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Prenatal diagnosis of hemoglobinopathies by chorionic villus sampling: A large single-center experience

Koryon villus örneklemesi ile hemoglobinopatilerin prenatal tanısı: Geniş ölçekli tek merkez deneyimi

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Abstract

Objective: Hemoglobinopathies are among the most common inherited disorders worldwide. Given the high prevalence and carrier rates in our region, this study aimed to evaluate the obstetric, genetic, and procedure-related outcomes of pregnancies undergoing chorionic villus sampling (CVS) for prenatal diagnosis.

Materials and Methods: This retrospective observational study included 1,330 pregnant women referred for hemoglobinopathy screening between January 2008 and December 2012. Data regarding gestational age, indication for CVS, placental location, number of insertions, complications, and genetic results were analyzed. Transabdominal CVS was primarily performed between 10 and 14 weeks of gestation.

Results: The mean gestational age at CVS was 12.4±1.03 weeks. Late referral (≥14 weeks) was observed in 8.8% of cases. Adequate sampling was achieved with a single insertion in 88.3% of procedures. The overall complication rate was 2.6%, with a fetal loss rate of 1.8% and an incidence of chorioamnionitis of 0.07%. Multiple insertions (p=0.036) and posterior placental location (odds ratio: 2.21; 95% confidence interval: 1.11-4.38; p=0.033) were significantly associated with an increased risk of complications. Genotype analysis showed that 50.2% of fetuses were carriers, 25.4% were normal, and 21% were affected. Pregnancy termination was performed in most of the affected cases (n=266), while 11 cases resulted in live births. Hemoglobin S (HbS) was the most frequent variant (31%), followed by HbD and HbE. The most common β-thalassemia mutation was IVS-I-110 (G>A), and the most frequent α-thalassemia mutation was $-\alpha^{3.7}$ deletion.

Conclusion: CVS is a reliable and effective method for early prenatal diagnosis of hemoglobinopathies. Procedure-related risks are influenced by technical factors, such as the number of insertions and placental location. Standardization of techniques and operator experience may reduce complications. In high-prevalence regions, the integration of carrier screening and early prenatal diagnosis is essential to reduce the disease burden.

Keywords: Chorionic villus sampling, hemoglobinopathies, prenatal diagnosis, β-thalassemia, sickle cell disease

Öz

Amaç: Hemoglobinopatiler dünya genelinde en sık görülen kalıtsal hastalıklar arasında yer almaktadır. Bölgemizdeki yüksek prevalans ve taşıyıcılık oranları göz önünde bulundurularak, bu çalışmada prenatal tanı amacıyla koryon villus örneklemesi (CVS) uygulanan gebeliklerin obstetrik, genetik ve işleme bağlı sonuçlarının değerlendirilmesi amaçlandı.

Gereç ve Yöntemler: Bu retrospektif gözlemsel çalışmaya, Ocak 2008-Aralık 2012 tarihleri arasında hemoglobinopati taraması amacıyla merkezimize başvuran ve CVS uygulanan 1330 gebe dahil edildi. Gebelik haftası, CVS endikasyonu, plasenta lokalizasyonu, giriş sayısı, komplikasyonlar ve genetik sonuçlara ait veriler analiz edildi. Transabdominal CVS işlemi ağırlıklı olarak 10-14. gebelik haftaları arasında uygulandı.

PRECIS: Chorionic villus sampling provides reliable prenatal diagnosis of hemoglobinopathies, while multiple needle insertions and posterior placental location increase procedure-related complications.

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Bulgular: CVS uygulama haftası ortalama 12,4±1,03 hafta idi. Olguların %8,8'inde geç başvuru (≥14 hafta) saptandı. Yeterli örnekleme işlemlerin %88,3'ünde tek giriş ile sağlandı. Toplam komplikasyon oranı %2,6, fetal kayıp oranı %1,8 ve koryoamniyonit insidansı %0,07 olarak bulundu. Giriş sayısının artışı (p=0,036) ve posterior plasenta yerleşimi (olasılık oranı: 2,21; %95 güven aralığı: 1,11-4,38; p=0,033) komplikasyon riski ile anlamlı olarak ilişkiliydi. Fetüslerin %50,2'si taşıyıcı, %25,4'ü normal ve %21'i etkilenmiş olarak saptandı. Etkilenmiş olguların çoğunda gebelik sonlandırıldı (n=266), 11'i canlı doğumla sonuçlandı. En sık hemoglobin varyantı hemoglobin S (HbS) (%31) olup, bunu HbD ve HbE izledi. En sık β-talasemi mutasyonu IVS-I-110 (G>A), en sık α-talasemi mutasyonu ise -$\alpha^{3.7}$ delesyonu idi.

Sonuç: CVS, deneyimli merkezlerde uygulandığında hemoglobinopatilerin erken prenatal tanısında güvenilir ve etkili bir yöntemdir. İşleme bağlı komplikasyonlar giriş sayısı ve plasenta lokalizasyonu gibi teknik faktörlerden etkilenmektedir. Yüksek prevalanslı bölgelerde taşıyıcı taraması ve erken prenatal tanının entegre edilmesi hastalık yükünün azaltılmasında kritik öneme sahiptir.

Anahtar Kelimeler: Koryon villus örneklemesi, hemoglobinopatiler, β-talasemi, orak hücre hastalığı

Introduction

Hemoglobin is the main component of erythrocytes and the primary protein responsible for oxygen transport to tissues. The predominant form of hemoglobin in adults, hemoglobin A (HbA, $\alpha_2\beta_2$), has a tetrameric structure encoded by two separate globin gene clusters located in different regions of the genome. Hemoglobinopathies, which are genetic disorders affecting hemoglobin synthesis, constitute the most common group of monogenic diseases worldwide. These disorders are caused by deoxyribonucleic acid (DNA) variants located in the genes encoding globin chains or in their regulatory regions[1]. Hemoglobinopathies may lead to quantitative or qualitative abnormalities in globin chain synthesis. Reduced production of α or β globin chains results in α- and β-thalassemia syndromes, whereas structural abnormalities due to amino acid substitutions in globin chains lead to sickle cell disease and other abnormal hemoglobin variants. Structural hemoglobinopathies alter the solubility, stability, and oxygen-binding properties of hemoglobin, leading to hemolytic anemia and clinical complications related to chronic anemia and tissue hypoxia. These disorders are mostly inherited in an autosomal recessive pattern and are commonly associated with anemia[1].

It is estimated that 5-7% of the global population carry a structural variant that leads to defective hemoglobin synthesis. This results in approximately 300,000-500,000 affected newborns annually, the majority of whom have sickle cell disease, whereas a smaller proportion have transfusion-dependent β-thalassemia major. Although hemoglobinopathies are particularly prevalent in Africa, Asia, and Mediterranean countries, increasing migration has made them an important public health issue in Europe, the Americas, and Australia[2,3].

Structural hemoglobin variants arise from amino acid substitutions in globin chains. The most commonly encountered variants in clinical practice are HbS, HbD, HbE, and HbC. HbS is the most common and the first identified hemoglobin variant worldwide, with carrier rates reaching 10-40% in some regions of Africa[3]. In Türkiye, particularly in the Çukurova region, the carrier rate of HbS has been reported as 8.2%. The second most common structural hemoglobin variant in our country is HbD Los Angeles, with a carrier rate of 0.2%. HbE, the third most common variant, is predominantly observed in the Çukurova region, with reported carrier rates ranging from 0.6% to 2.4%[4].

To date, 42 different structural hemoglobin variants have been identified in the Turkish population[4]. Due to the high prevalence and carrier rates of hemoglobinopathies in our region, the Hereditary Blood Diseases Application and Research Center established at Çukurova University in 1994 to prevent births affected by hemoglobinopathies and to conduct advanced diagnostic, therapeutic, and research activities. Chorionic villus sampling (CVS) has been performed for prenatal diagnosis since 1992, and the transabdominal single-needle technique is currently the standard method. Since the initiation of prenatal diagnostic services, approximately 5,000 cases have been evaluated. Due to the large caseload and archival limitations, this study included 1,330 cases diagnosed with hemoglobinopathies between January 1, 2008, and December 31, 2012.

Materials and Methods

Approximately 5,000 cases have undergone CVS for prenatal diagnosis at the Department of Obstetrics and Gynecology, Çukurova University Faculty of Medicine since 1992. Due to the large number of cases and archival limitations, a total of 1,330 cases evaluated for hemoglobinopathies between January 1, 2008, and December 31, 2012, were included in this study.

All pregnant women scheduled for CVS for prenatal diagnosis received genetic counseling prior to the procedure. They were informed about the procedure technique, possible complications, and their individual genetic disease risk relative to the population risk. In patients who accepted the procedure, blood groups and routine laboratory tests were evaluated, and gestational age, indication for CVS, placental location, pregnancy complications, and CVS results were recorded in the medical history and procedural records.

CVS was performed via the transabdominal route between 10 and 21 weeks of gestation. Sterile conditions were ensured prior to the procedure; during the intervention, villus samples were aspirated using a 20-gauge needle and a syringe containing 5 mL of heparinized saline solution.

Ultrasonographic evaluation was performed using a 3.5 MHz convex probe (Voluson 730 Pro, GE Healthcare). Routine analgesia was not administered during the procedure, and prophylactic anti-D immunoglobulin was given to patients at risk of Rh incompatibility.

Fetal DNA was isolated from the obtained samples in the Molecular Biology and Gene Laboratory of the Department of Medical Biochemistry, Çukurova University Faculty of Medicine. Mutation analysis was carried out using amplification-refractory mutation system (ARMS), restriction fragment length polymorphism (RFLP), or both. On average, the results were reported within two weeks. Follow-up of pregnancies with normal mutation analysis results continued at different centers. In fetuses with high-risk parental genotype combinations, pregnancy termination was performed with the family's consent and in accordance with the decision of the relevant ethics committee.

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Çukurova University Faculty of Medicine Non-Interventional Clinical Research Ethics Committee (approval number: 13, date: 04.04.2013). Written informed consent was obtained from all participants.

Statistical Analysis

Statistical analyses were performed using SPSS version 20.0 (IBM Corp., Armonk, NY, USA). Categorical variables were summarized as numbers and percentages, while continuous variables were expressed as mean ± standard deviation or median (minimum-maximum). The chi-square test was used to compare categorical variables. Normality of continuous variables was assessed using the Kolmogorov-Smirnov test; depending on the distribution, either the independent samples t-test or the Mann-Whitney U test was applied. A p-value <0.05 was considered statistically significant.

Results

A total of 1,330 cases undergoing CVS for prenatal diagnosis were included in the study. The mean gestational age at presentation to the clinic was 10 weeks; 8.8% of cases presented at or after 14 weeks of gestation (Table 1).

The earliest gestational age at which CVS was performed was 10 weeks, and the latest was 21 weeks and 5 days. The mean gestational age at the time of the procedure was 12.4±1.03 weeks, with a median of 12 weeks and 2 days. The distribution of cases according to gestational age at the time of the procedure is presented in Table 2.

Genotypic characteristics related to hemoglobinopathies in pregnant women presenting to our clinic are shown in Table 3. Accordingly, the most frequently detected maternal genotype was heterozygous HbS carrier (HbAS) (n=812), followed by heterozygous IVS-I-110 (G>A) mutation, consistent with β-thalassemia carrier status (n=216).

Table 1. Gestational week at admission of cases scheduled for chorionic villus sampling

Gestational weeks	n	%
4	1	0.1
5	1	0.1
6	21	1.6
7	76	5.7
8	124	9.3
9	226	17
10	274	20.6
11	245	18.4
12	166	12.5
13	80	6
14	54	4.1
>14	62	4.7
Total	1330	100

Table 2. Distribution of cases undergoing chorionic villus sampling according to gestational age

Gestational weeks	n	%
10	1	0.1
11	65	5
12	480	36
13	435	32.8
14	194	14.6
>14	152	11.5
Total	1330	100

Table 3. Genotypic characteristics of pregnant women presenting to our clinic

Genotype	n	%
HbAS (heterozygous HbS carrier)	812	61.1
β-thalassemia carrier: IVS-I-110 (G>A)	216	16.2
β-thalassemia carrier: IVS-I-6 (T>C)	31	2.3
Indeterminate genotype	30	2.3
α-thalassemia: -$\alpha^{3.7}$ deletion	27	2
HbAS + α-thalassemia (-$\alpha^{3.7}$)	24	1.8
β-talasemi: Codon 39 (C>T)	19	1.4
HbAD (heterozygous HbD)	16	1.2
HbAE (heterozygous HbE)	14	1.1
β-thalassemia: -30 (promoter mutation)	14	1.1
HbSS (homozygous HbS)	14	1.1
β-thalassemia: Codon 8 (-AA)	11	0.8
Other	102	2.7
Total	1330	100

Table 4 shows the genotypic characteristics of partners of pregnant women presenting to our clinic with respect to hemoglobinopathies. Accordingly, the most frequently detected genotype was the heterozygous HbAS (n=821), followed by the heterozygous IVS-I-110 (G>A) mutation, consistent with β-thalassemia carrier status (n=180).

The number of insertions performed to obtain adequate samples in cases undergoing CVS is presented in Table 5.

Table 4. Genotypic characteristics of partners of pregnant women presenting to our clinic

Genotype	n	%
HbAS (heterozygous HbS carrier)	821	61.7
β-thalassemia carrier: IVS-I-110 (G>A)	180	13.5
β-thalassemia carrier: IVS-I-1 (G>A)	39	2.9
α-thalassemia: -$\alpha^{3.7}$ deletion	32	2.4
Indeterminate genotype	27	2.0
β-thalassemia carrier: IVS-I-6 (T>C)	26	2.0
β-thalassemia: Codon 39 (C>T)	22	1.7
β-thalassemia: Codon 8 (-AA)	20	1.5
HbAS + α-thalassemia (-$\alpha^{3.7}$)	18	1.4
HbAE (heterozygous HbE)	17	1.3
β-thalassemia: -30 (promoter mutation)	12	0.9
HbAD (heterozygous HbD)	11	0.8
HbSS (homozygous HbS)	8	0.6
Other	97	7.3
Total	1330	100.0

Table 5. Number of insertions performed to obtain adequate material in cases undergoing chorionic villus sampling

Number of insertions	n	%
Single insertion	1175	88.3
Two insertions	134	10.1
Three insertions	19	1.4
Four insertions	1	0.1
Five insertions	1	0.1
Total	1330	100

Adequate material was obtained with a single insertion in 1,175 cases (88.3%), while two insertions were required in 134 cases (10.1%) and three insertions were required in 19 cases (1.4%).

Adequate samples were obtained and successfully analyzed in 1,284 of 1,330 pregnancies (96.6%); no diagnostic result was obtained in 46 cases (3.4%). Among these, 38 cases with inconclusive results are presented in detail in Table 6. In these cases, maternal contamination was identified in 5 cases, the mutation was not detected in 16 cases, and samples were insufficient in 17 cases. Considering the gestational age, repeat CVS was performed in 17 cases, whereas cordocentesis was carried out in 21 cases.

Among the 38 cases that required a repeat procedure, a single insertion was performed in 32 cases, two insertions were performed in 5 cases, and three or more insertions were performed in 1 case. Of the 17 cases with insufficient sample acquisition, 13 underwent a single insertion (76.4%), 3 required two insertions (17.8%), and 1 required three or more insertions (5.8%). Among the 5 cases with maternal contamination, 4 underwent a single insertion (80%) and 1 required two insertions (20%). Of the 16 cases in which the mutation could not be detected, 15 underwent a single insertion (93.7%), and 1 required two insertions (6.3%).

Complications occurring after CVS are presented in Table 7. Of the 1,330 cases undergoing CVS, 34 developed complications within the first two weeks. Post-procedural complications included missed abortion in 20 cases (1.5%), amniotic fluid leakage in 6 cases (0.5%), vaginal bleeding in 4 cases (0.3%), spontaneous abortion in 3 cases (0.2%), and sepsis in 1 case (0.1%). The overall complication rate was determined to be 2.6%.

The overall fetal loss rate following the procedure was determined to be 1.8%. A statistically significant increase in the risk of complications was observed with an increasing number of insertions (p=0.036). The incidence of chorioamnionitis after CVS was 0.07%.

The relationship between placental location and the risk of complications is presented in Table 8. The risk of complications was significantly higher in cases with posterior placental localization than in those with non-posterior localization (odds ratio: 2.21; 95% confidence interval: 1.11-4.38; p=0.033).

Table 6. Distribution of repeat procedure indications according to the number of insertions in chorionic villus sampling

Number of insertions	Failure to detect mutation	Contamination	Insufficient material	Total
1	15 (46.9)	4 (12.5)	13 (40.6)	32
2	1 (20.0)	1 (20.0)	3 (60.0)	5
≥3	0 (0.0)	0 (0.0)	1 (100.0)	1
Total	16 (42.1)	5 (13.2)	17 (44.7)	38

The relationship between the number of insertions performed during CVS and the development of complications is presented in Table 9. A statistically significant increase in the risk of complications was observed with an increasing number of insertions (p=0.036).

The mean turnaround time for CVS results among cases presenting to our clinic was 9 days. The genotypic characteristics of the fetuses, according to CVS results, are presented in Table 10. Accordingly, the most frequently detected structural hemoglobin variant was HbS (31%), while HbD and HbE were observed at lower frequencies.

When thalassemia mutations were evaluated, the most common mutation associated with β-thalassemia was IVS-I-110 (G>A) (7.9%), whereas the most frequent mutation for α-thalassemia was the -$\alpha^{3.7}$ deletion (2%).

Mutational characteristics detected in cases undergoing CVS are presented in Table 11. Accordingly, heterozygous mutations were identified in approximately 50.2% of cases, while no mutations were detected in 25.4% of cases. Homozygous mutations were observed in 21% of cases, and genotype determination could not be performed in 3.4%.

Pregnancy outcomes of women undergoing CVS are presented in Table 12. A total of 636 infants (47.8%) were born heterozygous carriers of hemoglobinopathies, whereas 329 infants (24.8%) had no detectable structural hemoglobin variant and were healthy at birth. Of the 279 fetuses diagnosed with homozygous mutations by CVS, pregnancy termination was performed in 266 cases (20.2%). Despite the presence of homozygous mutations, pregnancies were continued in 11 cases, all of which resulted in live births, while 2 cases ended in missed abortions.

In 46 cases (3.4%), no diagnostic result could be obtained. All 6 cases resulting in stillbirths were found to have heterozygous mutations. In one case resulting in preterm delivery, no mutation was detected. Among the 9 cases ending in spontaneous abortion, 5 had heterozygous mutations, whereas no mutation was identified in the remaining 4 cases.

The comparison between pregnancy outcomes and maternal education levels is presented in Table 13. Notably, among infants born with an affected genotype, 10 out of 11 (90.8%) had mothers who were either illiterate or had completed only primary education.

Among cases undergoing CVS for hemoglobinopathies, two pregnancies were diagnosed with trisomy 21 following amniocentesis and cytogenetic karyotype analysis, which were performed because an increased risk was identified on

Table 7. Complications observed following chorionic villus sampling

Outcome	n	%
No complication	1296	97.4
Complication (+)	34	2.6
Missed abortion	20	1.5
Amniotic fluid leakage (PROM)	6	0.5
Vaginal bleeding	4	0.3
Spontaneous abortion	3	0.2
Sepsis	1	0.1
Total	1330	100

PROM: Premature rupture of membranes

Table 8. Placental location in cases with complications following chorionic villus sampling

Placental location	Complication (+)	Complication (-)	Total	p	Odds ratio
Posterior	16 (4.1)	372 (95.9)	388 (29.2)	0.033	2.21
Others	18 (1.9)	924 (98.1)	942 (70.8)		
Total	34 (2.6)	1296 (97.4)	1330 (100)		

Table 9. Relationship between the number of insertions and complications in chorionic villus sampling

Number of insertions	Complication (+)	Complication (-)	Total	p
1	26 (2.2)	1149 (97.8)	1175 (100)	
>1 (multiple)	8 (5.2)	147 (94.8)	155 (100)	0.036
Total	34 (2.6)	1296 (97.4)	1330 (100)	

Table 10. Genotypic characteristics of fetuses according to CVS results

Genotype	n	%
HbAS (heterozygous HbS)	412	31.0
HbAA (normal)	337	25.3
HbSS (homozygous HbS)	177	13.3
β-thalassemia carrier: IVS-I-110 (G>A)	105	7.9
Indeterminate genotype	46	3.4
α-thalassemia: -$\alpha^{3.7}$ deletion	26	2.0
β-thalassemia: IVS-I-1 (G>A)	20	1.5
HbAS + α-thalassemia (-$\alpha^{3.7}$)	15	1.1
β-thalassemia: IVS-I-6 (T>C)	13	1.0
β-thalassemia: Codon 8 (-AA)	12	0.9
HbAD (heterozygous HbD)	9	0.7
β-thalassemia: Codon 39 (C>T)	9	0.7
HbAE (heterozygous HbE)	8	0.6
β-thalassemia: -30 (promoter mutation)	7	0.5
Other	134	10.1
Total	1330	100.0

CVS: Chorionic villus sampling

second-trimester triple screening. Both pregnancies were subsequently terminated. In one case, a cystic hygroma was detected, and the pregnancy resulted in intrauterine fetal demise at 23 weeks' gestation. In another case, the pregnancy was terminated following the diagnosis of a tracheoesophageal fistula.

The CVS genotypes of the cases diagnosed with trisomy 21 were HbAS and heterozygous IVS-I-110 (G>A) mutation, respectively. In both cases, which presented with cystic hygroma and tracheoesophageal fistula, CVS results revealed HbAS.

Table 11. Fetal mutation characteristics in cases undergoing chorionic villus sampling

Mutation status	n	%
Heterozygous genotype (carrier)	668	50.2
No mutation detected (normal genotype)	337	25.4
Homozygous or compound heterozygous genotype (affected)	279	21.0
Genotype undetermined	46	3.4
Total	1330	100

Table 12. Pregnancy outcomes of women presenting to our clinic

Outcome	n	%
Heterozygous carrier newborn	636	47.8
Newborn with normal genotype	329	24.8
Pregnancy termination	269	20.3
Cases without diagnostic result	46	3.4
Missed abortion	23	1.8
Newborn with affected genotype	11	0.8
Spontaneous abortion	9	0.6
Stillbirth (intrauterine fetal demise)	6	0.4
Preterm delivery	1	0.1
Total	1330	100.0

Discussion

In this study, obstetric, genetic, and procedure-related outcomes in a large case series of patients undergoing CVS for the prenatal diagnosis of hemoglobinopathies were evaluated. The findings indicate that CVS is a reliable and effective prenatal diagnostic method when performed in experienced centers. Hemoglobinopathies are inherited disorders caused by DNA variants affecting globin genes and constitute one of the most common groups of monogenic diseases worldwide[1,5]. E arly prenatal diagnosis is critically important not only for preventing affected births but also for enabling families to make informed reproductive decisions. In a series of 5,500 CVS procedures conducted by Podobnik et al.[6] in Croatia, the fetal loss rate was reported as 1.19%. Martins et al.[7] reported a rate of 0.2% in a study including 1,523 pregnancies. Similarly, Gil et al.[8] demonstrated that the risk of fetal loss following CVS is approximately 1%. In our study, the overall fetal loss rate was 1.8%, which, although slightly higher than rates reported in the literature, can still be considered within acceptable limits.

The increased risk of complications observed in cases with posterior placental localization may be related to the technical challenges of CVS. In such cases, a longer needle trajectory and increased manipulation may prolong the procedure and increase tissue trauma. International guidelines emphasize that CVS should be performed under ultrasound guidance, with the minimum number of insertions possible, and in experienced centers[6,9,10]. In this context, our findings support current guideline recommendations. In particular, the significant association between an increased number of insertions and a higher risk of complications highlights the technical sensitivity of the procedure and the importance of operator experience. This observation is also supported by the multicenter retrospective study by Navaratnam et al.[11], which reported that multiple insertions are associated with increased risks of fetal loss and infection[6]. These findings are consistent with previous studies. Recent studies have further demonstrated that the procedure-related risk of fetal loss following CVS is lower than previously estimated, particularly when performed in experienced centers.

Table 13. Comparison of pregnancy outcomes according to maternal education level

Outcome	Illiterate	Primary education	High school	University	Total	p
Heterozygous carrier newborn	16 (3.0)	407 (64.0)	148 (23.0)	65 (10.0)	636 (100)	
Newborn with normal genotype	15 (3.0)	191 (60.0)	83 (25.0)	40 (12.0)	329 (100)	
Pregnancy termination	6 (2.0)	161 (60.0)	75 (28.0)	27 (10.0)	269 (100)	
Newborn with affected genotype	4 (36.3)	6 (54.5)	1 (9.2)	0 (0.0)	11 (100)	
Other pregnancy outcomes	85	-	-	-	85 (100)	
Total	1330					**<0.001***

* Statistical significance was evaluated using the chi-square test; p<0.05 was considered statistically significant

Contemporary evidence suggests that CVS-related pregnancy loss is comparable to that of amniocentesis and may be close to the background risk in low-risk populations. Advances in ultrasound guidance and operator experience have contributed to improved safety profiles of invasive prenatal diagnostic procedures[12]. However, our cohort represents clinical practice between 2008 and 2012. Therefore, the reported complication rates and diagnostic performance should be interpreted within the context of ultrasound technology, procedural experience, and molecular diagnostic approaches available during that period. Continuous improvements in imaging quality, invasive procedure techniques, and genetic testing platforms may have further optimized current outcomes. These findings support the continued role of CVS as a first-line diagnostic tool, especially during early gestation, when timely diagnosis is essential for clinical decision-making.

Evaluation of the fetal genotype distribution revealed that 21% of cases had homozygous or compound heterozygous (affected) genotypes, reflecting the high carrier frequency of hemoglobinopathies in our region. Globally, approximately 5-7% of the population are carriers of a pathogenic hemoglobin variant, and 300,000-500,000 affected neonates are born annually. The majority of these cases consist of sickle cell disease and transfusion-dependent β-thalassemia[3,13]. In our study, the majority of pregnancies with fetuses carrying affected genotypes were terminated, highlighting the significant role of prenatal diagnosis in reducing the burden of hemoglobinopathies.

The most frequently detected structural hemoglobin variant in our study was HbS, which is consistent with expectations for the Mediterranean basin and Middle Eastern populations. Sickle cell disease is one of the most common monogenic disorders worldwide, affecting approximately 7.7 million individuals, resulting in an estimated 515,000 affected births annually. The more than 40% increase in global prevalence between 2000 and 2021 is largely attributed to population growth in high-burden regions such as sub-Saharan Africa[3,12,14]. Similar experiences from Mediterranean hemoglobinopathy prevention programs have demonstrated the effectiveness of combining population-based carrier screening, genetic counseling, and early prenatal diagnosis. National programs in countries with a high prevalence of β-thalassemia and sickle cell disease, including Cyprus, Italy, Greece, and Türkiye, have substantially reduced the number of affected births through systematic screening and CVS-based molecular diagnosis. Our findings are consistent with these programs and support the role of early invasive prenatal diagnosis in high-risk populations[15,16]. Among β-thalassemia mutations, the most frequently detected mutation was IVS-I-110 (G>A), which is consistent with the mutation spectrum reported in Türkiye and neighboring countries[17,18]. This finding underscores the importance of considering regional mutation distributions when planning prenatal diagnostic strategies.

Another important consideration is the molecular diagnostic methodology used in this study. Mutation analysis was performed using ARMS and RFLP, which were standard approaches during the study period. Although these methods are reliable for detecting known mutations, they may have limitations in identifying rare or novel variants compared to current high-throughput techniques such as next-generation sequencing (NGS). Nevertheless, given that the mutation spectrum in our region is well characterized and largely consists of common variants, these methods remain clinically adequate for targeted prenatal diagnosis. Future studies incorporating advanced molecular techniques may further improve diagnostic accuracy.

The success of prenatal diagnosis programs depends not only on the implementation of invasive diagnostic procedures but also on the integration of preconception screening, identification of carriers, and effective genetic counseling services. The World Health Organization and other international health authorities recommend an integrated approach combining carrier screening and prenatal diagnosis for hemoglobinopathies[15,16]. CVS offers a significant advantage over amniocentesis by allowing earlier prenatal diagnosis, thereby enabling families to make timely decisions.

Study Limitations

One of the major strengths of this study is the inclusion of a large case series reflecting extensive single-center experience accumulated over many years. However, several limitations should be acknowledged. First, the retrospective design of the study may introduce inherent bias. Although several factors such as gestational age at CVS, maternal characteristics, placental accessibility, and procedural variables may influence complication risk, a multivariable logistic regression model could not be reliably performed because of the limited number of adverse events. Performing such an analysis with a small number of outcomes could result in unstable estimates. Second, the limited availability of long-term neonatal outcomes restricts the comprehensive evaluation of the clinical impact. Additionally, the study period (2008-2012) may limit the generalizability of the findings to current clinical practice.

Another important limitation is the use of conventional molecular techniques, such as ARMS and RFLP, for mutation analysis. Although these methods were standard at the time of data collection, they have lower sensitivity for detecting rare or novel mutations than current high-throughput techniques such as NGS.

Despite these limitations, the findings provide valuable contributions to both clinical practice and the development of regional prenatal diagnostic policies. Since this study

included only high-risk pregnancies referred to a tertiary prenatal diagnosis center, the observed mutation frequencies and genotype distributions should not be interpreted as representative of the general population. Referral bias may have influenced the frequency of specific hemoglobin variants and mutations. Overall, our results support the conclusion that CVS is a reliable, effective, and feasible method for the prenatal diagnosis of hemoglobinopathies. Particularly in regions with a high prevalence of hemoglobinopathies, the expansion of comprehensive prenatal diagnostic and genetic counseling programs conducted at experienced centers remains a cornerstone strategy for reducing disease burden.

Conclusion

This study demonstrates that CVS is a reliable and effective method for prenatal diagnosis of hemoglobinopathies. Findings derived from a large case series indicate that CVS provides an accurate genetic diagnosis during early gestational weeks with acceptable complication rates. The identification of technical factors such as the number of insertions and placental location as determinants of complication risk underscores the importance of performing CVS in experienced centers and in accordance with standardized protocols.

The distribution of fetal genotypes further indicates that severe hemoglobinopathies, particularly sickle cell disease and β-thalassemia, remain a significant public health concern in our region. The ability to detect affected fetuses at an early stage through prenatal diagnosis provides important advantages in pregnancy management and genetic counseling. In regions with a high prevalence of hemoglobinopathies, the integration of preconception screening, carrier detection, and prenatal diagnostic services represents a key strategy for reducing disease burden. When performed by experienced practitioners and with appropriate patient selection, CVS remains an effective and reliable method for the prenatal diagnosis of hemoglobinopathies.

Ethics

Ethics Committee Approval: This study was conducted in accordance with the Declaration of Helsinki and was approved by the Çukurova University Faculty of Medicine Non-Interventional Clinical Research Ethics Committee (approval number: 13, date: 04.04.2013).

Informed Consent: Written informed consent was obtained from all participants.

Footnotes

Authorship Contributions

Surgical and Medical Practices: S.A., F.T.Ö., Concept: S.A., F.T.Ö., Design: S.A., F.T.Ö., İ.C.E., S.C.D., E.Y., Ö.K.B., Data Collection or Processing: S.A., F.T.Ö., İ.C.E., S.C.D., E.Y., Ö.K.B., Analysis or Interpretation: S.A., F.T.Ö., İ.C.E., S.C.D., E.Y., Ö.K.B., Literature Search: S.A., F.T.Ö., İ.C.E., S.C.D., E.Y., Ö.K.B., Writing: S.A., F.T.Ö., İ.C.E., S.C.D., E.Y., Ö.K.B.

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