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Prenatal characteristics and management of pregnants with fetal cerebellar malformation: 4-year single center experience

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ABSTRACT

Introduction: Fetal cerebellar malformations (FCM) are known as very rare central nervous system malformations that occur as hypoplasia or agenesis of the cerebellum or vermis. In this study, the characteristics, diagnostic methods, risk factors and management of pregnant women diagnosed with FCM in the prenatal period were investigated.

Material and Method: The patients who diagnosed with prenatal FCM in the perinatology center between March 2017-February 2021 were included, retrospectively. The frequency of fetal magnetic resonance imaging (MRI), amniocentesis and/or karyotype analysis rates, and termination frequency were evaluated. In addition, the factors affecting the amniocentesis and the termination/follow-up decision were investigated.

Results: A total of 42 pregnant with FCM were included. The median gestational age was 24.0 years, and the mean gestational week was 25+2 (SD±5+1) weeks. Nearly half (40.5%) of patients were diagnosed before 24 weeks of gestation and 45.2% were primiparous. Cerebellar hypoplasia was observed in 47.6%, while vermis agenesis was observed in almost one third (31.0%); and also 19.0% had multiple FCM. The fetal USG was used in all pregnant women, fetal MRI was performed in only 4.8% for diagnosis of FCM. The rate of amniocentesis and karyotype analysis were 11.9% and 7.1%, retrospectively. No any complications were observed after the amniocentesis. The termination rate was 30.9%. The mean gestational week of those who had live birth was higher than those who were terminated (24+4 vs 20+5) (p=0.019).

Conclusion: The frequency of FCM diagnosis has increased with the development of modern medicine and technology. There is no relationship between demographic characteristics of pregnant women and FCM. Socio-economic levels and religious belief differences affect the termination and birth rates.

Keywords: Cerebellar malformation, cerebellar hypoplasia, vermis hypoplasia, pregnancy, termination

INTRODUCTION

Primary cerebellar malformations can be seen in isolation from other brain anomalies, or they can occur as part of a syndrome accompanied by anomalies of other organs. Generally, there is an underlying genetic etiology (1,2). There is no consensus on the terminology, definition and mechanism yet (3). There are many cerebellar malformations such as cerebellar hypoplasia/hyperplasia, isolated vermian hypoplasia, Dandy-Walker malformation, pontocerebellar hypoplasia and vermis hypoplasia, and they are usually a part of many genetic disorders and syndromes (1,2).

The fetal cerebellar malformations (FCM) were evaluated by fetal ultrasonography (USG) in 18-22 gestational weeks in the prenatal period. While the diagnosis of cerebellar malformations is usually made by prenatal USG, fetal magnetic resonance imaging (MRI) is also used in a few cases (4). Fetal MRI is mostly used in the second half of pregnancy, and it is used especially when cerebellar hemorrhage is suspected or when USG cannot be used adequately or sufficient images cannot be obtained with USG (5). Griffiths PD et al. (6) reported that in their multicenter prospective cohort study (MERIDIAN), fetal USG had an accuracy of 68% and fetal MRI was 93% accurate in the diagnosis of central

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nervous system anomalies. On the other hand, it has been shown that diagnostic accuracy rates in central nervous system anomalies are as good as fetal MRIs if fetal USGs are performed by specialist sonographers (7,8).

After diagnosing FCMs, amniocentesis and/or karyotype analysis are performed to detect congenital cardiac anomalies, other multiple anomalies and genetic etiology (9). Bahram et al. (10) reported that all of these fetuses had multiple anomalies, although the termination rate was reported as 26.0% in which pregnant women with fetal cerebellar anomaly (Blake's pouch cyst).

Our primary aim is to evaluate the characteristics, diagnostic methods (fetal USG/MRI), accompanying anomalies and risk factors of pregnant who are diagnosed with FCM in the prenatal period. The investigations of management, amniocentesis rates, genetic etiologies and termination rates were the second aim of the study.

MATERIAL AND METHOD

This study was carried out with the permission of University of Health Sciences, Kanuni Sultan Süleyman Training and Research Hospital Clinical Research Ethics Committee (Date: 19/01/2022, Decision No: 2022-25). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patients Selection

All pregnant women diagnosed with fetal cerebellar hypoplasia/aplasia and vermis hypogenesis/agenesis between March 2017 and February 2021 were included in the study, retrospectively. In case of anomaly accompanying FCM in pregnant women, the patient was excluded from the study. After giving written or verbal information about the study, written consent was obtained from the patients who agreed to participate in the study.

Data Collection and Assessment of Patients

Demographic data of pregnant women (gender, age, gestational week) were analyzed. Fetal USG/MRI usage rates, the frequency of amniocentesis and/or genetic analysis were investigated. The termination rates of the patients were recorded. In addition, the effects of demographic characteristics, gestational weeks and ages on the amniocentesis, genetic analysis and terminations were examined.

Statistical Analysis

Datas were analysed using the SPSS 25.0 (IBM, Armonk, NY: IBM Corp.) program Continuous variables were expressed as mean ± standard deviation, median (interquartile range, IQR), and categorical variables as numbers (n) and percentages (%). When the parametric test assumptions were met, t-test was used to compare differences between independent groups. When parametric test assumptions were not met, Mann-Whitney U test was used to compare differences between independent groups. The Chi-squared or Fisher's exact probability tests used to compare demographics. In all analyses, $p < 0.05$ was considered statistically significant.

RESULTS

A total of 64 pregnant women were diagnosed with FCM during the study period. Due to a lack of medical records, 22 cases were excluded from the study (**Figure**). Overall 42 patients were included. The median pregnancy age was 24.0 years (minimum 18.0-maximum 38.0, IQR 23.0-29.0). The mean gestational week at the time of diagnosis was 25+2 weeks (SD ± 5+1 weeks) (**Table 1**). The rate of prenatal diagnoses before 24 weeks was 40.5% (n=17) and 45.2% (n=19) were primiparous. The numbers of gravida, parity, abortion and curettage at the time of diagnosis are shown in **Table 1**.

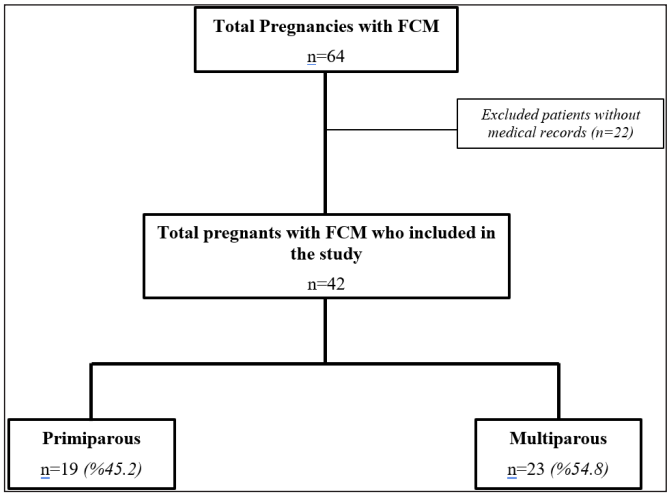

Figure. Distribution of patients enrolled in the study period.
*FCM: fetal cerebellar malformation

Table 1. Demographic characteristics of patients with FCM

Pregnancy age (year) [median (min-max, IQR)]	**24.0** (18-38, 23-29)
Gestational week (weeks) [mean (±SD)]	**25^{+2}** ($\pm5^{+1}$)
History (n) [median (min-max)]	
Gravida	2 (1-5)
Parity	1 (0-4)
Abortion	0 (0-2)
Curettage	0 (0-1)
The type of FCM [n (%)]	
Cerebellar hypoplasia	**20 (47.6)**
Cerebellar agenesis	**4 (9.5)**
Vermis hypoplasia	8 (19.1)
Vermis agenesis	13 (30.9)
Corpus callosum agenesis	6 (14.3)
Vermian cleft	2 (4.8)
Multipl FCM [n (%)]	8 (19.0)

FCM: fetal cerebellar malformation, IQR: interquartile range, min: minimum, max: maximum, SD: standart deviation

When fetal cerebellar malformations were examined in detail, cerebellar hypoplasia was observed in nearly half of the pregnant women (47.6%), and vermis agenesis was found in almost one-third (31.0%) (**Table 1**). In addition, it was observed that 19.0% (n=8) of the pregnant women had multiple FCM (**Table 1**). We found that there was no statistically significant relationship between pregnancy age, gestational week, number of abortions and/or curettage and FCM types.

While fetal USG was used in the diagnosis of all pregnants, fetal MRI was used in only 2 (4.8%) pregnant women. However, while amniocentesis was performed in 11.9% (n=5) of the pregnant women, karyotype analysis was performed in 7.1% (n=3) (**Table 2**). While no complications were observed in any of the pregnant women who underwent amniocentesis; No genetic anomaly was found in any of the fetuses whose karyotype analysis was performed. Termination occurred in 40.0% (n=2) of the pregnant women who underwent amniocentesis, and delivery in 60.0% (n=3). While 2 of the pregnant women who underwent amniocentesis and were terminated had multiple FCMs, only one had cerebellar agenesis.

Termination was performed in 30.9% (n=13) of the pregnant women diagnosed with FCM during the study period, while live birth was performed in all other pregnant women (**Table 2**). We observed the mean gestational week of the pregnant women with FCM who gave birth was statistically significantly higher than those who were terminated by Mann-Whitney U test (mean gestational week 24+4 vs 20+5) (p=0.019).

Table 2. The association of pregnancy age and gestational week with FCM types

	*Pregnancy Age (year) [median (min-max)]	§Gestational Week [median (min-max)]
Serebellar hipoplazi		
+	23 (19-34)	24^{+2} ($18-37^{+5}$)
-	26 (18-38)	26+5 (18-34)
Serebellar agenezi		
+	28 (23-37)	22^{+4} (20-28)
-	24 (18-38)	26 ($18-37^{+5}$)
Vermis hipoplazisi		
+	28 (18-38)	26^{+6} (18-34)
-	23 (19-37)	25^{+2} ($18-37^{+5}$)
Vermis agenezisi		
+	26 (21-31)	26^{+4} (18^{+3}-34)
-	23 (18-38)	27^{+2} (18 -37^{+5})
Korpus kallosum agenezisi		
+	23 (23-37)	24^{+6} (18-29)
-	24 (18-38)	25+2 (18 -37^{+5})

*No statistically significant relationship between pregnancy age and FCM types (p=0.493), *No statistically significant relationship between gestational week and FCM types (p=0.611)

Table 3. The diagnosis methods and interventions of pregnants with FCM

	n	%
Diagnosis with		
Fetal USG	42	100
Fetal MRG	2	4.8
Amniocentesis		
Yes	5	11.9
No	37	88.1
Karyotype analysis		
Yes	3	7.1
No	39	92.9
Results		
Live birth	29	69.1
Termination	13	30.9

FCM: fetal cerebellar malformation, MRI: Magnetic resonance imaging, USG: ultrasonography

DISCUSSION

Central nervous system malformations are the second most common congenital malformations after cardiac anomalies and constitute one-third of malformations diagnosed in the prenatal period (11, 12). Cerebellar malformations (hypoplasia, agenesis) is a term that generally defines the cerebellum as volume loss or embryological failure (13, 14). Although many factors play a role in its etiology, there is no consensus on the terminology, definition and mechanism yet. It may occur as a result of acquired or congenital genetic disorders with different neurodevelopmental outcomes (3, 13, 14). In this study, the characteristics, management and outcomes of pregnant women diagnosed with prenatal FCM are shown.

Although it is thought that central nervous system malformation is more common in primiparous women, this rate is controversial since curettage rates are not known clearly (15-18). Most of the migration and proliferation processes of neurons occur in the second trimester, and the majority of intrauterine central nervous system malformations are diagnosed at 18-20 weeks of gestation (19, 20). While nearly half of the pregnant women included in our study were primiparous, similar to the literature; the mean gestational week at the time of diagnosis was slightly higher than in the literature (mean 25+2 weeks). In our country, the inadequacy of regular follow-up rates of pregnant women and the low rate of reaching the perinatology center may explain the delayed diagnosis. In addition, it has been reported in the literature that the rate of fetal cerebellar hypoplasia is higher in multiparity pregnant women (21). In our study, the numbers of multiparous and primiparous pregnants were found to be similar.

Cerebellar hypoplasia is defined as a diffuse decrease in the cerebellar biometry in which the anatomy and echogenicity of the cerebellum are normal (3, 5). There may be hypoplasia of only the hemispheres or the vermis, or hypoplasia of both can be seen together (3, 5, 22). In recent years, with the development of technology and the use of fetal MRI, the detection rate of cerebellar hypoplasia has increased (23). Also, In the study of Howley MM et al. (24), it was shown that only 26.4% of cerebellar hypoplasia cases had isolated cerebellar hypoplasia and that other central nervous system malformations were accompanied in the majority of cases. In our study, it was observed that 19.0% of cerebellar hypoplasia/agenesia cases had accompanying multiple anomalies.

As part of normal follow-up during pregnancy, a fetal USG is recommended to determine fetal anatomy between 18 and 22 weeks of gestation. During these gestational weeks, major intracranial structures are embryologically formed and can be well visualized sonographically (25). However, fetal MRI can be used for diagnosis, since it cannot be determined whether vermian lobulation has been completed before the 24th gestational week (22, 25). In our study, while fetal USG was used in all pregnant women, fetal MRI was found to be less used. We thought that the high USG experience of the physicians in the perinatology center, the low rate of accompanying multiple anomalies and the low number of patients affected the use of fetal MRI.

Cerebellar malformations can also be seen together with aneuploidy (especially trisomy 21 and 18) and some congenital anomalies (3, 5). It is recommended to use advanced evaluation methods such as amniocentesis and/or karyotype analysis in cases where malformations are seen in fetal USG, accompanying genetic syndromes are detected, or there are uncertain findings in USG (26, 27). Although amniocentesis is a reliable diagnostic method, complications may develop after the procedure (28). In our study, the rate of amniocentesis was found to be 11.9%; karyotype analysis was performed at 7.1%. No genetic anomalies were detected.

In pregnant women with prenatal fetal central nervous system malformation, termination rates have been reported as 48-60% and live birth rates as 35-47% (29). Also, in the study performed by Tan Ag et al. (30), the termination rate was found to be 48.2% in pregnant women with fetal central nervous system anomaly; It was stated that 92.7% of these were done by medical induction, and only 7.3% of them were terminated by surgical method. In our study, the termination rate was lower than the literature, and the live birth rate was higher than the literature. It was thought that the low termination rates were explained by the lower socioeconomic levels of the pregnant women included in the study compared to European countries, and the difference in their religious beliefs.

Limitations of the study; (1) the single-center data of our study constitutes an important limitation in the generalization of our results; (2) Since it is retrospective, the follow-up of pregnant women and the postnatal life expectancy and development of fetuses with FCM are unknown.

CONCLUSION

We reported the results of a cohort study including the characteristics and management of pregnant women with FCM in our perinatology center. The frequency of diagnosis of FCM is increased with the development of modern medicine and technology. Socio-economic levels and religious belief differences of pregnant affect the termination and birth rates.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was carried out with the permission of University of Health Sciences, Kanuni Sultan Süleyman Training and Research Hospital Clinical Research Ethics Committee (Date: 19/01/2022, Decision No: 2022-25).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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