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ORIGINAL PAPER

Assessment of Maternal Retinal Microvasculature in Preterm Pregnancy Using OCT-Angiography: a Cross-Sectional Study

Evita Evangelia CHRISTOU[a], Dimitrios RALLIS[b], Paraskevas ZAFEIROPOULOS[a], Christoforos ASPROUDIS[a], Maria STEFANIOTOU[a], Vasileios GIAPROS[b], Ioannis ASPROUDIS[a]

[a]University Ophthalmology Clinic, University of Ioannina, Faculty of Medicine, Ioannina, Greece

[b]Neonatal Intensive Care Unit, University of Ioannina, Faculty of Medicine, Ioannina, Greece

ABSTRACT

Background: *Pregnancy induces a cascade of hemodynamic changes that are likely to affect the maternal systemic and ocular circulation.*

Objectives: *The current study aimed to investigate retinal microvasculature alterations in women with preterm and full-term pregnancy using optical coherence tomography angiography (OCT-A).*

Design: *This was a cross-sectional, comparative, single-center study.*

Methods: *The present study included 21 women with preterm pregnancy, who were in the early postpartum period, and 18 controls with full-term pregnancy. Optical coherence tomography angiography imaging was performed to analyze macular microvasculature characteristics at the retinal superficial capillary plexus (SCP) and the choriocapillaris (CC).*

Results: *In females with preterm pregnancy, the mean values of vessel density (VD) at the SCP of the total macular area were significantly higher than those in females with full-term pregnancy (p=0.001), and the mean values of foveal, parafoveal and perifoveal VD at the SCP were higher, though not statistically significant. Similarly, the mean values of perfusion at the SCP of the total macular area were significantly higher in females with preterm pregnancy than controls (p=0.023), while the mean values of foveal, parafoveal and perifoveal perfusion were higher, though not statistically significant. The mean values of foveal avascular zone (FAZ) parameters (area, perimeter, circularity) at the SCP in females with preterm pregnancy did not have any significant differences from those of controls. Concerning the measurements of choroidal parameters, there were no statistically significant differences in subfoveal choroidal thickness, as well as the CC OCT-A characteristics between females with preterm and full-term pregnancy.*

Conclusions: *Our study indicates that retinal blood flow alterations may be present in the early postpartum period in women with preterm pregnancy. Increased macular vasculature may reflect the systemic perfusion changes compensating for placental insufficiency.*

Keywords: microvasculature, retina, prematurity, pregnancy, optical coherence tomography angiography.

Address for correspondence:
Evita Evangelia Christou, MD, PhD, FEBO
Faculty of Medicine, University of Ioannina, 45110, Ioannina, Greece
Tel: +306944368633; ORCID: 0000000279594854; email: evitachristou@gmail.com

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KEY MESSAGES

- Pregnancy induces a cascade of hemodynamic changes with resultant alterations of the retinal microvasculature.
- By carefully considering optical coherence tomography angiography (OCT-A) values, we may identify retinal blood flow alterations in the early postpartum period in women with preterm pregnancy as compared to full-term pregnancy.
- Increased macular vasculature could be associated with systemic perfusion changes compensating for placental insufficiency in preterm pregnancy.
- Prospective longitudinal studies are warranted to outline the accuracy of OCT-A parameters in clinical practice.

INTRODUCTION

Prematurity is a health concern with increasing prevalence, given the improved neonatal survival due to the widespread awareness and implementation of screening guidelines (1-5). Despite the well-established evidence on potential etiological factors of prematurity, there is limited understanding of the underlying pathophysiology; a notable aspect to consider is that premature birth may be associated with placental insufficiency and maternal vascular hypoperfusion. Indeed, the biological mechanisms involved in the onset of labour at both term and preterm need to be further elucidated, while the identification of effective predictive and preventive characteristics remains a challenge (1-5).

In the course of pregnancy, a number of physiologic adaptations occur to support the developing fetus (6, 7). Profound alterations in the reproductive, hematologic, cardiovascular and endocrine systems occur during the period of nine months and are reversed in the months following labour. Hemodynamic changes, which occur as a result of increased circulatory demands in pregnancy, are likely to affect the systemic and ocular circulation (6-13). The detailed quantification of placental perfusion is not currently available with routine obstetric examination, while imaging using contrast dye techniques is being avoided during pregnancy and postpartum (14). Similarly, retinal studies in pregnancy have been limited due to potential adverse effects of mydriatics and fluorescein dye. The advent of optical coherence tomography angiography (OCT-A) in recent years has given new insights in imaging and automated quantitative analysis of retinal microvasculature (15). Optical coherence tomography angiography is a novel non-invasive technology with depth-resolved capability to visualize microvessels without pharmacologic pupil dilation. This advanced imaging method has helped discover subtle anatomical differences that are otherwise clinically invisible (15).

To date, there is limited evidence concerning retinal vasculature in normal and pathologic pregnancy, while the aspect of retinal microvasculature postpartum remains largely unexplored. Based on recent evidence, increased circulatory demands and hormonal changes during the transient state of pregnancy seem to result in retinal capillary dilation (16-20). Nonetheless, it is unknown whether further retinal vascular modifications may occur in terms of prematurity.

We hypothesized that women with premature birth may have retinal blood flow alterations at the early postpartum period. Therefore, the aim of this study was to characterize the retinal and choriocapillaris (CC) microcirculation alterations utilizing OCT-A in preterm pregnancy and compare them to full-term. ❑

METHODS

Study design

The study was conducted in the Department of Ophthalmology of the University of Ioannina, Greece, between December 2021 and May 2022. The University Hospital is a regional tertiary center of Northwestern Greece where an average of 1500 infants are born annually, while almost 150 of them are born prematurely. Our sample comprised 10% of the total population with a premature birth born annually in this center. Approval from the institutional ethics committee was received. Written informed consent was obtained from all participants. The investigation adhered to the tenets of the Declaration of Helsinki.

Reporting of this study was conducted according to the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines (21). This was a cross-sectional, com-

parative, single-center study. Consecutive patients meeting eligibility criteria were recruited in collaboration with the Neonatal Unit. To be included, first group of patients should have a history of a singleton premature birth with a arrange from 28 to 36 weeks of gestation. The second group, the control group, consisted of women with a full-term pregnancy. Women in both groups were aged 19-37 years. Exclusion criteria for both groups consisted of pre-existing medical comorbidity, complications of pregnancy (gestational diabetes, hypertension, preeclampsia, infection) or any other ocular conditions that could affect retinal vascular circulation. A comprehensive ophthalmological examination was performed within two weeks postpartum for both groups, including anterior segment and fundus examination with slit-lamp biomicroscopy, visual acuity and intraocular pressure measurement. At the same time, OCT-A was obtained for all patients in both eyes. Detailed OCT-A imaging analysis was conducted based on the protocol described below.

Optical coherence tomography angiography imaging protocols

The scanning area was captured using the Zeiss Cirrus HD-5000 Spectral-Domain OCT with AngioPlex®, Jena, Germany. For each study participant, a scan of the macular area was captured using the eye tracking system to reduce motion artifacts. All angiograms were manually checked and corrected if there were segmentation errors. Images were reviewed for image quality including artifacts affecting microvasculature analysis, decentration of the macula and signal strength index (quality was considered sufficient if strength index was ≥7/10).

Optical coherence tomography angiography imaging was performed by acquiring a 6x6 mm^2 scan pattern automatically centered on the fovea. Each B-scan is repeated twice at the same position and contains 350 A-scans which are equally spaced along the horizontal dimension with 17.1 micrometers separation. Similarly, 350 B-scans are located in the vertical direction. The OCT-A system software generates en face images of retinal and choroidal vasculature which are based on automated layer segmentation. We examined macular capillary plexus parameters, in particular vessel density (VD) (mm/mm^2), perfusion (%) and foveal avascular zone (FAZ) characteristics of the superficial capillary plexus (SCP) which were automatically calculated. VD is defined as the total length of perfused vasculature per unit area and perfusion is defined as a percentage of perfused vasculature area per unit area. The 6x6 scan is divided into three topographic subfields; the fovea, a central circle with a diameter of 1 mm, the parafovea, an inner circle with a diameter of 3 mm and the perifovea, an outer circle of 6 mm. VD and perfusion SCP were calculated at each region of the 6x6 mm scan area. Concerning FAZ parameters, we measured the area (mm^2), perimeter (mm) and circularity (0 - 1).

In addition, we analyzed vascular changes of the CC. Optical coherence tomography angiograms were acquired at a 6x6 mm scan pattern; en face images of the CC were generated and automated layer segmentation was performed using a slab between 29 and 49 μm below the RPE. Each image was imported to Image J for analysis (22). Binarization was conducted by an automatic local thresholding with the Otsu method (radius, 15 pixels), with selection from gray-level histograms (23). The white zones corresponded to the lumen of vessels of the CC network and the black zones to the interstitial area. We assumed that the percentage of white zones was an indirect measure of the choroidal vascular flow area, therefore the percentage area occupied by the microvasculature defined perfusion. By this way, we quantified the percentage of perfusion in the total area, as well as the total number and average size of perfused areas (24). Choroidal thickness (μm) was manually measured at the subfoveal area after acquiring scans with the enhanced depth imaging (EDI) mode; measurements were performed using as landmarks the distance from the outer portion of the hyper-reflective line which corresponds to the Bruch's membrane, and the inner hyper-reflective line of the choroid-sclera interface (25).

Statistical analysis

Continuous variables were expressed as mean (standard deviation) and the comparisons of continuous variables were performed utilizing the student's unpaired t-test. The normality of the distributions of continuous variables was assessed by the Kolmogorov-Smirnov test. All tests were two-sided and a p-value less than 0.05 was considered statistically significant (alpha 0.05).

The data were analyzed using SPSS Statistics (IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY, US). ❑

RESULTS

A total of 24 females with preterm pregnancy were examined. After applying the exclusion criteria, a total of 21 women with preterm pregnancy (gestational age 29 to 35 weeks and five days of gestation, median: 31 weeks of gestation) were included in the analysis. The control group comprised 18 women with full-term pregnancy (gestational ages 39 to 41 weeks of gestation, median: 40 weeks of gestation).

Results of a generalized estimated equation analysis of the association between retinal OCT-A parameters and females with preterm and full-term pregnancy are shown in Table 1. In individuals with preterm pregnancy, the mean values of foveal, parafoveal and perifoveal VD at the SCP were higher, though not statistically significant, than those in individuals with full-term pregnancy, while the mean values of the total macular area VD were significantly higher in individuals with preterm pregnancy than in controls (p=0.001). Similarly, in individuals with preterm pregnancy, the mean values of foveal, parafoveal and perifoveal perfusion at the SCP were higher, though not statistically significant, than those in individuals with full-term pregnancy, while the mean values of the total macular area perfusion were significantly higher in individuals with preterm pregnancy than in controls (p=0.023).

Concerning FAZ parameters in the SCP, individuals with preterm pregnancy did not have any significantly changes concerning the mean values of FAZ area, perimeter and circularity as compared to those of individuals with full-term pregnancy in the 6x6 mm^2 OCT angiograms.

Results of a generalized estimated equation analysis of the association between calculated choroidal parameters and females with preterm and full-term pregnancy are shown in Table 2. Concerning the measurements of choroidal parameters, we did not find any statistically significant differences in subfoveal choroidal thickness, as well as the CC OCT-A characteristics, namely the percentage of perfusion in the total area and, the total number and average size of perfused areas in individuals with preterm pregnancy as compared to those with full-term pregnancy.

	Preterm (n=42 eyes)	Full term (n=36 eyes)	
Variable	**Mean (SD)**	**Mean (SD)**	**P-value**
FAZ area	0.071 (0.012)	0.072 (0.011)	0.492
FAZ perimeter	1.239 (0.096)	1.240 (0.099)	0.955
FAZ circularity	0.744 (0.017)	0.748 (0.019)	0.342
VD foveal	10.376 (0.970)	10.206 (0.726)	0.389
VD parafoveal	17.657 (0.484)	17.525 (0.398)	0.196
VD perifoveal	17.564 (0.461)	17.442 (0.408)	0.157
VD total	17.740 (0.427)	17.453 (0.284)	0.001
perfusion foveal	26.733 (0.831)	26.644 (0.811)	0.636
perfusion parafoveal	44.664 (1.058)	44.222 (1.580)	0.159
perfusion perifoveal	44.652 (1.109)	44.178 (1.544)	0.130
perfusion total	44.850 (1.037)	44.161 (1.495)	0.023

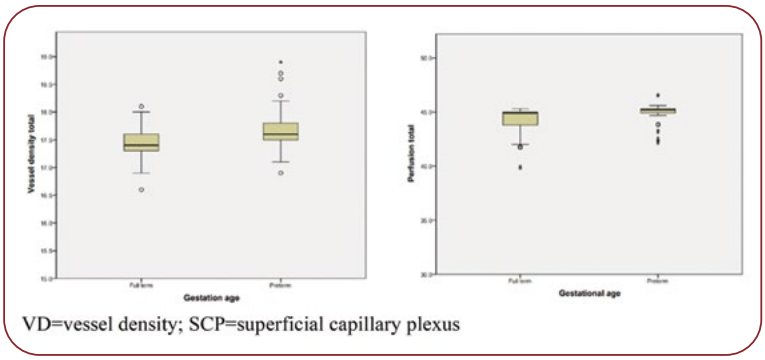
Continuous variables expressed as mean (standard deviation).
P of student's t-test. FAZ=foveal avascular zone;
VD=vessel density

TABLE 1. Retinal OCTA parameters between women with preterm and full-term pregnancy

	Mean (SD)		
Calculated parameters	**Preterm (n=42)**	**Full-term (n=36)**	**P-value**
Perfusion CC%	46.626 (1.734)	46.661 (1.731)	0.930
CC perfused areas count	612.86 (133.373)	635.42 (123.548)	0.444
CC perfused area average size	72.771 (23.532)	72.441 (19.222)	0.942
Subfoveal choroidal thickness	285.86 (25.724)	280.31 (17.789)	0.279

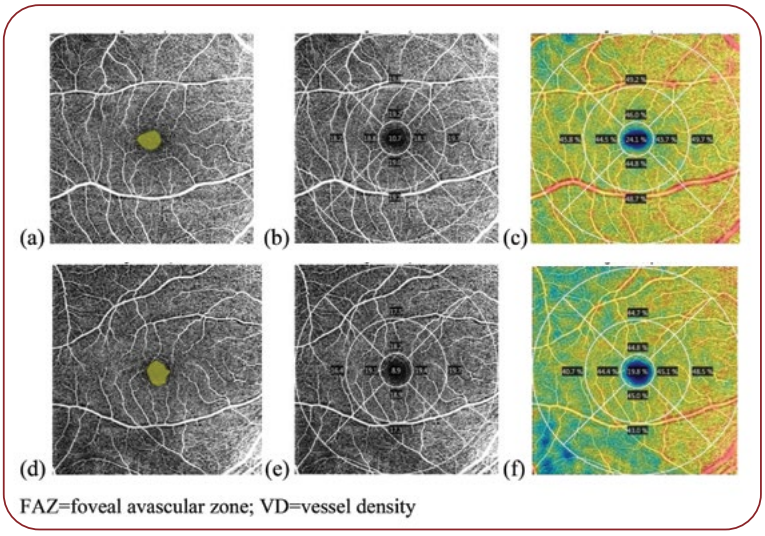
CC=choroicapillaris

TABLE 2. OCTA choroidal parameters at women with preterm and full-term and pregnancy



VD=vessel density; SCP=superficial capillary plexus

FIGURE 1. Boxplots showing the distribution of statistically significant calculated parameters (VD and perfusion SCP of total macular area) across patients with preterm and full-term pregnancy



FAZ=foveal avascular zone; VD=vessel density

FIGURE 2. Representative images of the macular area at the superficial capillary plexus of a female in preterm and full-term pregnancy, with OCT angiograms of macular area showing FAZ, VD and perfusion at fovea, parafovea and perifovea. Preterm pregnancy: (a) FAZ; (b) VD; and (c) perfusion. Full-term pregnancy: (d) FAZ; (e) VD; and (f) perfusion

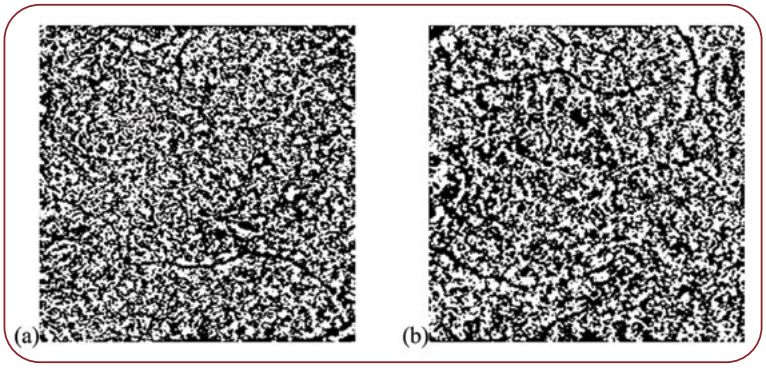


FIGURE 3. Representative images after binarization of the macular area at the choriocapillaris plexus indicating the perfused area of a female in preterm (a) and full-term (b) pregnancy

Distribution of statistically significant calculated parameters (VD and perfusion SCP of total macular area) across patients with preterm pregnancy and controls are shown in the boxplots of Figure 1.

Representative images of the retinal and the CC OCT-A characteristics of females with preterm and full-term pregnancy are shown in Figures 2 and 3, respectively. ❑

DISCUSSION

The findings of the current study indicated that macular subfield vasculature measurements were higher in the preterm pregnancy group as compared with the full-term, with that of the whole macular area being statistically significant. The increased flow density was notably not identified at the CC plexus. To the best of our knowledge, this is the first study to assess the relation between maternal macular microcirculation parameters and premature pregnancy utilizing OCT-A.

Pregnancy elicits profound physiologic adaptations in multiple systems, namely hematologic, vascular, metabolic, endocrine and immunologic to accommodate the developing fetus and prepare the mother for labour and delivery (6-13). The latter occur during the course of nine months with most of them being fully reversible in the next six weeks after delivery. Being a status characterized by increased circulatory demands, pregnancy induces a cascade of hemodynamic changes. Plasma volume expansion, which is a pivotal component of a successful pregnancy outcome, starts at six weeks of gestation to increase by 50% to a maximal volume around 32 weeks and reach a plateau thereafter until parturition. Of note, this important rise in plasma volume is characterized by increased cardiac output, however, with arterial under-filling due to 85% of blood volume residing within the venous circulation. In addition, hormonal alterations considerably upregulate nitric oxide and contribute to further decrease of peripheral resistance. Consequently, endothelial cells are likely affected promoting changes to the systemic and ocular circulation. Despite the temporary nature of pregnancy, it has been hypothesized that retinal microvasculature may undergo vasodilation due to increased blood volume; these alterations conceivably occur during the course of pregnancy and in the early postpartum period, until this state is fully reversed in the following months. It is noteworthy to mention that the failure of ma-

ternal plasma volume expansion may be implicated in adverse obstetric outcomes, such as fetal growth restriction and preterm birth (6-13). Besides, approximately 30% of individuals with preterm labour have placental lesions consistent with vascular hypoperfusion, which may be connected to placental insufficiency and in turn induce further systemic vascular adaptations (26).

Our study demonstrates changes in retinal vascular density and blood flow in individuals with preterm pregnancy as compared to those with full-term; in particular, VD and perfusion SCP were significantly higher in the whole macular area in females with premature births. Existing evidence indicates the presence of retinal changes in the third trimester of pregnancy (16-19). A previous study of healthy women exhibited that total macular volume and retinal thickness were increased toward the end of pregnancy, which was presumably attributed to a rise of body fluid and capillary hydrostatic pressure (27, 28). In an attempt to investigate retinal and choroidal vasculature during pregnancy, Chanwimol et al showed retinal microcirculation alterations in healthy pregnant individuals, further supporting the normal and compensatory changes that are known to occur during this state (16). Indeed, increased total body blood volume and high levels of progesterone associated with this condition may result in retinal capillary dilation (16). The authors notably indicated that perfusion density of deep capillary plexus (DCP) was significantly increased in pregnant women, however, this was not confirmed at the SCP (16). Due to physiologic differences in hydrostatic pressure, structure and function between the SCP and DCP, it may be plausible that they would be affected in a different way during pregnancy (29, 30). Recently, Su and co-authors found that women with small for gestational age infants had increases in selective retinal vascular layers, hypothesizing that these compensatory increases in microcirculation parameters were possibly related to placental insufficiency (20). Since preterm pregnancy is characterized by maternal vascular hypoperfusion, we could assume that a common pathophysiological basis in both cases would account for an apparent increase in vascular density and blood flow (20, 26). As previously supported, this mechanism could involve the retinal blood flow autoregulation through the release of vasoactive mediating molecules that lead to capillaries adaptations to alterations in the perfusion pressure and metabolic demands of the tissue (31, 32).

Concerning FAZ parameters, we did not observe any significant differences between females with preterm and full-term pregnancy. Likewise, alterations in FAZ have not been noticed during pregnancy in healthy females (16). Possibly, an explanation of undetected changes could be that the fovea is relatively devoid of vessels making small changes difficult to identify. Besides, the measurements in our study were made within two weeks postpartum and this fact could have concealed minor variations which might have been present during pregnancy or immediately after labour.

A number of studies have reported changes of choroidal thickness in specific subfields of the macula during pregnancy, though their results do not serve unequivocal perspectives; some studies found thickening of the choroid, while others mention no differences from non-pregnant women (33-35). Unlike choroidal thickness which has been widely analyzed, CC blood flow needs to be further investigated. Our analysis of OCT angiograms by the binarization method focused on the flow pattern of the CC. The results of our study notably indicate a uniform CC flow pattern in both preterm and full-term pregnancies. The vasculature of the CC has been previously evaluated in normal pregnancy by measuring CC flow voids (lack of vessels) on OCT-A proposing no evident differences between pregnant and non-pregnant women (16). Similarly to these findings, our study supports the hypothesis that the choroid has a relatively even and constant homeostatic response that differs from the complex retinal autoregulatory process.

To date, there is limited evidence concerning retinal vasculature in normal and pathologic pregnancy (16-20). Conceivably, this information may be considered relevant for clinical practice, as blood flow changes could serve as a predicting factor for the prognostication of the status of systemic circulation and the possibility of a premature birth. Given that hemodynamic changes resolve slowly after delivery within a period of several months, we speculate that our measurements that were taken in the early postpartum period, may reflect the vasculature status towards the end of pregnancy (6-13). Thus, retinal microcirculation alterations may comprise

predicting factors that are associated with premature labour. An interesting point that should be underlined is that we evaluated the retinal microvasculature of women with preterm pregnancy in comparison to those with full-term, demonstrating that apparent vascular alterations may possibly be associated with placental insufficiency. The aforementioned parameters along with the design may add strength to our study. In any case, our study contributes to a little-studied issue which undoubtedly warrants further investigation. Inevitably, the results of the current study should be interpreted with certain limitations. Firstly, our patients were examined in the postpartum period. One could suggest that examination during pregnancy could provide more specific evidence regarding the vasculature changes, however, even examination at this time point enabled the detection of significant differences between women with preterm and full-term labour. Moreover, hemodynamic resolution occurs within the following months and, due to strict inclusion criteria, we analyzed OCT angiograms of cases that were imaged promptly. Secondly, we should not ignore the intrinsic limitations of the imaging technology used. It can be argued for instance, that that a swept-source system would offer more detailed analysis than a spectral-domain device; they are considered comparable for measurements of the superficial retinal layers, but they may differ for the visualization of the CC (36). Thirdly, the present study was performed in a single center, therefore more controlled evidence should be available before generalizing. Fourthly, sample size/power analysis was not performed for this study. Lastly, it should be noted that our results regarding CC vasculature were produced using a well-known image-processing software and a procedure (binarization) that has been used for other studies. Theoretically, employing different imaging platforms could have produced different results. ❑

CONCLUSIONS

The current study points out that retinal blood flow alterations may be present at the early postpartum period in women with preterm pregnancy; in particular, increased macular vasculature could be associated with systemic perfusion changes compensating for placental insufficiency. Additional prospective longitudinal studies are warranted to validate our findings, correlate the retinal microvasculature with uteroplacental or systemic circulation and determine the accuracy of OCT-A characteristics as predicting factors for preterm births in clinical practice. ❑

Ethics statement: All authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Conflicts of interest: none declared.

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Ethical approval: The study was approved by the institutional ethics committee of the University Hospital of Ioannina (e.s.13/14-6-2021 θ.6), Greece on 22-6-2021.

Author contributions: Evita Evangelia Christou – conceptualization, data curation, investigation, methodology, project administration, and writing the original draft;

Dimitrios Rallis – data curation, methodology, project administration, supervision, and writing, including review and editing;
Paraskevas Zafeiropoulos – data curation, investigation, methodology, visualization;
Christoforos Asproudis – data curation, investigation, methodology, visualization;
Maria Stefaniotou – data curation, methodology, project administration, supervision, and writing, including review and editing;
Vasileios Giapros – conceptualization, methodology, project administration, supervision, writing, including review and editing;
Ioannis Asproudis – conceptualization, data curation, methodology, project administration, supervision, and writing, including review and editing.

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