Article published online: 2020-10-31

The Relationship between Serum Ischemia-Modified Albumin Levels and Uterine Artery Doppler Parameters in Patients with Primary Dysmenorrhea

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Rev Bras Ginecol Obstet 2020;42(10):630–633.

Abstract

Objective Primary dysmenorrhea occurs due to abnormal levels of prostanoids, uterine contractions, and uterine blood flow. However, the reasons for pain in primary dysmenorrhea have not yet been clarified. We examined the blood flow alterations in patients with primary dysmenorrhea and determined the relationship between ischemia-modified albumin (IMA) levels, as an ischemia indicator, and primary dysmenorrhea.

Methods In the present study, 37 patients who had primary dysmenorrhea and were in their luteal and menstrual phase of their menstrual cycles were included. Thirty individuals who had similar demographic characteristics, who were between 18 and 30 years old and did not have gynecologic disease were included as control individuals. Their uterine artery Doppler indices and serum IMA levels were measured.

Results Menstrual phase plasma IMA levels were significantly higher than luteal phase IMA levels, both in the patient and in the control groups ($p < 0.001$). Although the menstrual phase IMA levels of patients were significantly higher than those of controls, luteal phase IMA levels were not significantly different between the two groups. Menstrual uterine artery pulsatility index (PI) and resistance index (RI) of primary dysmenorrhea patients were significantly different when compared with luteal uterine artery PI and RI levels. There was a positive correlation between menstrual phase IMA and uterine artery PI and RI in the primary dysmenorrhea.

Conclusion Ischemia plays an important role in the etiology of the pain, which is frequently observed in patients with primary dysmenorrhea. Ischemia-modified albumin levels are considered as an efficient marker to determine the severity of pain and to indicate ischemia in primary dysmenorrhea.

Keywords
- ischemia-modified albumin
- primary dysmenorrhea
- uterine artery Doppler

Introduction

Dysmenorrhea is one of the most frequently encountered gynecological complaints, and it is characterized by cramps in the pelvic or lower abdominal region that initiate either just before or together with menstruation. Dysmenorrhea is classified as primary or secondary dysmenorrhea, and there is presence of pain in primary dysmenorrhea, even though there is no pelvic pathology.[1] Although primary dysmenorrhea is associated with abnormal myometrial contractions

received
April 16, 2020
accepted
June 29, 2020

DOI https://doi.org/10.1055/s-0040-1715141.
ISSN 0100-7203.

due to abnormal elevation in the levels of prostaglandins, reduction in uterine blood flow, and generalized ischemia due to vasoconstriction, the underlying cause of pain in primary dysmenorrhea has not yet been clarified.[2]

During the menstrual cycle, there is a decrease in the uterine artery pulsatility index (PI) values parallel to blood flow in the uterine artery during the luteal phase to ensure compliance with implantation. However, it is observed that the uterine artery PI values are high during the menstrual cycle.[3] In clinical studies, the PI and resistance index (RI) of patients with primary dysmenorrhea in the arcuate and uterine arteries in the first day of menstrual cycle were significantly higher than those of asymptomatic patients.[4] Decreased uterine blood flow most probably leads to strong and abnormal uterine contractions, and, thus, myometrial ischemia pelvic pains, such as cramps. occur. Observing higher uterine artery resistance compared with asymptomatic controls in uterine artery Doppler studies also supports the relationship between primary dysmenorrhea and ischemia.[5]

Even though the mechanism has not yet been clarified, it has been thought that ischemia-modified albumin (IMA) is formed as a result of the alteration in metal-binding sites of albumin due to the effect of reactive oxygen species. Amino terminal (N-terminal) of the albumin molecule is the binding site for metals such as cobalt, nickel, and copper. This binding site alters in case there are ischemia, acidosis, and free-radical damage and the binding capacity is decreased for metals. This different form of the albumin is named as IMA.[6] Ischemia-modified albumin is a promising marker in the evaluation of ischemic events, and serum IMA levels increase in various diseases related to ischemia. It has been shown that IMA is not only associated with cardiac ischemia, it is also increased in patients with liver cirrhosis, pulmonary embolism, end-stage renal disease, cerebrovascular disease, cancer, systemic sclerosis, preeclampsia, habitual miscarriage, and polycystic ovary syndrome.[7]

Up to the present, IMA levels have not yet been examined in patients with primary dysmenorrhea. In the present study, we aimed to determine whether or not there is a relationship between Doppler parameters and IMA levels in uterine arteries in the menstrual and luteal phases.

Methods

In the present prospective cross-sectional study, we included 37 patients who were admitted to our hospital with primary dysmenorrhea and 30 healthy individuals with similar demographic characteristics and who did not have menstrual pain during the menstrual period as a control group. The study was approved by the local ethics committee of Ankara Numune Training and Research Hospital, where the present study was performed. Medical and gynecological histories of all patients were recorded. Here are the eligibility criteria of the patients: being between 18 and 35 years old, nulliparity, having a regular menstrual cycle (24–38 days), having at least 4 painful periods from previous 6 menses, and having normal ultrasound findings on the uterus and adnexa. The exclusion criteria were as follows: having recurrent pelvic and lower abdominal pain outside the menstrual period, such as secondary dysmenorrhea, and other diseases of the reproductive organs, such as endometriosis or uterine fibroids; having a history of abnormal vaginal discharge; having a history of significant gastrointestinal, genitourinary, endocrine, rheumatic, or surgical procedure; being pregnant and in the lactation period; using prostaglandin synthesis inhibitors or any other concomitant drugs. The control group was composed of nulliparous individuals, in the same age group, without dysmenorrhea and abdominal pain during the menstrual period. We recorded the demographic features, weight (in kilograms [kg]), height (in meters [m]), and body mass index (BMI) (kg/m2) of patients.

Evaluation of Ultrasound Results

The 6.5-MHz abdominal transducer with a color Doppler capability Medison SONOACE X8 4D Convex Ultrasound Probe 3DC2-6 (Samsung Group, Seoul, South Korea) was used to perform the ultrasonographic assessments. In all patients, we performed the sonographic assessments in the menstrual (1–4th days) and luteal (21–23th days) phases of the spontaneous menstrual cycles. The conventional B-mode ultrasound technique was used to observe the uterus and ovaries. Color Doppler imaging lateral to the internal cervical os, in a longitudinal plane, was used to observe the uterine arteries. Then, a pulsed Doppler range gate was applied across the vessel to ensure that the angle between the Doppler beam and the vessel was close to 00. We calculated the RI and the PI by using the following formula: PI = (S- D)/mean, RI = (S - D)/S, where S is the peak shifted Doppler frequency, D is the minimum Doppler shifted frequency, and 'mean' is the mean maximum Doppler shifted frequency over the cardiac cycle. It was observed that the lowest values of uterine artery PI and RI were not significantly different between the right and the left uterine arteries. Only one researcher performed sonographic and Doppler techniques to avoid the false positive interobservation variations.

Ischemia-Modified Albumin Measurement

We collected blood samples in the day of the Doppler flow analysis. Blood samples were left to clot for 30 minutes, and then they were centrifuged 10 minutes at 4,000 rpm. Supernatants were collected and stored at -80°C. Reduced cobalt to albumin binding capacity (IMA level) was tested by using the rapid and colorimetric method, and findings were shown as absorbance units (ABSUs).

Statistical Analysis

The Statistical Package for the Social Sciences for Windows version 20.0 (IBM Corp., Armonk, NY, USA) was used to analyze the data. All data were shown as mean ± standard deviation (SD). Student *t*-test and Pearson tests were used to perform statistical analyses for normally distributed continuous data. Pearson or Spearman coefficients were calculated. Statistical significance was set as $p < 0.05$.

Results

In ►**Table 1**, demographic, biochemical, and pelvic Doppler sonographic parameters of primary dysmenorrhea patients

Table 1 Clinical, biochemical, and pelvic Doppler sonographic parameters of women with primary dysmenorrhea and of the control group[a]

Dysmenorrhea	Primary	Control	*p*-value
	($n = 37$)	($n = 30$)	
Age (years)	19.57 ± 2.89	20.90 ± 4.43	NS
BMI (kg/m^2)	21.57 ± 4.07	22.80 ± 4.05	NS
Menstrual UAPI	3.41 ± 0.15	2.76 ± 0.29	0.001*
Luteal UAPI	2.75 ± 0.21	2.72 ± 0.30	NS
Menstrual UARI	0.91 ± 0.14	0.82 ± 0.13	0.001*
Luteal UARI	0.82 ± 0.12	0.81 ± 0.17	NS
Menstrual IMA (ABSU)	0.55 ± 0.07	0.47 ± 0.08	0.001*
Luteal IMA (ABSU)	0.40 ± 0.04	0.39 ± 0.03	NS

Abbreviations: ABSU, absorbance unit; BMI, body mass index; IMA, ischemia-modified albumin; NS, not significant; UAPI, uterine artery pulsatility index; UARI, uterine artery resistance index.
[a]Values are given as mean ± SD.
*$p < 0.05$.

Table 2 Correlation of uterine artery pulsatility and resistance indices with the ischemia-modified albumin levels of women with primary dysmenorrhea and of the control group

	Menstrual IMA			Luteal IMA	
	PD	Control		PD	Control
r	r	r		r	r
Menstrual UAPI	0.357*	0.417*	Luteal UAPI	0.036	0.101
Menstrual UARI	0.451*	0.378*	Luteal UARI	0.090	0.712

Abbreviations: IMA, ischemia-modified albumin; PD, primary dysmenorrhea; UAPI, uterine artery pulsatility index; r, Pearson correlation coefficient; UARI, uterine artery resistance index.
*$p < 0.05$.

and of the control group can be seen. The age and body mass index (BMI) values were not significantly different between the patient and control groups. Mean uterine artery PI and RI values in the menstrual phase were significantly higher in the primary dysmenorrhea group when compared with the control group ($p < 0.05$). There was no difference between the two groups in terms of the mean PI and RI values in the luteal phase. Mean uterine artery PI and RI values in the menstrual phase were significantly higher when compared with the values of the luteal phase. Even though the mean PI and RI values in the menstrual phase were higher when compared with the values of the luteal phase in the control group, this difference was not statistically significant. The menstrual phase IMA levels of the primary dysmenorrhea group were significantly higher than those of the control group. However, there was no difference between the two groups in terms of their IMA levels in the luteal phase. The menstrual IMA levels of both primary dysmenorrhea and control groups were significantly higher compared with their luteal IMA levels.

The uterine artery PI and RI as well as the IMA of the primary dysmenorrhea and control groups can be seen in ►**Table 2**.

There was a positive correlation between the menstrual period uterine artery Doppler PI and RI values of primary dysmenorrhea patients. However, there was no relationship between IMA values and Doppler indices in the luteal phase. In the control group individuals, there was a positive correlation between menstrual phase uterine artery Doppler PI and RI values, whereas no significant relationship was observed in the luteal period IMA values and Doppler indices.

Primary dysmenorrhea is commonly observed among young women, and it is an important social problem that can negatively affect women's occupational and academic lives. Even though the reason for pain in primary dysmenorrhea has not yet been explained, it is believed that it occurs due to increased prostaglandin levels that lead to abnormal myometrial constructions; thus, generalized ischemia occurs due to the decreased uterine blood circulation.[2] There is an increased prostaglandin production in the endometrium due to the decreased progesterone levels as a result of the luteal phasing in patients with primary dysmenorrhea. Prostaglandin F2 α (PGF2 α) is a strong myometrial stimulant and vasoconstrictor, and it can lead to pelvic pain due to the myometrial contractions and ischemia. Furthermore, it has been detected that there is a positive correlation between endometrial prostaglandin levels and the severity of pain.[8]

In studies performed with patients with primary dysmenorrhea, even though there are uterine artery blood flow changes in the menstrual period depending on the myometrial contractility and increased intrauterine pressure, the reasons for these changes have not yet been explained. Dmitrović[9] detected that uterine artery PI and RI values of primary dysmenorrhea patients were higher in the first day of the menstrual cycle. In another study, it was observed that uterine artery PI and RI values were higher in patients with severe dysmenorrhea compared with patients with the mild version of the condition.[10] In a study performed by Altunyurt et al,[4] similarly to our study, the uterine artery mean PI and RI values of patients with primary dysmenorrhea were significantly higher when compared with the values of the midluteal phase. In this study, the higher uterine artery resistances of patients compared with asymptomatic controls support the relationship between the primary dysmenorrhea and ischemia. Even though we did not find a statistically significant difference in the control group, it was detected that uterine artery Doppler indices in the menstrual period were higher. These findings show that there is an intrauterine pressure increase in women without primary dysmenorrhea during the menstrual period. However, this increase is lower compared with the values of patients with primary dysmenorrhea.

Ischemia-modified albumin is a modified form of serum albumin, and it is formed as a result of binding of metal atoms such as cobalt, nickel, or copper to the N-terminal of albumin because of the superoxide and oxygen free radicals produced due to the oxidative stress.[11] Even though IMA is detected in

the circulation as a secondary response of ischemia in the hypoxic myocardial tissue, it has been recently used as the indicator for the hypoxic intrauterine area.[7,12]

Conclusion

In our study and in other studies in which uterine artery Doppler is used to diagnose dysmenorrhea, the role of ischemia in the development of dysmenorrhea is supported. Recently, our study is the first one in which the increased IMA levels in ischemic processes are examined by using the Doppler technique. In our study, the mean menstrual phase IMA values of the primary dysmenorrhea group were significantly higher when compared with the mean menstrual period IMA values of the control group. Furthermore, it was observed that there was a positive correlation between IMA values and uterine artery Doppler PI and RI values in patients with primary dysmenorrhea during the menstrual period. These findings support the relationship between the pain and ischemia in patients with primary dysmenorrhea. Conclusively, our findings show that ischemia has important roles in the etiology of pain in patients with primary dysmenorrhea, and IMA level measurement can be used as a promising marker to indicate the ischemia process during primary dysmenorrhea. In further studies in which the relationship between the severity of pain and ischemia is assessed, in case there is an association between pain and IMA levels, this relationship can be used to determine the medications for the effective treatment or to indicate the severity of the pain of these patients.

Contributors
All of the authors contributed to the conception and design of the present study, to the data collection, or to the analysis and interpretation of data, as well as to the writing of the article or to the critical review of the intellectual content and final approval of the version to be published.

Conflicts of Interests
The authors have no conflict of interests to declare.

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