The number of neonatal excitus, birth weight and APGAR (activity - pulse - grimace - appearence - respiration) score were similar in both groups (p=0.258, 0.246 and 0.348, respectively).

Table 1. Examination of continuous variables

	Antibody Positive	Antibody Negative	p
Gravida	3.8±0.1	3.5±0.3	0.333
Parity	1.1±0.1	0.8±0.1	0.071
Alive	1±0.09	0.7±0.1	0.059
Abort	2.3±0.1	2.5±0.2	0.659
Neo ex	0.06±0.03	0.1±0.04	0.258
Intrauterine fetal death	0.1±0.06	0.01±0.01	0.030*
Gestational age (weeks)	35.7±0.8	34±1.5	0.047*
Birth weight (g)	2649.5±193.5	2227.5±389.3	0.246
APGAR	7±0.3	5.1±1.3	0.348

*Values are expressed as mean±standard deviation. Abbreviations: Neo ex; Neonatal excites, APGAR; activity - pulse - grimace - appearence - respiration. Significant values (p<0.05) are indicated with **

In Table 2, among the categorical variables, intrauterine growth retardation (IUGR) was present in 16% of the patients. There was no statistically significant difference between antibody positive and negative groups in terms of IUGR (p=0.623). Antibody positivity was found in 33% of patients with oligohydramnios and there was no statistically significant difference between the two groups (p=0.074). Antibody positivity was found in 71% of pregnant women with gestational diabetes and 85% of pregnant women without gestational diabetes. There was no significant difference in antibody status in the gestational diabetes group (p=0.312). In the gestational hypertension group, antibody positivity was present in 78%. There was no statistically significant difference between both groups in this patient population (p=0.626). In the patient population using acetylsalicylic acid, previous operation, and low molecular weight heparin, both groups were found to be statistically similar (p=0.11, 0.264, 0.743, respectively). However, antibody positivity was present in 100% of pregnant smokers.

Table 2. The comparison of patients' characteristics in APS and Control groups

	APS n=133	Control n=57	p
IUGR (n=50) Positive Negative	 6 (%12) 35 (%70)	 2 (%4) 7 (%14)	0.623
Oligohydroamniosis (n=52) Positive Negative	1 (%2) 42 (%81)	2 (%4) 7 (%13)	0.074
Gest DM(n=56) Positive Negative	 5 (%9) 42 (%75)	 2(%4) 7 (%13)	0.312
Gest HT (n=56) Positive Negative	 7 (%13) 40 (%71)	 2 (%4) 7 (%13)	0.626
ASA (n=56) Positive Negative	 14 (%26) 49 (%88)	 0 (%0) 13 (%23)	0.110
Previous op (n=86) Positive Negative	 18 (%21) 56 (%65)	 1 (%1) 11 (%13)	0.264
Smoking (n=54) Positive Negative	 12 (%22) 30 (%56)	 0 (%0) 12 (%22)	0.049*
LMWH (n=103) Positive Negative	 20 (%19) 43 (%42)	 30 (%29) 10 (%10)	0.743

*IUGR; intrauterine growth retardation, GestDM; Gestational Diabetes Mellitus, GestHT; Gestational Hypertension, Asa; Acetylsalicylic acid, Previous op; previous operation, LMWH; Low molecular weight heparin. Significant values (p<0.05) are indicated with **

Anti-cardiolipin antibody or aβ2GP1 antibody was positive in 71% of non-smokers. There was a statistical difference between both groups (p=0.049). Table 3 show clinical characteristics of patients with and without adverse pregnancy outcomes in the APS group.

Table 3. Results according to advers and non-advers outcome

	Advers (n=24)	Non-Advers (n=32)	p
Maternal age	31.2±5.9	31.1±5.7	0.832
Primiparous	5 (21%)	11 (34%)	0.025*
Multiparous	19 (79%)	21 (66%)	0.042*
Abort	2 (0; 8)	2 (0; 5)	0.169
Gestasionel Age	35.8±5.1	36.2±5.3	0.258
ACA	1 (4%)	1 (3%)	0.093
aβ2GP1	7 (29%)	14 (44%)	0.037*

*Data are presented as the mean ± standard deviation, n (%) or median (min-max). aβ2GP1: anti-β2- glycoprotein-1, aCA anticardiolipin antibody; *Statisticly significant value*

Discussion

APS is an autoimmune disease characterized by the occurrence of arterial or venous thrombotic events and/or pregnancy morbidity in the presence of at least one of three circulating antiphospholipid antibodies; aCA, aβ2GP1 antibody and lupus anticoagulant [14]. APS is considered a rare disease although it has an estimated prevalence in the general population, which is 0.05% [15]. However, it is 3.5 times more common in women than in men. Women with APS are at risk of adverse pregnancy outcomes including preeclampsia, pregnancy loss, thromboembolism, premature delivery, and perinatal death [16]. In this study, no difference was found in terms of obstetric complications including abortion, neonatal death, IUGR, oligohydramnios, gestational diabetes, gestational hypertension in pregnant women with aCA or aβ2GP1 positivity, but in terms of intrauterine fetal death, antibody-positive patients were found to be significantly higher than antibody-negative patients.

The mechanism behind the presence of aCA in the sera of pregnant women who experience miscarriage is currently largely believed to be undergoing structural changes in phospholipids in the cell membrane; these changes stimulate overproduction of aCA [17-19]. As a result, the miscarriage rate is increased in patients who test positive for aCA. Some pregnant women may experience a normal pregnancy despite positivity for aCA, but the likelihood of miscarriage in pregnant women who test positive for both antibodies may be 2 to 4 times higher than in those with the presence of only one of both antibodies [20,21]. In this study, abortion rates were found to be similar in antibody-positive and antibody-negative pregnant women. The reason for this may be that the development time of microthrombosis in antibody-positive patients varies up to 10 years. In some patients who were positive for antibodies but were not affected by placental microcirculation thrombosis formation during pregnancy, half of these patients were found to develop thrombosis within 3 to 10 years after delivery, especially during follow-up visits planned for patients positive for aCA, and approximately 10% of these patients developed lupus erythematosus [22,23].

Fetal morbidity stands out as a distinctive clinical presentation of APS, encompassing occurrences like early and late pregnancy miscarriages, intrauterine growth restriction, and premature births. In addition, maternal morbidity (pre-eclampsia, eclampsia and placental abruption) is also relatively common in pregnant patients with APS [24]. In this study, in parallel with the literature, intrauterine fetal death was found to be significantly higher in the group with antibody positivity. Bagger et al. [25] found that aCA was positively correlated with intrauterine fetal death in 158 pregnant women with fetal loss. Lee et al. [26] found that aβ2GP1 levels were not associated with fetal death or abortion in 414 pregnant women who were negative for aCA but positive for anti aβ2GP1. In the meta-analysis conducted by Xu et al. [27], a statistically significant association between aβ2GP1 and late fetal loss was observed in four of the eight selected studies. Two investigations established a favorable yet statistically insignificant correlation. However, the results showed a nonsignificant association between aβ2GP1 and late fetal loss (OR 3.13, 95% CI .75-5.50) [28,29]. According to the subgroup analysis by study type, no statistical association of aβ2GP1 with late fetal loss was found in the cohort studies group (OR 3.53, 95% CI-2.74 to 9.79) or the case-control studies group (OR 3.07, 95% CI .51-5.63). Furthermore, one case-control study showed a nonsignificant association between aβ2GP1 and late fetal loss (OR .83, 95% CI .26-2.65) [30]. Moderate heterogeneity was observed in many of these analyses [31].

aβ2GP1 and aCA, which cause antiphospholipid antibody syndrome and which we examined in this study, may cause IUGR by affecting placental circulation because they cause arterial and/or venous thrombosis [10]. In this study, no significant difference was found between the patient group with antibody positivity and the group with negative antibody positivity in terms of IUGR. While IUGR was found in 12 (18.5%) of 65 pregnant women with systemic lupus in Madazlı et al. [32] study, 16% IUGR was found in parallel with this in our study. In the meta-analysis conducted by Xu et al, a correlation was found between IUGR and aCA levels in 4976 pregnant women with aCA positivity [33]. In the same study, a strong correlation was found between aβ2GP1 and IUGR. aβ2GP1 is rare among antibodies identified alone in patients with clinical characteristic of antiphospholipid antibody syndrome. However, it is the main target of antiphospholipid antibodies and plays an important role in the pathogenesis of unfavorable obstetric outcomes [34]. Saccone et al. [35] suggested that aβ2GP1 was associated with the lowest live birth rate and the highest incidences of IUGR, very early IUGR and stillbirth compared to aCA.

In this study, smoking was found to be significantly higher in the antibody positive group compared to the antibody negative group. Many studies have been conducted to determine whether antiphospholipid antibodies are an independent risk factor for thrombotic events such as myocardial infarction and stroke. Most of these studies have used matched controls to eliminate the effect of smoking because tobacco use is an established risk factor for thrombosis. The strategy of matching smoking rates in anti-phospholipid antibody (aPL)-positive and aPL-negative patient groups was first used to describe the antibody profiles of myocardial infarction survivors [36]. In this study, aCA-positive patients were found to be active smokers; these patients were matched with 49 aCA-negative patients, of whom 43 were active smokers and 3 were ex-smokers. Certainly, it is noteworthy that 92% of patients with myocardial infarction were smokers, but the authors did not comment on this finding. As a result of the widespread use of this approach to define control groups, the association between smoking and the presence of aPL could not be determined in many studies [37].

In the study conducted by Yang et al. [38], out of a group of pregnant women, adverse effects were observed in 64 of them, while 256 of them were taken as a control group of healthy pregnancies. When both groups were compared, no difference was observed between the group with adverse effects and the group without adverse effects in terms of ACA, consistent with our study. Contrary to ACA, sera aβ2GP1 levels were found to be higher in the non-adverse group compared to the group with adverse effects [38].

Limitations of the Study

The fact that it was a retrospective and single-center study is the main limitation of the present study. Another limitation was that aCA and aβ2GP1 antibodies, which are among the antibodies harboring APS, were examined in our study, while lupus anticoagulant was not. The small patient population is another limitation of our study.

Conclusion

In our study, the number of intrauterine fetal deaths was significantly higher in pregnant women with positive aCA and aβ2GP1 antibodies. In other pregnancy complications such as IUGR, oligohydramnios, gestational diabetes mellitus and gestational hypertension, there was no significant result between antibody positivity and negativity. Even if we have contributed to the literature on this subject,

prospective, multicenter studies are needed.

Ethics committee approval

This study was approved by Non-Interventional Clinical Research Ethics Committee of xx (Date: 5.04.2023 and Decision no: 2023/03-5).

Disclosure

Authors have no potential conflicts of interest to disclose.

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Original Article

The association between cervical HPV and female fertility

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ABSTRACT

Objective: Genital human papillomavirus (HPV) infection is the most common sexually transmitted viral infection worldwide with a prevalence of 10-12% in the female population in the reproductive age; few studies addressed the effect of HPV infection on fertility. It is aimed to investigate the presence of HPV infection in infertile women in the present study.

Materials and methods: In this retrospective cross-sectional study; the outpatient infertility clinic records between July 2020 and January 2023, were evaluated. Infertility examination and evaluation were performed following the guidelines. Infertile female individuals and control group's HPV results were analyzed.

Results: 234 infertile and 340 non-infertile females were included in the study, HPV positivity was found %11.5 for all infertile women. No significant relationship was found between and HPV (p=0.850).

Conclusion: No significant association was found between female infertility and HPV. Still HPV may play a role in infertility with different genotypes. Further studies should include HPV genotypes.

Keywords: HPV; infertility; women

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Introduction

Infertility is a common condition which is experienced by 15% of all couples and defined as failure to achieve pregnancy within twelve months of unprotected intercourse or therapeutic donor insemination in women younger than thirty five years or within six months in women older than thirty five years[1]. While the cause of infertility can be male or female, and sometimes both, the cause cannot be determined in 25-30% of couples[2]. Couple infertility who tried to conceive for at least one year and who could not achieve pregnancy despite the presence of patent fallopian tube, normal uterine cavity, adulatory menstrual cycle in women and normal semen analysis in men; should be evaluated in the unexplained infertility group[1, 3]. Sexually transmitted diseases (STDs) are responsible for 20% to 60% of female infertility by causing pelvic inflammation and tubal injury[4, 5],. Pathological changes in the fallopian tubes may affect fertilization and embryo transfer, and endometrial lesions may impair sperm capacitation and embryo implantation. Some viruses are considered as one of the most common sexually transmitted pathogens, in addition to mycoplasma, chlamydia trachomatis and neisseria gonorrhoeae[4, 5].

Human papillomavirus (HPV) is a DNA virus from the papillomaviridae family, containing more than 170 identified types[6]. HPV represents a well-established and most common infectious cause for different types of cancer in females as well as males[7, 8].

Recently association between spontaneous abortion and HPV has been studied[9].Although genital HPV infection is the most common sexually transmitted viral infection worldwide with a prevalence of 10-12% in the female population in the reproductive age, few studies addressed the effect of HPV infection on fertility[6, 10]. While it is suggested that HPV has a role in male infertility by impairing the quality and progressive motility of sperm, its effects on female fertility are not clearly known[11-12]. However,in the Population-Based Cohort Study conducted in 2020, women with HPV infection had an increased risk of infertility compared to the non-HPV cohort [13]. The aim of this study is to evaluate HPV infection in infertile women.

Material and methods

In this retrospective cross-sectional study; the outpatient infertility clinic records between July 2020 and January 2023, were evaluated. In the clinic, the diagnosis and evaluation of infertility were performed in accordance with the American College of Obstetricians and Gynecologists (ACOG) guidelines. Detailed anamnesis and routine gynecological examination of women were performed; furthermore ovarian reserve of the patients by serum

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antimullerian hormone (AMH) and/or basal hormone tests and antral follicle count on transvaginal ultrasound, and hysterosalpingography was performed. Male individuals with detailed anamnesis and semen analysis were evaluated and infertility categorized by the clinic. Infertile individuals were classified in advance. Female individuals' age, body mass index (BMI) and duration of infertility were noted. Control group included random healthy women without any missing data, referred to the gynecology clinic for routine HPV screening and no registration for any other diagnosis in the last year of the study.
As a part of the community cervical cancer screening program, all women aged 30 and over are examined free of charge for HPV in the country by the ministry of health. Patients screened for HPV were included. Results were noted as given by ministry of health HPV 16, HPV18 or HPV others. HPV others includes HPV 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68 genotypes. Results with two or more genotype concomitantly were excluded. Also women under the age of thirty which screening is not covered by government insurance policy, women with secondary infertility and mullerian anomalies were excluded from the study.

Statistical Analysis and Ethical Approval

Data analysis was performed with SPSS (version 24.0; IBM Corp). All data were presented as the mean (±SD) or rate (%). A 1-sample Kolmogorov–Smirnov test was performed to analyze the distribution of clinical variables. The Mann–Whitney U test and the $\chi 2$ test were used for the comparison of the non-parametric variables. A P value of less than .05 was considered statistically significant. The study was approved by the local ethics committee (2023/03-43).

Results

234 infertile and 340 non-infertile women were included in the study. Mean age of the patients was 32.25 ± 1.63 (30-38). Overall HPV, HPV 16, HPV 18 and HPV others prevalence were 11.8% (n=68), 2.4% (n=14), 3.5% (n=20), 5.9% (n=34) respectively.
Infertile HPV positive females'; mean age (years), mean BMI and duration of infertility (months) were 32.23±1.65 (30-38), 23±1.56 (21-28) kg/m2 and 23.34±1.67 (12-28) respectively. Control patients mean age and BMI were 32.29±1.61 (30-36) years and 23±1.44 (20-28) kg/m2.
The characteristics and HPV positivity between control and infertility group were summarized in table (Table 1).

Table 1. HPV and characteristics of the patient

	Control (n=340)	Infertility (n=234)	*p*
Age (years)	32 (31-33)	32 (32-33)	*0.567**
BMI(kg/m^2)	23(22-24)	23(22-24)	*0.094**
HPV (+)	%12.1 (n=41)	%11.5 (n=27)	*0.850#*

**Mann-Whitney U test, #Pearson's Chi-square*

There was no significant difference between the groups in terms of age (p=0.567) and BMI (p=0.094). HPV positive patients were detected at a rate of 11.5% (n=27) in the infertile group and 12.1% (n=41) in the control group. There was no significant difference in the measure of patient with positive HPV test, between the groups (p=0.850). In control group HPV 16, 18, and others prevalence were 2.6% (n=9), 3.8% (n=13), and 5.6% (n=19) respectively. In infertile group HPV 16, 18, and others prevalence were 2.1% (n=5), 3% (n=7), and 6.4% (n=15) respectively. There were no significant differences in the comparing the HPV genotypes (Table 2).

Table 2. HPV genotypes vs Infertility

	Control (n=340)	Infertility (n=234)	*p*
HPV (+)	%12.1 (n=41)	%11.5 (n=27)	*0.850*
HPV 16	%2.6 (n=9)	%2.1 (n=5)	*0.909*
HPV 18	%3.8 (n=13)	%3 (n=7)	*0.762*
HPV others	%5.6 (n=19)	%6.4 (n=15)	*0.818*

Chi-square test

Discussion

Sexually transmitted diseases are one of the main causes of primary infertility. It is known that other microorganisms in the vaginal microbiome, especially Chlamydia trachomatis and Neisseria gonorrhea, play a role in infertility by causing salpingitis [9]. While comprehensive studies were carried out in the oncogenic effect of HPV on female genital tract recently, very limited information about infertility due to HPV has emerged. This study provides considerable insight into relation between HPV and female infertility.

As reported Spandorfer et al. HPV positivity was 16% in the patients who underwent in vitro fertilization (IVF) [14]. Lundqvist et al. extended current information of incidence of HR-HPV in infertile women undergoing IVF, was found similar in fertile women [15]. Also another study found that HPV was detected in 15% of infertile women planned for IVF and reported almost all (92%) the test results were HR-HPV type [16]. Present results slightly differ from previous findings reported in the literatüre [17].
There are studies in the literature showing that HPV may have negative effects on fertility. A significant association between HR-HPV infection and infertility has been reported by Rocha et al [18]. A systematic review underlined the association between HPV and poor fertility outcomes are caused by triggering apoptosis in embryonic cells as well as its negative effects on semen[9,19]. Also it is demonstrated that HR-HPV infection is not an independent cause for female infertility, but is a potential risk factor[4]. Interestingly Duan et al. reported that infected sperm play a role in HPV transfection into the oocyte during fertilization, and this situation causes low fertility success [20]. A lower pregnancy rates were reported in HPV positive women, and suggested that HPV infection reduces success of IUI pregnancy by six-fold [14-17].
Even though present results differ some earlier studies, they are consistent with those of Lundqvist et al. and Strehler et al.'s [15,21]. In those studies neither IVF nor artificial reproductive technologies (ART) were appeared to be effected by HPV. Likewise persistent or non-persistent infection could not be linked to female infertility [22]. These values corroborate with others' suggesting no association between HPV and ART success [23-25]. The evidence we also found, supports those assumptions, and added no significant relation between HPV positive women with infertility.
It is plausible that a number of limitations could have influenced the results obtained. The first is the non-categorization for the patients and male exclusion for testing HPV. The second is not pointing out the pregnancy outcomes. These limitations reveal the difficulty of collecting data on infertile couples. However the considerable size of the patients should be noted.
The present findings have some implications for solving the relation between HPV and infertility. Future studies should target on the cellular inflammation responses and different viral genotype.

Conclusion

No significant association was found between female infertility and HPV. The incidence of HPV in women with infertility is not different from the population. Different types of HPV may play a role in infertility. Epidemiological studies including HPV types are needed.

Disclosure

Authors have no potential conflicts of interest to disclose.

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Original Article

The effect of an antioxidant agent-multivitamin complex food supplement on spermiogram in infertile men

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ABSTRACT

Objective: Oxidative stress (OS) occurs due to overproduction of reactive oxygen radicals (ROS) or weakening of anti-oxidant mechanisms and may harm fertility. Our study aimed to investigate the effects of combined support therapy containing antioxidant agents and vitamin complexes on fertility.

Materials and methods: In this retrospective case-control study, 300 randomly selected infertile men were included. For four months, the effect of daily intake of an antioxidant-multivitamin complex containing astaxhantin (5mg), Coenzyme Q10 (100mg), L-Arginine (250mg), L-Carnitine (250mg), Selenium (100mcg), Zinc (10mg), Folic acid (400mcg), Vitamin E (100mg) and Vitamin C (100mg) on spermiogram parameters was investigated.

Results: In Semen volume (2.21 ml -3.05 ml; p=.004), sperm concentration (9.60 million/ml -14.10 million/ml; p=.000), progressive motility sperm count (16.50% -26.65%; p=.000), sperm vitality rate (48% -68%; p=.001) in patients receiving nutritional support a statistically significant increase was found. In addition, it was determined that the treatment provided a significant decrease (77% - 61%; p=.002) in the number of patients with abnormal morphology (at least 4% of patients who could not achieve normal morphology according to Kruger criteria).

Conclusion: It was determined that antioxidant-multivitamin-containing nutritional supplements containing Astaxhantin, coenzyme Q10, L-arginine, L-carnitine, selenium, zinc, vitamins E and C provided significant improvement on semen volume, sperm morphology, vitality and motility. In this context, we predict that the antioxidant-multivitamin complex can be used as a food supplement for supportive treatment in male infertility.

Keywords: male infertility; astaxhantin; oxidative stress; spermiogram

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Introduction

Infertility is defined as the inability to achieve clinical pregnancy success within 12 months despite regular unprotected sexual intercourse, which is seen in 15% of couples [1,2]. Subfertility is defined as difficulty and delay in spontaneous fertilization [3,4]. The most critical parameter that can predict the possibility of unexpected pregnancy is the time that couples spend without using contraception due to their desire for fertility. The chance of pregnancy with regular intercourse in the first six cycles is approximately 80% [4].

The role of the male in fertility depends on the production of functional spermatozoa [1]. Decreased motility (asthenospermia), abnormal morphology (teratozoospermia), reduced number (oligospermia), or absence of sperm in the ejaculate (azoospermia) reduces the chance of pregnancy [5].

The role of oxidative stress (OS) on female and male fertility has gained importance in recent years and has begun to be studied more closely. OS occurs due to overproduction of reactive oxygen radicals (ROS) or the weakening of antioxidant mechanisms [6,7]. A balanced ratio of ROS; is required for spermatogenesis, capacitation, acrosome reaction and attachment of sperm to the zona pellucida [7]. However, the increasing number of ROSs, which are already unstable, can easily interact with lipids, nucleic acids and proteins in the cell structure and cause damage [8]. As a result of detecting DNA damage with advanced technology, the adverse effects of ROS on reproductive cells have begun to be understood [9].

The efficacy of various antioxidant agents, which increase the fertility capacity of infertile women and men, and nutritional supplements containing vitamins and minerals with known antioxidant activity have been demonstrated. In this context, many studies in the literature report the positive effects of Astaxhantin, Coenzyme Q10, Glutathione, L-Arginine, L-Carnitine, Selenium, Zinc, Vitamin E and Vitamin C on fertility. [7,10-13].

Our study aimed to investigate the effects of combined support therapy containing antioxidant agents and vitamin complexes on fertility.

Material and methods

This study was carried out in the Department of Obstetrics and Gynecology, University of Health Sciences, Tepecik Training and Research Hospital, a tertiary center. In this study, spermiogram data of 300 infertile men randomly selected among the patients treated in our infertility clinic between March and June 2022 were used. The retrospective study we conducted has been approved by the ethics committee on January 11, 2023, under research number 810 and decision number 830.

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In the design and implementation of the study, the articles of the Helsinki Convention were adhered to.
Male patients aged 18-55 years, without any systemic disease, and who had not taken any urological medicine or undergone surgery in the last six months were included in the study.
Sperm samples were taken after at least three days of sexual abstinence. Volume, sperm concentration, total sperm count, total motility percentage, progressive motility percentage, morphology and vitality parameters were evaluated according to WHO 2010 criteria [14].
First and foremost, our study focused on examining the impact of a daily intake of an antioxidant-multivitamin complex on spermiogram parameters among our 150 patients. This complex contains astaxhantin (5mg), Coenzyme Q10 (100mg), L-Arginine (250mg), L-Carnitine (250mg), Selenium (100mcg), Zinc (10mg), Folic acid (400mcg), Vitamin E (100mg), and Vitamin C (100mg). Our primary aim was to observe potential improvements in sperm quality over a four-month period. We comparatively analyzed volume, concentration, total motility, progressive motility, abnormal morphology, and vitality parameters in spermiogram tests. These tests were taken from patients at the beginning and again at the end of the 4th month.
On the other hand, 150 patients whose mean age was similar to the study group and who did not want to use nutritional supplements were included in the control group. At the end of the 4th month, the volume, concentration, total motility and progressive motility parameters in the spermiogram tests taken from 300 patients, 150 of whom were from the study group and 150 from the control group, were ranked according to their numerical values. The patients were divided into two groups according to the median value of each parameter. The group of 150 people below the median value was called GROUP I, and the group of 150 people above the median value was called GROUP II. The proportions of patients using antioxidant-multivitamin complex in both groups were calculated and the statistical significance of the distribution was analyzed.

Statistical analysis

Statistical Package for Social Sciences (SPSS) 26.0 software program was used to analyze the data of the patients included in the study. Wilcoxon Signed Ranks Test was applied to examine the effect of the patients on the values before and after the drug. Pearson Chi-Square test was used to examine the relationship between the groups.

Results

In this study, it was determined that using antioxidant agent-multivitamin complex for 4 months significantly improved spermiogram parameters. In Semen volume (2.21 ml -3.05 ml; p=.004), sperm concentration (9.60 million/ml -14.10 million/ml; p=.000), progressive motility sperm count (16.50% -26.65%; p=.000), sperm vitality rate (48% -68%; p=.001) in patients receiving nutritional support a statistically significant increase was found. There was an increase in the total motile sperm count (36.65% -37.50%; p=.006). In addition, it was found that the treatment provided a significant decrease (77% - 61%; p=.002) in the number of patients with abnormal morphology (patients who could not achieve at least 4% normal morphology according to Kruger criteria) (Table 1).
Table 2 compares those who take nutritional supplements and those who do not. Accordingly, a statistically significant association was found between dietary supplement intake and increased sperm volume, concentration, progressive and total motile sperm count. According to this, 65% (n=97; p=.000) of the patients whose sperm volume was above the median value, 70% (n=105; p=.000) of the patients whose sperm concentration was above the median value and

Table 1. Effect of antioxidant agent-multivitamin food complex on spermiogram

Semen analysis	Before Treatment	After Medication	p
Age/year	33		
Volume/ml	2.21	3.05	0,004
Concentration/10^6 ml	9.6	14.1	<0,001
Total Motility/%	36.65	37.5	0,006
Progressive Motility/%	16.5	26.65	<0,001
Abnormal Morphology/%	77	61	0,002
Vitality/%	48	68	0,001

respectively 72% (n=108; p= .000) and 80% (n=120; p=.001) of the patients whose total and progressively mobile sperm count was above the median value were found to use antioxidant agent-multivitamin complex (Table 2).

Table 2. Antioxidant agent-multivitamin complex usage rate between groups

Variable	Group I (n=150)	Group II (n=150)	p
Volume (n)	53(35%)	97(65%)	<0,001
Concentration (n)	45(30%)	105(70%)	<0,001
Total Motility (n)	42(28%)	108(72%)	<0,001
Progressive Motility (n)	30(20%)	120(80%)	0,001

Discussion

Although the exact cause of suboptimal semen quality is not clearly understood, environmental factors, mainly caused by oxidative stress, are blamed as well as genetic factors [15]. Studies have reported a negative correlation between the amount of ROS and the proportion of sperm with normal and borderline morphology [16, 18].
Assisted reproductive techniques can overcome infertility due to tubal factors or low sperm count. However, little progress has been made regarding the adverse effects of advancing age on ovarian function [1]. There are theories stating that this change in oocytes occurs secondary to increased oxidative stress and ROS imbalance secondary to abnormal vascularization and decreased perfusion [19]. PCOS, hyperglycemia, obesity, and endometriosis increase ROS in women [6,20].
There are many studies in the literature on the positive effects of antioxidant agents on fertility. Evaluated as a powerful antioxidant, Astaxhantin is a yellow-orange oil-soluble natural carotenoid. In addition to its antioxidant effect, it has attracted wide attention with its anti-inflammatory, anti-apoptotic and immunomodulatory properties. It has been used as a multi-purpose pharmacological agent in various diseases [21]. It has been reported to protect against oxidative stress by supporting the mitochondrial redox system [22]. It has been reported that astaxhantin protects sperm capacitation and has a protective and beneficial effect on sperm quality [23-25]. Studies have reported that astaxhantin supports blastocyst development and protects the oocyte against oxidative stress [26].
Coenzyme Q10, which has an antioxidant effect, improved the number of motile sperm and increased fertilization with

spontaneous and assisted reproductive treatment methods. Similarly, a positive impact on fertility was found in women by increasing serum inhibin B levels and decreasing FSH levels [7,27-29].

Studies on subfertile men have reported improvement in sperm parameters with daily use of arginine, a semi-essential amino acid [7,30,31].

L-carnitine has a strong antioxidant effect as well as an energy support for the cell. It effects on motility by taking part in the transition of transportable fatty acids from the cytosol to the mitochondria. The use of carnitine has been associated with increased sperm motility and decreased ROS levels. It has been reported to have beneficial effects in treating female infertility [7,32-34].

Selenium is an antioxidant trace element that acts on glutathione peroxidase, by using its which Increased sperm motility has been reported [7,35,36].

Zinc is an essential micromineral found in the body, especially in the prostate gland, 2-4 mg. It is involved in repairing DNA damage. It is involved in testicular development and spermiogenesis. Its deficiency causes hypogonadism, testicular-seminiferous tubule atrophy, and retardation in developing secondary sexual character. [7,37,38] Seminal zinc deficiency may be a risk factor for sperm abnormalities and idiopathic male infertility. Infertile men who smoke are at risk for zinc deficiency. Zinc acts as an antioxidant against oxidative stress, which increases in smoking men. Poor nutritional status from zinc is a risk factor for poor sperm quality and idiopathic infertility [39].

Vitamin E and Vitamin C are water-soluble antioxidants. Degeneration of testicular germinal epithelium is detected in vitamin C deficiency. Ascorbic acids increase the effectiveness of gonadotropin treatments. It is recommended to use 90 mg daily. A reduction in sperm DNA damage has been reported with the combined use of vitamins C and E for two months [7,40]. Adequate intake of folic acid, vitamin C, vitamin E and selenium have been reported to have a protective effect on fertility [41].

Improvement in sperm parameters was observed in infertile men with supportive treatment consisting of L-carnitine, coenzyme Q-10, selenium, vitamins C and E, zinc and folic acid; It has been determined that it provides an increase in fertility by strengthening the antioxidative system in infertile women. It also increased the likelihood of spontaneous or ICSI pregnancy [7,42–44].

In modern societies, the age of becoming a parent is increasing daily. Increasing ROS due to factors such as smoking and alcohol use, improper diet rich in fat-obesity, exposure to radiation, exposure to UV rays, chemical agents-pesticides, and plastic waste threatens the human body. The adverse effects of OS on fertility are inevitable [6,8].

Although exposure to risk factors for ROS can be controlled in some cases, it often develops against our will. For this reason, dietary and lifestyle changes, as well as nutritional supplements with antioxidant content, are gaining importance.

In our study, daily astaxhantin (5 mg), coenzyme Q10 (100mg), L-Arginine (250mg), L-Carnitine (250mg), Selenium (100mcg), Zinc (10mg), Folic acid (400mcg), Vitamin E (100mg) and Vitamin C (100mg) antioxidant-multivitamin supplement, we found significant improvement in semen volume, sperm count, progressively motile sperm ratio, morphology and viability parameters at the end of the 4th month in infertile men. In addition, an increase in the number of motile sperm was observed. According to our other data; When compared to the group that did not take nutritional supplements, it was determined that the use of antioxidant-multivitamin complex was accompanied by increased semen volume, sperm concentration, and total and progressively motile sperm count, which was statistically significant. Our results were similar to the relevant literature.

Conclusion

It was determined that antioxidant-multivitamin-containing nutritional supplements containing Astaxhantin, coenzyme Q10, L-arginine, L-carnitine, selenium, zinc, and vitamins E and C provided significant improvement in semen volume, sperm morphology, vitality and motility. In this context, we predict that the antioxidant-multivitamin complex can be used as a food supplement for the supportive treatment of male infertility. Prospective or randomized studies should be done for getting better outcomes in this subject.

Disclosure

Authors have no potential conflicts of interest to disclose.

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Original Article

The predictive effect of serum AMH and FSH levels alone or in combination on fertility outcome

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ABSTRACT

Objective: To explore the roles of anti-mullerian hormone (AMH) and follicle stimulating hormone (FSH) in predicting clinical pregnancy.

Materials and Methods: Forty patients who were decided on IVF/ICSI due to different infertility etiologies were included in the study. The patients were divided into two groups according to their AMH and FSH values as having a good prognosis or a poor prognosis. The clinical pregnancy and miscarriage rates of 33 cycles with good prognosis and 17 cycles with poor prognosis were compared.

Results: In the good prognosis group, the FSH value was significantly lower than the poor prognosis group (5.98±1.04 mIU/mL vs. 13.6±3.07 mIU/mL, p<0.01), while the serum AMH level was significantly higher. (3.80±1.32 ng/mL vs 0.54±0.02 ng/mL, p<0.01). The rate of chemical pregnancy in the group with good prognosis was twice as high and significant compared to the group with poor prognosis (12 (36.3%) vs 5 (29.4%), p<0.02). In terms of clinical pregnancy rates, the group with good prognosis showed a higher frequency (33.3% vs. 23.5%, p<0.001), while miscarraige rates were higher in the group with poor prognosis (9.0% vs. 25%, p<0.003).

Conclusions: Evaluation of AMH and FSH together is critical in determining clinical pregnancy rates.

Keywords: AMH; FSH; clinical pregnancy; age; BMI

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Introduction

Although many serum and radiological markers are used to determine functional reserve of ovary in women of reproductive age, AMH and FSH are considered the best indicators of ovarian reserve. The main problem with AMH and FSH is that there is no specific cut-off value for both hormones. Obtaining pregnancies with low AMH and high FSH values in rare cases has led to the questioning of the effects of these two hormones on fertility outcome. Despite their significant effects on ovarian reserve, the weaker effects on pregnancy rates have made the combined use of these two hormones widespread [1,2].

Anti-Mullerian hormone (AMH) is a glycoprotein hormone belonging to the transforming growth factor beta family and is synthesized and secreted by granulosa cells. It continues to be released from the primary follicle to the early-stage antral follicle. As the follicles respond to FSH, AMH release also decreases and disappears. Preovulatory follicle, atretic follicles, and corpus luteum are the stages in which AMH activity is completely absent. No AMH activity has been reported in follicles larger than 8 mm [1,2]. Considering the efficiency of AMH to be superior to FSH in determining ovarian reserve has led to the predictive use of this molecule in many areas. Determining the fertility outcome according to AMH values is one of these areas [3]. Since there is no marker to measure the primordial follicle pool directly, the primary follicles indirectly show the primordial pool.

Functional ovarian reserve can be modeled in three different ways according to the number of quality embryos, FSH and AMH values. The common feature of all three models is that maternal age is the determinant.

The higher the number of embryos in the embryo model, the higher the improvement in fertility outcome linearly. In FSH modeling, fertility outcome and AMH values are inversely proportional. The higher the FSH, the more negatively the fertility outcome will be affected. The relationship between AMH values and fertility outcome shows a polynomial course. Mid-range values of AMH give the best fertility results. Low and very high AMH values, on the other hand, decrease the occurrence of pregnancy and increase the risk of abortion [4,5]. The combined use of AMH and FSH is critical in identifying groups with good or poor prognosis. AMH>1.1 ng/ml and FSH <10 mIU/ml suggest good ovarian reserve. Deviation of AMH and FSH values from the above values indicates poor ovarian response [6,7]. This study was planned to determine the clinical pregnancy rates of patients who were divided into groups as ovarian reserve with good or poor prognosis according to AMH and FSH values.

Material and methods

Medical files of 100 patients who were treated for infertility at Gözde Akademi Hospital IVF Center between 2019 and 2021 were retrospectively analyzed. A total of 40 patients with serum AMH and FSH values, who completed their cycles, had fresh or FET cycles, and had demographic data, and 50 cycles were included in the study. The participants were divided into two groups according to their AMH and FSH values as good prognosis (n=33 cycle) and poor prognosis (n=17 cycle). Cases with AMH greater than 1.0 ng/ml and FSH smaller than 10 mIU/ml were included in the group with good prognosis [4,5].

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Cases with AMH less than 1.0 ng/ml and FSH bigger than 10 mIU/ml constituted the group with poor prognosis. Serum follicular stimulating hormone levels were measured with chemiluminescent enzyme immunoassay. Serum AMH levels were measured by using AMH ELISA kit. Informed consent was not obtained because the study was retrospective. Ethical approval was obtained from Diyarbakır Gazi Yaşargil Training and Research Hospital on 30.12.2022 with protocol number 250.

An antagonist protocol was applied to all participants and frozen embryo transfer was performed following artificial endometrial preparation. Serum beta-hCG, clinical pregnancy rate (CPR) and miscarriage rates were calculated. Serum beta-hCG levels were measured 12 days after the transfer. The presence of a gestational sac on ultrasonography at the fourth gestational week was considered clinical pregnancy. Fetal losses before the 20th gestational week were considered miscarriage.

Statistical analysis

SPSS 21 (SPSS Inc., Chicago, IL, USA) program was used for whole data analysis. The t-test was used for normally distributed parameters, and Mann-Whitney U was used for non-normal ones. If the frequencies were smaller than expected, the Fischer exact test was preferred. $p<0.05$ was considered significant.

Results

Demographic, laboratory and fertility outcome data of groups with good (AMH ≥1 ng/ml; FSH <10 mIU/mL) and poor (AMH <1 ng/ml; FSH ≥10 mIU/mL) prognosis are detailed in Table 1.

Table 1. Comparison of demographic, laboratory and fertility data of groups with good and poor prognosis.

	Good prognosis	Poor prognosis	P
Cycle, n(%)*	33 (66%)	17 (34%)	*<0.01*
Age (years) *	26.4±6.2	29.3±8.4	0.02
BMI (kg/m^2) *	25.3±8.3	26.1±5.0	>0.05
FSH (mIU/mL) *	5.9±1.0	13.6±3.0	<0.01
AMH (ng/mL) *	3.8±1.3	0.54±0.02	<0.01
Embryo transferred	1	1	>0.05
Beta hCG, n(%)	12 (36.3%)	5 (29.4%)	0.02
Clinical Pregnancy, n(%)	11 (33.3%)	4 (23.5%)	<0.001
Miscarriage, n(%)	1 (9.0%)	1 (25%)	0.003

**Data are presented as Mean±SD*

The number of cycles of the good prognosis group was approximately two times higher than the number of cycles of the group with poor prognosis (66% vs 34%, $p<0.01$). The mean age of the participants in the poor prognosis group was significantly higher than the good prognosis group. BMI values of both groups were found to be similar. FSH value measured in the group with good prognosis was approximately 2.5 times lower than the group with poor prognosis (5.98±1.04 mIU/mL vs. 13.6±3.07 mIU/mL, $p<0.01$). The serum AMH level of the good prognosis group was found to be significantly higher than the poor prognosis group (3.80±1.32 ng/mL vs 0.54±0.02 ng/mL, $p<0.01$). The number of embryos transferred in both groups was similar. The number of patients with positive pregnancy test in the group with good prognosis was twice as high as in the group with bad prognosis, and the difference was recorded as significant (12 (36.3%) vs 5 (29.4%), $p<0.02$). Clinical pregnancy rates were significantly higher in the good prognosis group than in the poor prognosis group (33.3% vs 23.5%, $p<0.001$). Miscarriage rates were found to be significantly higher in the poor prognosis group (9.0% vs 25%, $p<0.003$)

Discussion

AMH is superior to FSH in showing ovarian reserve and fertility outcome [8]. However, when we used AMH and FSH in combination, these two hormones were more predictive than AMH alone or FSH alone in determining clinical pregnancy rates. However, we do not know clearly whether the hormone that increases the predictive value in the combined use of these two markers is AMH or FSH. In order to make a comment on this issue or to say which of the two hormones is more predictive, analysis using generalized additive mixed models is required. Only by using such a statistical method we can reveal the nonlinear fixed and predictive effect of FSH and AMH on clinical pregnancy rates [9]. The total number of 50 cycles in our study did not provide enough power for us to conduct such an analysis. In a recent study using generalized additive mixed models, when FSH and AMH were used together, AMH provided a significant advantage over FSH in determining fertility outcome (1].

We can classify the possible reasons why AMH is superior to FSH in determining the fertility outcome as follows. While AMH defines functional ovarian reserve, FSH determines the amount of granulosa cell mass capable of synthesizing estrogen. FSH has no feature to define functional ovarian reserve. Neither AMH nor FSH can identify the primordial follicle pool. AMH activity begins with the growth of primordial follicles. Since the growing follicle pool reflects the active granulosa cell mass for AMH, AMH is superior to FSH in determining fertility outcome. Sometimes, despite the sufficient growing follicle pool, FSH may be elevated because insufficient estrogen will be synthesized due to failed follicle development. For this reason, high FSH does not always indicate that ovarian reserve and fertility outcome are bad (10,11].

Both the number of hCG positive pregnant women and clinical pregnancy rates were significantly higher in the good prognosis group compared to the poor prognosis control group. Micarriage rates were higher in the poor prognosis group. While FSH values were >13 mIU/mL in the poor prognosis group, AMH values were recorded as 0.54 ng/mL. In infertile women (>0.6 ng/mL) with AMH values above a certain cut-off, a FSH >10 mIU/mL may not be very important. Büyük et al [10] reported that the oocyte count and clinical pregnancy rates were higher in cases with AMH>0.6 ng/mL despite high FSH compared to cases with AMH<0.6 ng/mL [1,12]. When the literature data and our findings are evaluated together, we can argue that the high FSH value in cases with high AMH levels does not affect the fertility outcome much [4,5]. The inverse relationship of FSH levels with fertility outcome, and the polynomial pattern of AMH will enable the functional ovarian reserve to be determined more clearly when both markers are used together. Thus, the predictivity of FSH and AMH association will increase more significantly [5]. However, we can reach a definite conclusion with more comprehensive studies, after which value of FSH affects the fertility outcome. We could not establish a link between increased miscarriage rates and elevated FSH or decreased AMH in the poor prognosis group. High FSH and low AMH are indicators of deterioration in follicle development quality. For this reason, abortion rates may also be high, as an embryo with a high risk of DNA damage will have a higher chance of being transferred.

The small number of cases is an important limitation of our

study. Also, since AMH is affected by both oral contraceptive use [13] and BMI [14], these two parameters need to be considered. Since the BMI values of our patients were similar, this does not constitute a discrepancy. However, the use of oral contraceptives by the participants was not taken into account. This study is important in terms of showing that the combination of AMH and FSH is more effective than AMH and FSH alone in determining the fertility outcome.

Disclosure

Authors have no potential conflicts of interest to disclose.

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Original Article

Evaluation of maternal and neonatal outcomes of emergency cesarean deliveries in cases of placenta previa uncomplicated with placenta acreata spectrum

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ABSTRACT

Objective: The management and surgery of placenta previa describe a challenging process that requires experience. It is important to decide on the timing of planned cesarean section in women with placenta previa, taking into account the balance between possible maternal severe bleeding and possible neonatal morbidities.

Material and methods: In the present study, the data of 349 singleton pregnant women with a diagnosis of placenta previa uncomplicated by placenta accreta spectrum were analyzed. Patients who underwent planned (68%, n=236) or emergency cesarean section (32%, n=113) were divided into two groups. In this study, maternal demographic and clinical information, surgical procedures and maternal/neonatal outcomes were studied.

Results: The proportion of patients who underwent uterine compression suture and Bakri balloon was found to be significantly higher in the emergency cesarean section group compared to the planned cesarean deliveries group ($p<0.001$). The operation time, hospital stay, urinary tract infection rate, decrease in hemoglobin and need for blood transfusion were found to be significantly higher in the emergency cesarean section group compared to the planned cesarean section group ($p<0.001$, $p<0.001$, $p<0.001$, $p<0.001$, $p<0.001$, $p<0.001$, respectively). In addition, a significant association was detected between emergency cesarean section and prematurity, low birth weight, low APGAR score, increased neonatal intensive care unit hospitalization and neonatal mortality.

Conclusion: Cases of placenta previa are at risk of emergency cesarean delivery, which can be complicated by poor maternal and neonatal outcomes. Equipped centers and experienced teams are of great importance in reducing fetomaternal morbidity and mortality caused by placenta previa.

Keywords: placenta previa; emergency cesarean delivery; bleeding; planned cesarean delivery

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Introduction

Placenta previa (PP) is a condition in which the placenta implants in the lower uterine segment and completely or partially covers the endocervical os and complicates 3 to 10 per thousand deliveries [1, 2, 3]. PP may coexist with maternal morbidities such as antenatal bleeding, peripartum bleeding, peripartum hysterectomy, postpartum transfusion, sepsis, thrombophlebitis, and long hospital stay. In addition, it can coexist poor neonatal outcomes such as prematurity, intrauterine growth retardation, neonatal anemia, respiratory distress syndrome, low APGAR score and increased need for neonatal intensive care. PP is associated with an increased risk of maternal and fetal death [4, 5, 6]. Although the pathogenesis is not clear, increasing cesarean delivery, advanced age pregnancies, smoking-cocaine use and increasing use of assisted reproductive techniques enhance the incidence of PP [3]. Risk factors include previous previa, previous uterine surgery, multiparity, multiple pregnancy, recurrent pregnancy loss that may damage the decidua and myometrium, curettage or manual removal of the placenta [1, 2, 3]. Diagnosis of PP can be made after 16 weeks of gestation, preferably by transvaginal ultrasound examination. It is diagnostic when the placenta completely covers the cervical os or if the distance between the placental border and the cervical os is less than 20 mm [7].

Placental accreta spectrum (PAS) refers to placenta accreta, increta, and percreta, which occur as a result of abnormal invasion of placental villi past the decidua base into the myometrium and it can be complicated by devastating bleeding, multiple complications, and even death. There is an increased risk of PAS in pregnant women with placenta previa [1, 8].

It is important to decide on the timing of the planned cesarean section in women with PP, to ensure the balance between possible severe postpartum hemorrhage and possible neonatal morbidities. In stable PP, planned cesarean delivery should be accomplished at 36-37 weeks of pregnancy [9, 10, 11]. However, approximately 40% of PP patients have preterm delivery before the planned cesarean delivery date can be reached [12].

In the current study, it was aimed to compare the emergency cesarean deliveries (ECD) performed in PP cases uncomplicated with PAS with planned cesarean deliveries (PCD) in terms of poor maternal and neonatal outcomes.

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Material and methods

In this retrospective study, the data of 349 singleton pregnant women having cesarean section with the diagnosis of PP between January 1, 2017 and January 1, 2022 at Health Sciences University Izmir Tepecik Training and Research Hospital were included. Ethical approvals comply with the principles of the Declaration of Helsinki and have been approved by the medical ethics committee (decision no. 15/02/2022-43).

Pregnant women with PAS diagnosis, multiple pregnancies, pre-eclamptic and diabetic pregnant women that may be complicated with emergency delivery, pregnant women with bleeding or coagulation disorders or using anticoagulant drugs were excluded from the present study. The diagnosis of PP was done when the placenta completely covered the cervical os or was closer than 20 mm to there in the second trimester ultrasound examination [7]. Patients with a diagnosis of PP were followed up in our perinatology clinic and operated by the same team. After sterilization, 16-18 Fr foley urinary catheter was applied to the pregnant women on the operating table. Preoperatively, the hemoglobin value of the patients was ensured to be >10g/dl and 4 units of erythrocyte suspension were reserved for all planned cesarean sections. While 2 grams (3 grams in pregnant women over 120 kg) of cefazolin antibiotic prophylaxis [13] was administered 60 minutes before cesarean section, was continued for no longer than 24 hours in surgeries lasting longer than 4 hours and in which blood loss of more than 1500 ml. The shape of the skin incision was decided according to the condition of the patient and the surgical team. The PAS clinical diagnosis was made intraoperatively based on the FIGO guidelines [14]. According to the severity of bleeding during cesarean section, uterine compression sutures (Hayman, B-Lynch), Bakri balloon application, uterine artery ligation, internal iliac artery ligation and hysterectomy procedures were performed when necessary. Pregnant women who underwent emergency cesarean delivery (ECD) due to some reasons such as fetal or maternal life-threatening bleeding, PPROM, and unreliable fetal heart tracing in cardiotocography constituted the study group, while pregnant women who underwent uncomplicated scheduled cesarean delivery (PCD) formed the control group. Groups based on maternal age, obstetric history, placental location, additional surgical/non-surgical procedures performed, operation and hospitalization times, changes in maternal hemoglobin values, blood transfusion, postoperative wound infection, birth week and weight of the newborn, APGAR score and intensive care unit were compared.

Statistical analysis

Data were analyzed using R statistical computing software (version 4.1.1, https://www.r-project.org/) and The Statistical Package for the Social Sciences (SPSS), Version 26.0 (SPSS Inc., Chicago, IL). Shapiro-Wilk test is used to test normality and Levene's test is used to test equality of variances for the continuous variables. The ones violating the normality assumption were compared based on Mann-Whitney U tests (Wilcoxon rank-sum test). For the categorical variables, chi-squared tests or Fisher exact tests were conducted, where appropriate. Pairwise comparisons for categorical variables were conducted via two-sided test of equality for column proportions with Bonferroni correction. The descriptive statistics are given as mean ± standard deviation and median (interquartile range) for the continuous variables, frequency (percentage) for the categorical variables. The two-tailed significance level is set to 0.05.

Results

Our study included 349 pregnant women who were not complicated with PAS, 68% (n=236) were made PCD and 32% (n=113) were made ECD (Table 1). The mean age for all pregnant women was calculated as 30.8 ± 5.9 years.

Table 1. Demographic and Clinical Characteristics

	Planed CD (n=236)	Emergency CD (n=113)	p
Age, year	31.16 ± 5.31	30.15 ± 6.91	0.363[w]
Gravida	2.70 ± 1.30	3.03 ± 1.84	0.373[w]
Parity	1.50 ± 0.96	1.80 ± 1.63	0.388[w]
Spontaneous abortion	0.17 ± 0.51	0.31 ± 0.87	0.177[w]
Curettage	0.03 ± 0.17	0.03 ± 0.16	0.872[w]
Previous cesarean section	1.08 ± 0.75	1.03 ± 0.88	0.413[w]
ART	5 (2.12%)	1 (0.88%)	0.668[f]
History of hemorrhage	199 (84.32%)	104 (92.04%)	0.068[c]
Placental localization			0.094[f]
Lateral	11 (4.66%)	5 (4.42%)	
Anterior	52 (22.30%)	39 (34.51%)	
Posterior	173 (73.31%)	69 (61.06%)	

Data are presented as mean ± sd and median (interquartile range) for continuous variables and frequency (percentage) for categorical variables. w, f and c represent Wilcoxon rank-sum test, Fisher exact test and Chi-squared test, respectively.

Throughout this study, 87% (n=303) of the pregnant women were complicated with antenatal bleeding. The mean operation time for all patients was 81 ± 31 min., hospital stay was 7.2 ± 5.7 days. Bakri balloon 6.9% (n=24), uterine compression suturing in 11% (n=39), internal iliac artery ligation in 10% (n=35) and hysterectomy in 2.9% of the patients (n=10; 6 of them during re-operation) was performed.

Table 2. Surgical Procedure and Maternal Outcomes

	Planed CD (n=236)	Emergency CD (n=113)	p
Vertical skin incision	18 (7.63%)	7 (6.19%)	0.792[c]
Uterine compression suture	20 (8.47%)	19 (16.81%)	0.033[c]
Bakri balloon	4 (1.69%)	20 (17.7%)	<0.001[c]
İnternal iliac artery lig.	22 (9.32%)	13 (11.5%)	0.657[c]
Hysterectomy	4(1.69%)	6 (5.31%)	0.083[f]
Re-operated	2 (0.85%)	4 (3.54%)	0.089[f]
Blood transfusion	30 (12.71%)	89 (78.76%)	<0.001[c]
Wound infection	4 (1.69%)	5 (4.42%)	0.156[f]
Urinary tract infection	29 (12.29%)	48 (42.48%)	<0.001[c]
Length of stay. days	2.8 ± 0.6	3.4 ± 0.8	<0.001[w]
Operation time. min.	63.90±23.38	115.58 ± 8.34	<0.001[w]
Hemoglobin preoperative	10.97 ± 1.42	11.29 ± 1.21	0.024[w]
Hemoglobin postoperative	7.75 ± 0.77	7.13 ± 0.42	<0.001[w]
Hemoglobin change	3.22 ± 1.61	4.16 ± 1.27	<0.001[w]

Data are presented as mean ± sd and median (interquartile range) for continuous variables and frequency (percentage) for categorical variables. w, f and c represent Wilcoxon rank-sum test. Fisher exact test and Chi-squared tes, respectively.

While blood transfusion was applied in 34% (n=119) of the patients, re-operation was required in 1.7% (n=6) of patients due to refractory bleeding to medical treatment. Hysterectomy was performed on all re-operated patients. There were no maternal deaths due to PP during this study. The surgical procedures and maternal outcomes are summarized in Table 2. There was no significant difference between the groups in terms of skin incision type, per-op iliac artery ligation and hysterectomy, re-operation, and postoperative wound infection. The proportion of patients who were subjected to uterine compression sutures in the ECD group (16.81%) was found significantly higher than in the PCD group (8.47%, p=0.033). Bakri balloon application was found significantly higher in the ECD group compared to the PCD group (17.7%; 1.69%, respectively). Longer operative time (115.58 ± 8.34 min; 63.90 ± 23.38 min. p<0.001, respectively), longer hospital stays (3.4 ± 0.8 days; 2.8 ± 0.6 days respectively, p<0.001) and higher rate of urinary tract infection (42.48%; 12.29%, p<0.001, respectively) in the ECD group compared to the PCD group. Also, higher rate of decrease in hemogram (4.16 ± 1.27; 3.22 ± 1.61, p<0.001) and higher need for transfusion (78.76%; 12.71%, p<0.001, respectively) were detected in the ECD group compared to the PCD group (Table 2).

Neonatal outcomes are summarized in Table 3. Compared to the PCD group, the newborns in the ECD group had earlier birth weeks (36.12 ± 0.89 vs 31.45 ± 4.68 p<0.001, respectively), lower birth weight (2666.83 ± 659.79gr vs 1938.10 ± 766.86 p<0.001, respectively), lower 1st and 5th minute APGAR scores (7.89 ± 0.44 vs. 5.03 ± 0.51 p<0.001 and 8.00 ± 1.16 vs 6.89 ± 0.72 p<0.001, respectively) and higher neonatal intensive care admission rates (63.56% vs. 94.69% p<0.001, respectively). The mortality rate was found significantly higher in newborns in the ECD group compared to the PCD group (Table 3).

Table 3. Neonatal Results of participants

	Planed CD (n=236)	Emergency CD (n=113)	P value
Gestational week	36.12 ± 0.89	31.45 ± 4.68	<0.001[w]
	36.00 (35.00- 37.00)	32.00 (29.0- 34.0)	
Birth weight	2666.83 ± 659.79	1938.10 ± 766.86	<0.001[w]
	2777.50 (2300-3092.5)	1860 (1445- 2535)	
1. min. APGAR	7.89 ± 0.44	5.03 ± 0.51	<0.001[w]
	8.00 (8.00- 8.00)	5.00 (5.00- 5.00)	
5. min. APGAR	8.00 ± 1.16	6.89 ± 0.72	<0.001[w]
	8.00 (8.00- 9.00)	7.00 (7.00- 7.00)	
NICU	n=150 (63.56%)	107 (94.69%)	<0.001[c]
Neonatal mortality	n=10 (8.8%)	n=1 (0.4%)	<0.001[c]

Data are presented as mean ± sd and median (interquartile range) for continuous variables and frequency (percentage) for categorical variables. w and c represent Wilcoxon rank-sum test and Chi-squared test, respectively.

Discussion

PP is associated with increased maternal and neonatal morbidity and mortality. Women with PP are at risk of bleeding throughout pregnancy, especially in the third trimester. These patients also have an increased risk for peripartum hysterectomy, blood transfusion, postpartum hemorrhage, sepsis, and poor neonatal outcomes [4, 15, 16, 17]. In this study, maternal and neonatal outcomes of pregnancies with PP uncomplicated with PAS that were subjected to by planned or emergency cesarean section were compared. Also, longer operation and hospitalization times, more frequent urinary tract infections, more hemorrhage and need for transfusion were found in the ECD group compared to the PCD group. Compared to the PCD group, the newborns of the ECD group pregnants were associated with increased prematurity, low birth weight, low APGAR scores and intensive care hospitalization risk.

In the previous studies, it was observed that maternal age, gravida, parity, spontaneous abortion history, number of ART pregnancies and dominant placental localization parameters were not associated with emergency or planned cesarean section in pregnant women with PP [1, 2, 3]. On the contrary, Morlando et al. found a significant association between increased parity and the risk of emergency cesarean section [18]. Ozköse found a significant relationship between antepartum hemorrhages and ECD. Morlando, on the other hand, reported antepartum hemorrhages as the only parameter with significant predictive value for ECD risk [1, 18]. In this study, no significant relationship was found between maternal age, obstetric history (gravida, parity, spontaneous abortion, curettage, previous cesarean section and ART), predominant placental localization, antepartum bleeding history and emergency cesarean section risk.

Erfani and Morlando reported that there was no significant difference between patients who underwent ECD or PCD due to PP in terms of estimated blood loss and blood product transfusion requirement [3, 18]. Ozköse reported lower hemoglobin values in the ECD group both at first admission and at discharge compared to the PCD group,but did not compare the groups in terms of hemoglobin decreased [1]. Durukan reported that ECD was significantly associated with lower preoperative hemoglobin values, increased blood loss and transfusion need when compared to PCD [2]. In this study, preoperative and postoperative hemogram values were detected significantly lower in ECD patients compared to the PCD group. The lack of time for preoperative planned transfusion can be interpreted as the reason for the preoperative low hemoglobin values in the ECD group. In addition, a significant decrease in hemoglobin value and a significant increase in the need for blood transfusion were found in the ECD group. It can be said that the ECD procedure is associated with a significant increase in total blood loss.

In PP cases, peroperative interventions such as skin incision type or compression suture, balloon application, arterial ligation and even hysterectomy may vary depending on the patient's condition and the practice of the team. Fan et al. reported that vertical skin incision was used significantly more in the ECD group [5]. Ozköse did not report a significant difference between the groups in terms of uterine compression suture, balloon tamponade, internal iliac artery ligation and hysterectomy procedures applied during cesarean section for hemorrhage control [1]. Durukan found a significant increase in the rate of intraoperative intervention in addition to cesarean section in the ECD group. While they reported a significant increase in the rate of hysterectomy, it was found that there was no significant difference between the groups when the Bakri balloon, uterine compression suture, iliac artery ligation, abdominal packing and re-operation procedures were compared alone [2]. In the present study, no significant difference was found between the groups in terms of vertical skin incision. Compared to the PCD group, there was a significant increase in procedures with relatively lower morbidity, such as uterine compression suture and Bakri balloon application, in the ECD group. In addition, there was no important difference in the application of high morbidity procedures such as internal iliac artery suturing, hysterectomy and re-operation. It is thought that the adequate facilities and experienced human resources in patient follow-up in the

postpartum period allow more conservative interventions during cesarean section.

Studies have reported that longer hospital stays were observed in the ECD group compared to the PCD group [1, 2, 3]. Increased rates of postoperative maternal morbidity (fever, wound infection, sepsis, organ failure, intensive care hospitalization) have been reported in patients in the ECD group [1, 5, 18]. In this study, prolonged hospitalization and increased urinary tract infection rate were found in ECD group patients. It has been reported that prolonged urinary catheterization is a facilitating factor in urinary tract infection [19].

Poor neonatal outcomes in pregnant women who underwent ECD due to PP are not surprising. There are many studies stating that newborns of ECD group pregnant women are complicated with prematurity, low birth weight, low APGAR score, increased neonatal intensive care hospitalization rates and neonatal mortality compared to PCD group [1, 2, 5]. On the other hand, Morlando et al. reported that low birth weight increased in newborns in the ECD group, but no significant difference was found between the groups in terms of APGAR scores and neonatal intensive care unit (NICU) admissions [18]. In this study, a significant association was found between ECD and prematurity, low birth weight, low APGAR score, NICU hospitalizations and mortality, similar to the literature. It has been revealed that the main cause of poor neonatal outcomes is prematurity, even does not have time for steroid administration for fetal lung maturation in most cases.

Being retrospective constitutes the weakness of our study. There were deficiencies in accessing medical records related to the antenatal process. On the other hand, the strength way of the current study is the higher number of patients compared to other similarly designed studies in the literature. It is also found that performing the surgery by the same team provides standardization and increases the reliability of our results.

PP cases have a risk of ECD, which causes poor maternal and neonatal outcomes. Compared to the PCD group, patients in the ECD group had a significant increase in poor maternal outcomes such as bleeding, blood transfusion, additional per-operative interventions (compression suture and Bakri balloon), prolonged hospital stay, and urinary tract infection. In addition, newborns in the ECD group were significantly associated with poor neonatal outcomes such as prematurity, low birth weight, low APGAR score, and intensive care admission.

Disclosure

Authors have no potential conflicts of interest to disclose.

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Aegean Journal of Obstetrics and Gynecology 5/2

Aegean Journal of Obstetrics and Gynecology

Case Report

Hysteroscopic management of infected and partially discharged desidual cast in an adolescent: A case report and review of the literature in adolescents

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A B S T R A C T

Objective: Decidual cast in other words membranous dysmenorrhea is a rare entity. Hereby, we report the first infected case of an adolescent caused by drospirenon containing contraceptive use and managed successfully by hysteroscopy.
Case presentation: A 13 years-old girl started on drospirenon containing contraceptive theraphy since her menarche resulted in menorrhagia and anemia that requires transfusion. On follow up, she developed a partially discharged infected mass revealed to be a decidual cast on pathological review.
Discussion: Membranous dysmenorrhea occurs more frequently in the adolescent and young adult population. All cases in this review were on hormonal theraphy except one occured spontaneously. Cast formation of the immature uterus after menarche is an exaggerated response to dose-independent increased progestin levels.
Keywords: decidual cast; hysteroscopy; infection; membranous dysmenorrhea; oral contraceptives

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Introduction

"Decidual cast'' or ''membranous dysmenorrhea'' is referred to discharge of endometrial cast in the shape of endometrial cavity per the uterine cervix amd vagina [1]. It is a rare entity mentioned in the literature by case reports and case series. The differential diagnosis of tissue passed through vagina in an adolescent includes aborted pregnancy, rhabdomyosarcoma (sarcoma botryoides), foreign body, polyp and a very rarely decidual cast. Pathologic examination is the only way for diagnosis [2]. Theories put forward are due to an increase in the production of estrogen and progesterone, infection, exaggerated decidual reaction of menstrual cycle, intense development of spiral arterioles and high blood levels of endogenous or exogenous progesterone [1]. Menorrhagia is one of the common menstrual disorders encountered in adolescent girls and is diagnosed in 34% to 37% of the adolescent population. Oral contraceptives are frequently used to treat adolescent menorrhagia. Treatment with hormonal contraceptives provides hemostasis and endometrial stabilization [3]. Decidual cast formation can be seen as an unusual side effect during or after cessation of treatment [4]. Hereby we aimed to present an infected and partially discharged case caused by drospirenon containing oral contraceptive use and managed successfully by hysteroscopic approach. enign neoplasms of the ovaries are of epithelial origin in 50%. Mucinous tumors are the second most common type of epithelial tumors and comprise 8–10% of ovarian tumors. They may macroscopically reach massive dimensions, although the size of the tumor is not included as a criterion for malignancy. All of mucinous neoplasms, 80 % are benign. Ovarian mucinous cystadenomas are characteristically unilateral, with only 5% presenting bilaterally [1].

Benign mucinous tumors typically have a lobulated, smooth surface, and contain mucoid material within the multilocular. Laparoscopy has become the standard of care in the management of ovarian cysts, because of the lower morbidity rate, improved postoperative recovery. Conservative procedures such as ovarian cystectomy may be preferred in patients with ovarian benign tumors who desire to retain their fertility. Recurrent mucinous cystadenoma after optimal excision is very rare.However, when faced with a huge mass, saving the ovarian tissue may be difficult. . If the cystectomy procedure is not completed thoroughly, recurrences may occur. The data on recurrence of benign ovarian mucinous cystadenomas are limited. A literature search resulted in 11 cases from the first report in 2001 to the present.
This report a 22-year-old nulliparous. women with a huge benign mucinous cystadenoma managed by laparoscopic cystectomy, followed by recurrence within 2 years. Left salpingo-oophorectomy was performed on a repeat laparoscopy. This report discusses a patient, who underwent a laparoscopic unilateral salpingoophorectomy after recurrent mucinous cystadenoma.

Case Report

A 13 year-old girl presented to our emergency department with a complaint of heavily bleeding lasting for 20 days after menarche. Based on laboratory findings, hemoglobin level was 8.9 gr/dL whereas platelet count, prothrombin time, activated partial prothrombin time, international normalized ratio and bleeding time were in the normal range.

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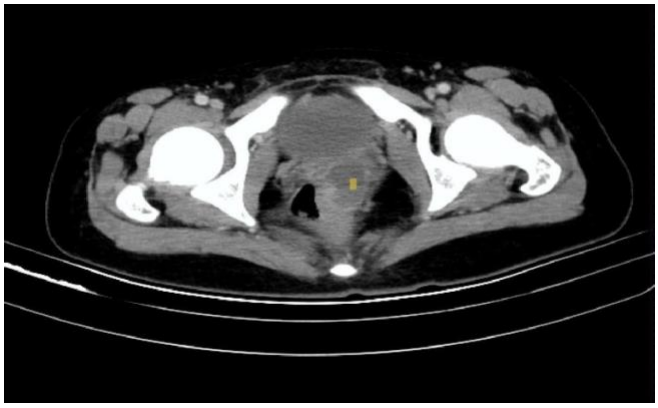
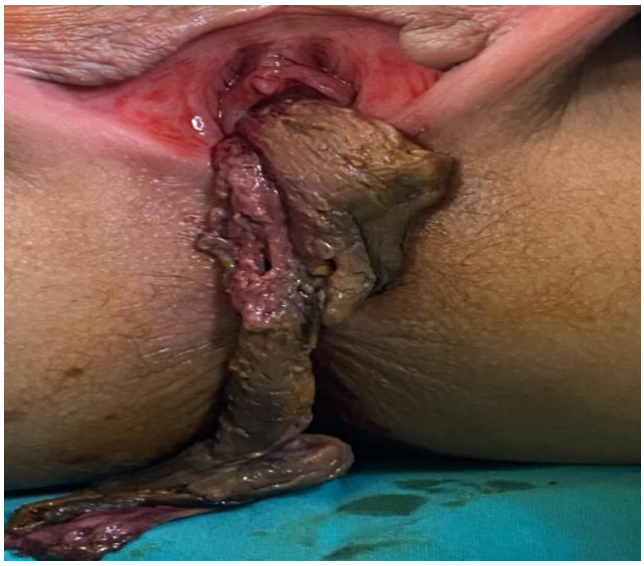
Regarding her history, three units of erythrocyte suspension were transfused and she started on drospirenon and ethinyl estrodiol containing oral contraceptive for the treatment of menorrhagia in another medical unit. Her family history was noncontributory. She was consultated by a pediatric hematology department and called for follow up. Her bleeding disorder workup (von Willebrand antigen, factor VIII antigen, coagulation panel, and thyroid panel) was negative. After a month, she admitted to the emergency department with complaints of heavily bleeding, abdominal pain and vomiting on the 6th day of her cycle. Her blood tests revealed anemia (hemoglobin 8.7 gr/dL), leukocytosis (15.4 × 109/L), and elevated acute phase reactants (procalcitonin was 0.25 ng/mL(normal range 0-0.046), CRP was 10.1 mg/L (normal range 0-5)). Serum human chorionic gonadotropin level was within non pregnant levels. On computed tomography imaging, heterogenous fluid collection in the endometrial cavity and cervix was reported (Figure 1).

Figure 1. Computed tomography image of uterus (endometrial cavity is pointed)



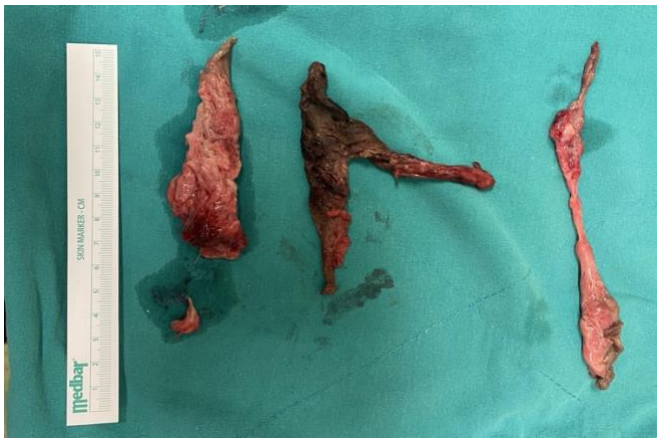
On gynaecologic consultation foul smelling bleeding was recorded. A mass protruding per hymenal ring was inspected. When provoked to cough, a part of the mass passed the hymenal ring and a piece was excised for pathological examination. A transabdominal ultrasound revealed an enlarged uterus(10 × 7 × 6.5 cm) and distended cervix filled with soft tissue extending per vagina. An urgent pathological review revealed decidualizated endometrium. She was hospitalized and administered broad spectrum antibiotherapy. During the 48 hour of theraphy, foul smell disappeared and an examination under general anesthesia was planned (Figure 2).

Figure 2. Adherent mass bulging from vaginal introitus.



On examination, taking care of the hymenal ring, the protruding tissue was carefully held by an instrument and pulled through the vagina. Since the tissue broke off via pulling, a cystoscope no: 11 was inserted through the intact hymenal ring to observe the vagina and the uterine cavity. The remaining part of the tissue through cervical canal was removed spontaneously by the extander effect of running water (Figure 3).

Figure 3. Excised decidual cast material.



On final view, uterine cavity and vagina were normal. She was discharged and oral antibiotheraphy was prescribed for a week. However, she failed to attend her follow up.

Discussion

To the best of our knowledge this is the first case of an infected decidual cast managed successfully by hysteroscopy and also the first case reported while on drospirenon use among adolescents.

On the literature search, terms such as 'decidual cast'' and ''membranous dysmenorrhea'' were used among adolescents (aged 10-19 years) and only 16 cases were found [4-14] (Table 1). The average age of the cases was 14.9 (range 10.8-19) years. Membranous dysmenorrhea occurs more frequently among the adolescent and young adult population. In a review including all ages, 12 out of 21 cases were under the age of 20 [7]. All of the cases were after menarche. Progesterone levels tend to rise incrementally after menarche. Although the progesterone and progesterone containing agents induce decidualization and cycle stability , the mystery of membranous dysmenorrhea still remains unclear [15].Only thirteen cases were found to suffer from pain, a type of secondary dysmenorrhea, which occurs from the passage of tissues through the non-dilated cervix [16].

Physiologic and supraphysiologic doses of progestin causes an exaggerated response of the immature uterus resulting in excessive endometrial growth and cast formation [4-14]. An immature uterus differs from a mature uterus by immature uterine natural killer (uNK) cells. uNK cells matures with each cycle to form effective spiral artery and placental vasculature development during pregnancy. Increased progesterone on uNK cells may lead to an ineffective spiral artery development and makes adolescents more sensitive to form an endometrial cast [5]. Depomedroxyprogesterone acetate has been reported in the decidual cast development and was cited in 50% of reported adolescent cases. Oral contraceptives are related with another 25% of cases whereas the hormonal patch is in 12.5%. All cases were on hormonal therapy except for one that occured spontaneously This demonstrates that cast formation of the immature uterus after menarche is not attributable to the dose given but rather to an exaggerated response due to increased progestin levels [5].

Table1. Demographic and clinical features of the cases

Case	Age (years)	Symptom	Suspicious for Etiology	Pathological confirmation	Additional history/finding	Management	Follow-up
Parkes et al.2021 (5)	12	dysmenorrhea	COC for heavy bleeding	Yes	Menorrhagia	Discontinued COC	NR
Van Gaal et al.2016 (6)	18	painful vaginal tissue loss	COC	Yes	NR	NR	NR
Topçu et al.2015 (7)	17	dysmenorrhea and painful tissue passage	none	Yes	leukocytosis (14.8 × 109/L) attiributed to inflammatory substances of pain	Follow up	8 months, uneventful
Rabinerson et al. 1995 (8)	18	NR	COC	NR	NR	NR	NR
Omar et al.2007 (9)	12	Vaginal tissue discharge and dysmenorrhea	estrogen and progestine patch for dysmenorrhea	Yes	Cerebral palsy, dysmenorrhea	DMPA for dysmenorrhea	3 years, uneventful
Omar et al.2007 (9)	13	Painful vaginal discharge	DMPA for dysmenorrhea	Yes	Dysmenorrhea	Continued to use DMPA	4 years, uneventful
Omar et al.2007 (9)	15	Painful vaginal discharge	Transdermal patch for contraception on the 5th cycle	Yes	NR	Continued to use transdermal patch	NR
Omar et al.2007 (9)	16	Painful vaginal bleeding	DMPA for contraception on 15th month	Yes	NR	Continued to use DMPA	3 years, uneventful
Omar et al.2007 (9)	17	Painful vaginal discharge	COC for contraception on 7th month	Yes	NR	Discontinued COC, started DMPA	2 years, uneventful
Omar et al.2007 (9)	16	Painful vaginal discharge	DMPA postpartum	Yes	NR	Continued to use DMPA	2 years, uneventful
Sen et al.2013 (4)	10.8	Painful vaginal discharge	Oral contraceptive	Yes	Menorrhagia	Discontinued oral contraceptive	4 months, uneventful
Appelbaum. 2010 (10)	16	Cramping, tissue discharge and irreguler bleeding	norethindrone acetate	Yes	Endometriosis and mullerian abnormality	Discontinued norethindrone acetate	Multiple surgeries and hormonal agents for four years
Torres et al.2009 (11)	13	Vaginal tissue discharge after bleeding	monophasic oral contraceptive	Yes	Heavy bleeding	Continued OC until withdrawal then cyclic progestogen	4 months, uneventful
Malik et al.2015 (12)	13	Vaginal tissue discharge after cramping and bleeding	COC on 10th month	Yes	menorrhagia	Discontinued COC	NR
Ekmekci et al.2016 (13)	13	Pain and abnormal bleeding	COC	Yes	Abnormal uterine bleeding	Hysteroscopic view, spontaneous discharge on follow up	NR
Strauss.2018 (14)	19	Spotting,vaginal tissue discharge	DMPA	NR	Sexually active	NR	NR

There are no long-term effects of the situation. The longest follow up period was four years with DMPA. Fourteen out of 16 cases were confirmed by pathology. Treatment options were controversial. Five cases under contraceptives had discontinued taking contraceptive pills probably because of recurrence fear but no recurrences were found despite ongoing hormonal contraceptives or progesterones.As a result, this suggests that patients can safely continue hormonal contraceptive therapy. Only one case report presented the use of hysteroscopy to view the mass that was later spontaneously discharged on follow up [13].

We conclude that membranous dysmenorrhea should be kept in mind as a differential diagnosis of adolescents with lower abdominal pain, especially for ones under hormonal contraceptive therapy. The infection risk of undischarged tissue is not rare and may cause a misdiagnosis of malignancy and treatment delay. Hysteroscopic approach is safe for partially discharged cases.

Disclosure

Authors have no potential conflicts of interest to disclose.

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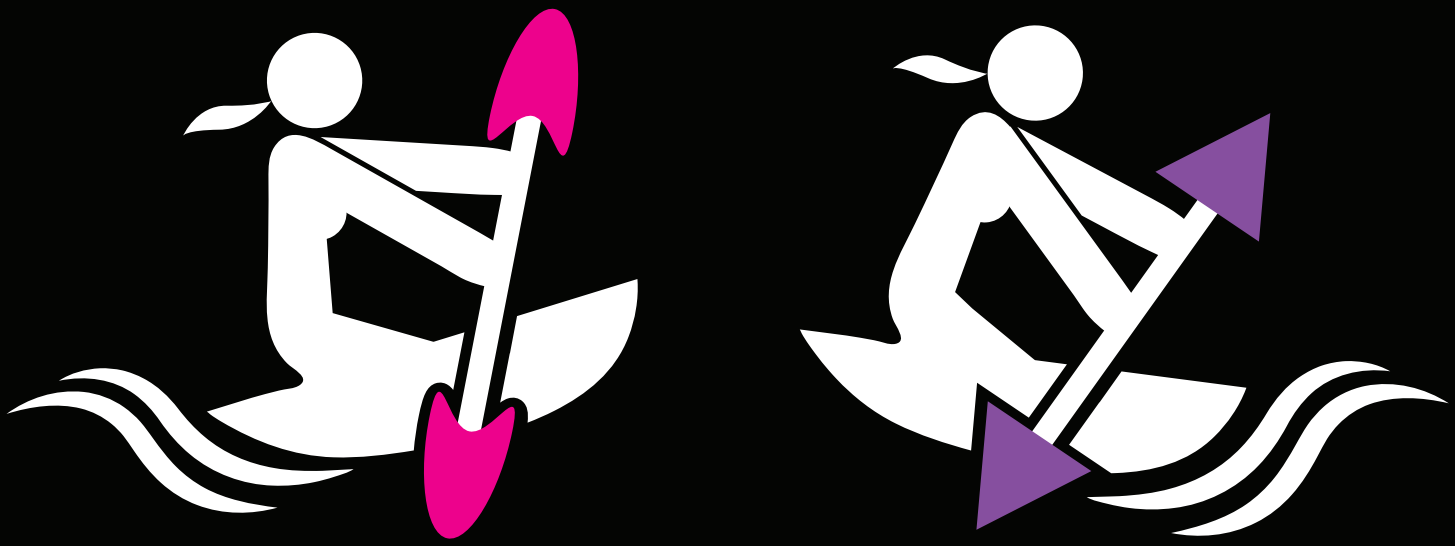

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