Ann Med Res

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Annals of Medical Research

journal page: www.annalsmedres.org

Implications of familial Mediterranean fever on the fetal adrenal gland: A case-control study

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ARTICLE INFO

Keywords:
Familial Mediterranean fever
Chronic inflammation
Pregnancy
Fetal adrenal gland

Received: Sep 19, 2023
Accepted: Nov 22, 2023
Available Online: 27.11.2023

DOI:
10.5455/annalsmedres.2023.09.254

Abstract

Aim: To investigate fetal adrenal dimensions in pregnant women diagnosed with familial Mediterranean fever (FMF) and healthy pregnant women.

Materials and Methods: This study was conducted with 36 women diagnosed with FMF and 72 healthy pregnant women who were followed up and delivered in the perinatology clinic. Fetal adrenal dimensions were evaluated ultrasonographically in axial and coronal sections between the $34^{0/7}$ and $37^{0/7}$ weeks of gestation. Height, length, and width were measured in the total adrenal length (TAL), width (TAW), height (TAH), and fetal zone adrenal length (FAL), width (FAW), height (FAH), and the volume (TAV and FAV) were calculated. Participants' birth week, birth weight, and Apgar scores were recorded. The case group was divided into colchicine users and those who did not require colchicine use during pregnancy.

Results: The sociodemographic and obstetric characteristics of the participants were similar. TAH, TAV, FAL, and FAV were significantly higher in the FMF group ($p<0.001$). The mean value of the FAV/TAV was 0.15 cm^3 in the FMF group and 0.14 cm^3 in the control group. Although the mean value of the volume ratio was increased in the FMF group, there was no statistically significant difference between them ($p=0.505$). TAH was found to be significantly increased in the group not using colchicine ($p=0.014$).

Conclusion: This is the first study conducted on the fetal adrenal gland in pregnant women diagnosed with FMF. Exposure to intrauterine stress due to chronic inflammation might result in increased fetal adrenal gland sizes.

Introduction

Familial Mediterranean Fever (FMF) is characterized by sterile inflammation of the membranes, often manifested by episodes of febrile abdominal pain and polyserositis [1]. The occurrence of this syndrome was prevalent in the societies of the eastern Mediterranean, but it has since gained worldwide recognition, predominantly in Western Europe, during the 20th century. Its incidence within these societies is roughly 1 in every 500 individuals [2]. The diagnosis is based on typical clinical findings in a patient of appropriate ethnicity, supported by a response to colchicine [3]. The gene responsible for FMF, the Mediterranean Fever (MEFV) gene located on the short arm of chromosome 16, encodes the pyrin-marenostrin protein. Deterioration in the structure of this protein eventually causes amyloidosis in the long term. Amyloidosis, anemia, splenomegaly, decrease in bone mineral density, and cardiac dysfunction are associated with subclinical inflammation in FMF [4]. Even in relapse-free periods, increased cytokines and acute phase proteins cause complications. However, it has not yet been clarified why the inflammation remains limited to the serosal surfaces or how the attacks occur. Pregnancy and the reproductive period are associated with FMF because most patients' age at diagnosis is under 20 years of age [5]. The course of pregnancy may be different for each patient. While some do not experience attacks during pregnancy, the frequency and severity of attacks may increase in some patients. There are studies reporting that the frequency of preterm birth and abortion has increased [6].

Lifelong diseases that progress with chronic inflammation may cause changes in the intrauterine environment during pregnancy. It is thought that molecules that occur with the activation of the maternal immune system cause fetal effects through transplacental transmission [7]. Stimulators are especially Interleukin 1 effective on adrenal gland functions [8]. The adrenal gland plays a role in maintaining intrauterine homeostasis and promoting fetal development and maturation through steroid produc-

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tion. In other words, the immune system and the immune–hypothalamic–pituitary–adrenal (HPA) axis are closely related [9]. In some previous studies, the effect of maternal inflammation on the adrenal gland has been investigated [7, 10, 11].

The current study hypothesized that chronic inflammation in the fetuses of pregnant women with FMF may affect the size of the fetal adrenal gland. For this purpose, adrenal parameters and volumes were compared with healthy fetuses.

Materials and Methods

This cross-sectional study was carried out between July 2022 and September 2023 in the Perinatology division of Ankara City Hospital. Ethics committee approval was given by the medical research ethics department with the number E2-22-2082. Written and verbal consent forms were obtained from all patients.

Design and study population

The study was conducted with 36 pregnant women with FMF. Two control patients were included for each case. A total of 108 pregnant women were included in the study, together with 72 healthy pregnant women matched for gestational weeks. The standard effect size was 0.80, with a 5% margin of error and 95% power for the sample size. It was planned to include at least n=23 cases in each group. A total of 46 patients were targeted to be included. Pregnant women with another systemic disease, gestational-pregestational diabetes mellitus, hypertensive disease, multiple pregnancies, and fetal chromosomal or structural anomalies were excluded from the study. Patients who have colchicine-resistant disease and therefore use steroids or biological disease-modifying antirheumatic drugs (bDMARDs) were also not included in the study, as it may affect fetal adrenal gland development. Sociodemographic and obstetric histories were obtained in the routine evaluation of patients between $34^{0/7}$ and $37^{0/7}$ gestational ages and who met the criteria. The case group was divided into two: those who used colchicine and those who did not.

Ultrasound examination

Fetal measurements, a biophysical profile assessment, and a comprehensive anatomical evaluation were performed. Fetuses with growth restriction were excluded. Gestational age was confirmed according to first-trimester crown-rump length measurements. A single specialist made evaluations without knowing whether they were from the patient or control group (MY). The examination used the Voluson E8 ultrasound system (GE Medical System, Milwaukee, WI, USA) convex probe 4-8 MHz. The adrenal gland located on the upper pole of the kidney was identified. The side that is on the top and is easy to view was preferred. The cortex and fetal zone of the fetal adrenal gland were determined. Total adrenal length (TAL), width (TAW), and height (TAH), fetal zone adrenal length (FAL), width (FAW), and height (FAH) measurements were taken by taking sections in the axial and coronal planes (Figure 1). Volume was calculated

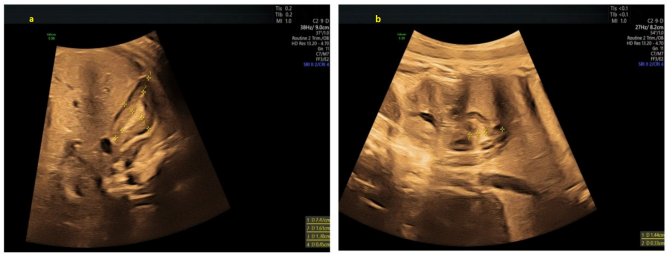

Figure 1. Length and width of the fetal adrenal gland in the axial plane (a); imaging and measurement of its height (b) in the coronal plane.

for both total gland and fetal zone (LxWxHx0.52). Fetal adrenal volume was divided by total adrenal volume (FAV/TAV).

Statistical analysis

The standard effect size was 0.80, with a 5% margin of error and 95% power for the sample size. It was planned to include at least n=23 cases in each group. A total of 46 patients were targeted to be included. The sample size was analyzed with G Power software (version 3.1; Franz Foul, Universitat Kiel, Kiel, Germany) [12]. Statistical analysis made using IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY. The normality of the data was tested with Kolmogorov Smirnov. Data with normal distribution were expressed as mean ± standard deviation. Data that were not provided were expressed as median (interquartile ranges). Parametrically distributed data were compared with independent t-tests. Mann-Whitney U test was used for data that did not meet parametric test assumptions. The error bar shows the change in TAV in Figure 2 and FAV between the case and control groups in Figure 3. Alpha values less than 0.05 were considered statistically significant.

Results

Age, gravida, parity, abortion numbers, and body-mass index data of 36 pregnant women in the case group and 72 in the control group were compared and no significant difference was found. The mean gestational week during sonographic examinations was 36 in both groups. The mean

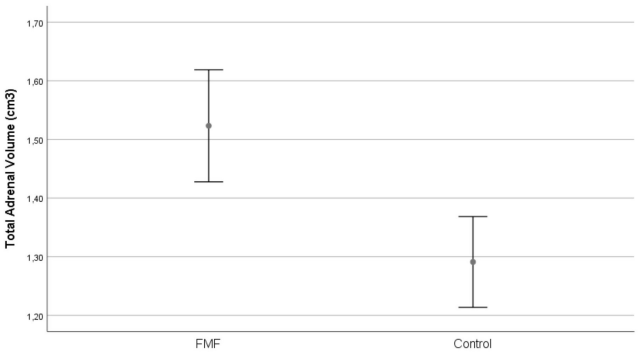

Figure 2. Comparison of total adrenal volume in pregnant women with FMF and healthy women.

Table 1. Socio-demographic and clinical characteristics of all participants.

	FMF (n=36)	Control (n=72)	p-value
Age (years) (arithmetic mean ± standard deviation)	29.4 ± 3.9	28.6 ± 4.8	.357*
Gravidity (n) (arithmetic mean ± standard deviation)	3 ± 1	3 ± 2	.411*
Parity (median, interquartile range)	1 (0-2)	1 (0-2)	.355†
Abortus (median, interquartile range)	0 (0-1)	0 (0-0)	.593†
BMI (kg/m²) (arithmetic mean ± standard deviation)	28.5 ± 4.1	29.2 ± 4.8	.451*
Sonographic examination week (arithmetic mean ± standard deviation)	36 ± 1	36 ± 1	.658*
Birth weight (gram) (arithmetic mean ± standard deviation)	3030 ± 514	3207 ± 365	.143*
Birth week (median, interquartile range)	38 (37-39)	39 (38-39)	.239†
1st minute Apgar (arithmetic mean ± standard deviation)	7 ± 1	8 ± 1	.804*
5st minute Apgar (arithmetic mean ± standard deviation)	9 ± 1	9 ± 1	.409*

Values are presented as mean+/- standard deviation or median (IQRs (Inter Quartile Ranges)) * Independent t-test † Mann Whitney U test BMI, body-mass index.

Table 2. The size of the total and fetal adrenal gland in the FMF and control groups.

	FMF (n=36)	Control (n=72)	p-value
Total adrenal length (TAL) (arithmetic mean ± standard deviation)	2.13 ± 0.26	2.07 ± 0.22	.195*
Total adrenal width (TAW) (arithmetic mean ± standard deviation)	1.01 ± 0.14	1.03 ± 0.19	.480*
Total adrenal height (TAH) (arithmetic mean ± standard deviation)	1.37 ± 0.16	1.16 ± 0.18	**<.001***
Total adrenal volume (TAV) (arithmetic mean ± standard deviation)	1.52 ± 0.28	1.29 ± 0.33	**<.001***
Fetal adrenal length (FAL) (arithmetic mean ± standard deviation)	1.40 ± 0.18	1.13 ± 0.24	**<.001***
Fetal adrenal width (FAW) (arithmetic mean ± standard deviation)	0.39 ± 0.04	0.38 ± 0.19	.758*
Fetal adrenal height (FAH) (arithmetic mean ± standard deviation)	0.76 ± 0.12	0.73 ± 0.21	.301*
Fetal adrenal volume (FAV) (arithmetic mean ± standard deviation)	0.22 ± 0.05	0.17 ± 0.12	**.043***
Fetal adrenal volume/ Total adrenal volume (arithmetic mean ± standard deviation)	0.15 ± 0.04	0.14 ± 0.02	.505*

Values are presented as mean+/- standard deviation or median (IQRs) * Independent t-test † Mann Whitney U test p<0.05 values indicate significance and are shown in bold.

values of birth weights in the case and control groups were 3030 and 3207 grams, respectively. The median values of the birth weeks were 38 and 39 weeks, respectively. The mean values of 1st-minute- and 5th-minute Apgar scores

Table 3. Sonographic parameters of pregnant women with FMF using and not using colchicine.

	Colchicine used (n=14)	Colchicine not used (n=22)	p-value
Total adrenal length (arithmetic mean ± standard deviation)	2.26 (2.04-2.42)	2.07 (1.89-2.36)	.205†
Total adrenal width (arithmetic mean ± standard deviation)	0.96 (0.88-1.16)	1.06 (0.92-1.14)	.833†
Total adrenal height (arithmetic mean ± standard deviation)	1.26 (1.17-1.41)	1.43 (1.34-1.50)	**.014†**
Total adrenal volume (arithmetic mean ± standard deviation)	1.46 (1.29-1.64)	1.58 (1.42-1.69)	.330†
Fetal adrenal length (arithmetic mean ± standard deviation)	1.33 (1.19-1.45)	1.47 (1.36-1.54)	.131†
Fetal adrenal width (arithmetic mean ± standard deviation)	0.39 (0.34-0.42)	0.40 (0.37-0.43)	.305†
Fetal adrenal height (arithmetic mean ± standard deviation)	0.77 (0.69-0.86)	0.74 (0.64-0.84)	.255†
Fetal adrenal volume (arithmetic mean ± standard deviation)	0.20 (0.18-0.24)	0.22 (0.19-0.25)	.475†
Fetal adrenal volume/ Total adrenal volume (arithmetic mean ± standard deviation)	0.15 (0.13-0.17)	0.14 (0.12-0.16)	.697†

Values are presented as mean+/- standard deviation or median (IQRs) * Independent t-test † Mann Whitney U test p<0.05 values indicate significance and are shown in bold.

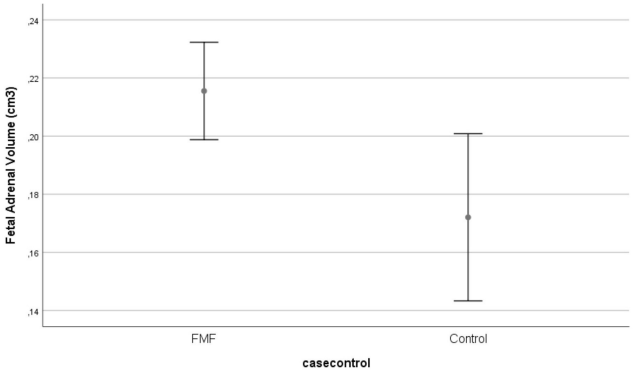

Figure 3. Demonstration of fetal adrenal gland volume in case and control groups.

were 7/8 and 9/9, respectively. The comparison of sociodemographic and obstetric characteristics of all participants is given in Table 1. Five participants in this study experienced exacerbation during pregnancy. Two patients had acute monoarthritis, one patient had erysipelas-like erythema, and two patients experienced abdominal pain (peritonitis) symptoms.

The data of total adrenal gland and fetal zone sizes between the case and control groups are presented in Table 2. The mean values of TAL, TAW, TAH, and TAV of the pregnant women in the case group were 2.13, 1.01, 1.37 cm, and 1.52 cm^3, respectively. The mean values of TAL, TAW, TAH, and TAV of the pregnant women in the control group were 2.07, 1.03, 1.16 cm, and 1.29 cm3, respectively. Of these measurements, TAH and TAV were significantly larger in the case group ($p<0.001$).

The mean values of FAL, FAW, FAH, and FAV of pregnant women in the case group were 1.40, 0.39, 0.76 cm, and 0.22 cm3, respectively. The mean values of FAL, FAW, FAH, and FAV of pregnant women in the control group were 1.13, 0.38, 0.73 cm, and 0.17 cm^3, respectively. Of these measurements, FAL and FAV were significantly larger in the case group ($p<0.001$). The mean value of the ratio of FAV/TAV was 0.15 cm3 in the FMF group and 0.14 cm^3 in the control group. Although the mean value of the ratio was bigger in the FMF group, there was no statistically significant difference between them ($p=0.505$).

Parameters were compared between pregnant women with FMF using colchicine and those not using colchicine in the case group (Table 3). TAH was found to be significantly increased in the group not using colchicine ($p=0.014$). Also, TAW, TAV, FAL, FAW, and FAV were found to be increased in the group not using colchicine, but there was no statistical difference. A comparison of fetal TAV between pregnant women with FMF and healthy women was shown by an error bar graph (Figure 2). Also, the comparison of FAV between pregnant women in the case and control groups was presented by an error bar graph (Figure 3).

Discussion

This study showed that fetuses of pregnant women diagnosed with FMF had increased adrenal gland sizes. The present study showed that TAH, TAV, FAL, and FAV parameters of the fetal adrenal gland were increased in pregnant women with FMF compared to healthy pregnant women. It was also demonstrated that TAH was bigger in patients not taking colchicine. The other parameters

showed a tendency to increase, although this was not statistically significant. We concluded that continuous exposure to maternal chronic inflammation may affect the fetal environment, stimulate the fetal HPA axis, and alter adrenal size. We also observed that the perinatal outcomes of pregnant women with FMF and low-risk pregnant women were similar.

The course of pregnancy is variable in patients diagnosed with FMF. While a population-based study concluded that FMF is a risk factor for preterm birth, its relationship with other perinatal outcomes has not been shown [6]. In the present study, perinatal outcomes of pregnant women with FMF and low-risk pregnant women (1^{st} and 5^{th} minute Apgar scores, week of birth, and birth weights) were found to be similar. According to a multicenter study, although remission may occur during pregnancy, the frequency and severity of attacks may increase in some cases [13]. Patients experiencing attacks are at risk of spontaneous abortion, preterm labor, and delivery [14]. In addition, although colchicine treatment does not change the outcome of pregnancy, it has a favorable effect on the course of the disease [14]. In the 1970s, it was recommended to leave at least three months between colchicine use and pregnancy [15]. Routine amniocentesis was recommended because colchicine is an alkaloid that affects microtubule formation and cell division [16]. Today, since colchicine use does not change the incidence of fetal anomaly and discontinuing treatment during pregnancy may cause exacerbations, it is recommended to continue it throughout pregnancy [14, 17].

Subclinical inflammation persists in FMF patients even during attack-free periods [4]. Symptoms that recur at regular intervals are just the tip of the iceberg. In FMF, mutated pyrin results in unregulated expression of Interleukin-1 β and inappropriate neutrophil activation and systemic inflammation [3]. Although many points in its pathogenesis have not been clarified yet, autoinflammation is triggered as a result. The impact of maternal systemic inflammation on fetal cardiac functions, fetal pulmonary circulation, and fetal thymus development has been previously investigated [18-20]. Another system closely related to the maternal immune system and auto-inflammation is the adrenal gland. The fetal adrenal glands are endocrine organs with significant roles in fetal development and adaptation to stress during intrauterine life [21]. These endocrine organs are relatively larger in the fetus than in the adult. Functionally and histologically, they have a cortex and a medulla. The cortex consists of the zona glomerulosa, zona fasciculate, and zona reticularis layers from the outside to the inside. The zona reticularis begins to form in the first few years after birth [9]. Any inflammation or stress that may affect the intrauterine milieu has the potential to impact fetal adrenal function and size by activating the HPA axis [22]. Interleukin-1, 2, and 6, enkephalins, adrenocorticotropic hormone (ACTH), various peptides, and beta-endorphins are responsible for this activation. The release of ACTH and endorphins from the pituitary gland is regulated by 'corticotropin releasing factor' released from the hypothalamus. Endorphins are crucial for the proper functioning of the immune system [7].

This study demonstrated that fetal adrenal gland size and volume increase due to maternal chronic inflammation. Previously, fetal adrenal gland volume was found to be significantly different in fetuses small for gestational age (SGA) compared to fetuses appropriate for gestational age [23]. Moreover, the authors suggested that FAV/TAV ratio could be used as a potential biomarker of SGA. In our study, this rate was higher in pregnancies with FMF, although there was no statistical difference. The results of a prospective case-control study in which the fetal adrenal gland was evaluated in 38 pregnant women who recovered after COVID-19 were similar to our research. The authors showed that maternal exposure to COVID-19 infection resulted in increased fetal adrenal dimensions and decreased adrenal gland blood supply [24]. Another study concluded that the fetal adrenal gland ratio could contribute to umbilical Doppler studies in detecting fetuses with fetal growth restriction [25]. A different study showed that increased fetal adrenal gland size is observed in gestational diabetes and is even associated with maternal biochemical markers [10]. A study examining growth-restricted fetuses suggested that increased adrenal size and decreased blood supply develop due to placental insufficiency and chronic hypoxia [11].

This is the first study on the fetal adrenal gland in pregnancies with FMF. The study's strengths are its prospective nature and the fact that it was conducted in a tertiary referral center. Limitations include the relatively small number of patients and the lack of neonatal confirmation. Future studies in which adrenal blood flow measurement is also performed, and neonatal comparative studies can be planned.

Conclusion

As a result, FMF leads to increased fetal adrenal gland sizes. Chronic subclinical autoinflammation appears to cause changes in fetal end organs by inducing an immune response in intrauterine life. Maternal and fetal multidisciplinary management is necessary in this patient group.

Conflicts of interest

The authors declare that they have no conflict of interest.

Ethical approval

Ethical approval was received from Ankara City Hospital No. 2 Clinical Research Ethics Committee (E2-22-2082).

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