Characteristics of Retinal Image Associated with Premature Ovarian Insufficiency

Jiaman Wu

Southern Medical University

Liya Tan

Guangzhou University of Chinese Medicine

Yan Ning

Southern Medical University

Wei-qu Yuan

Shenzhen Traditional Chinese Medicine Hospital

Zuowei Lee

CUHK Shenzhen Research Institute

Fei Ma

Southern Medical University

Erfeng Wang

Guangzhou University of Chinese Medicine

Yuanyuan Zhuo (✉ qinyuan64@163.com)

Shenzhen Traditional Chinese Medicine Hospital

Research Article

Keywords: retinal characteristics, premature ovarian insufficiency, retinal image analysis, biostatistics method, early clinical diagnosis

Posted Date: January 27th, 2022

DOI: <https://doi.org/10.21203/rs.3.rs-1289847/v1>

License: This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Purpose To establish a prediction model for premature ovarian insufficiency (POI) identification.

Methods A total of 78 women with spontaneous POI and 48 healthy women were recruited from the Affiliated Shenzhen Maternity & Child Healthcare Hospital in the study. Retinal characteristics were analyzed using an automated retinal image analysis system. Binary logistic regression was used to identify POI cases and develop predictive models.

Results Compared to the normal group, the POI group had larger central retinal artery equivalent (CRAE) ($P=0.006$), central retinal vein equivalent (CRVE) ($P=0.001$), index of venules asymmetry (Vasym) ($P=0.000$); larger bifurcation angles of arterioles (Aangle) ($P=0.001$), bifurcation coefficient of venule (BCV) ($P=0.001$) and more obvious arteriovenous nipping (Nipping) ($P=0.005$), but lower arteriole-to-venule ratio (AVR) ($P=0.012$). In the POI group, the odds ratio (OR) of Vasym was $6.72e-32$ (95% C.I. $4.62e-49-9.79e-15$, $P=0.000$), the OR of BCV was $5.66e-20$ (95% C.I. $1.93e-34-.0000$, $P=5.66e-20$) and the OR of Nipping was $6.65e-06$ (95% C.I. $6.33e-10-.0698$, $P=0.012$). Moreover, the area under the ROC curve for the binary logistic regression with retinal characteristics was 0.8582, and the fitting degree of regression models was 60.48% (Prob> chi-square = 0.6048).

Conclusion This study demonstrated that retinal image analysis can provide useful information for POI identification and certain characteristics may help with early clinical diagnosis of POI.

Introduction

Premature ovarian insufficiency (POI) is a clinical syndrome characterized by premature decline of ovarian function, abnormal menstruation (amenorrhea, hypomenorrhea or frequent menstruation), increased serum gonadotropin levels and decreased estrogen levels, resulting in the decrease of reproductive function [1]. The prevalence rate of POI in the general population was about 1% [2], and it is not rare among women of childbearing age. A recent national registry study involving 103,6918 women from Sweden showed that the overall prevalence of POI was 1.9% [3].

POI not only affects menstruation and fertility, but also leads to early menopausal symptoms and increased risk of long-term cardiovascular disease [4]. A study [5] in Korea demonstrated that patients with premature ovarian failure (POF) had significantly higher frequencies of vascular endothelial growth factor (VEGF). It was reported that decrease in level of endogenous estrogen can lead to vascular aging, including endothelial cell damage, intimal smooth muscle cell proliferation and other symptoms affecting atherosclerosis formation [6, 7]. Therefore, POI may associated with some vessels diseases or lead to vascular changes.

The clinical diagnostic of POI is mainly based on clinical symptoms and serum measurements [1]. However, drawing blood for serological examination is invasive. Besides, two or more blood tests with an interval of 4-6 weeks is needed for diagnosis, resulting in a relatively high cost.

Retinal images can reflect the state of micro vessels and provide a direct observation of the changes in fundus vessels. previous studies found a correlation between changes in fundus vessels and cardiovascular diseases [8-10]. The changes of vessels in POI patients maybe reflect in their retinal characteristics. The retinal image analysis could provide some helpful information for diagnosis of POI by monitoring how healthy their blood vessels are. In this study, we explored the fundus vascular characteristics related to POI, established retinal image diagnosis model with characteristics in retinal image, which may be used in early diagnosis of POI.

In this study, we observed the vessels in POI patient by using retinal images, and found out if there were some differences in retinal vasculature in the POI patient group when compared with the normal group, so as to establish the retinal characteristic diagnosis model to identify the POI patients.

Methods

Ethical Statement

This study was approved by the ethics committee of the Affiliated Shenzhen Maternity & Child Healthcare Hospital (Approval Number: SFYLS2020-012) and was performed in accordance with the guidelines of the Declaration of Helsinki (1964). This study was registered at Chinese Clinical Trial Registry (Registration No. ChiCTR2000029576).

Data collection

In this case-control study, 78 women with spontaneous POI and 48 normal women were recruited from the Affiliated Shenzhen Maternity & Child Healthcare Hospital from August 1st, 2018 to October 30th, 2020. Spontaneous POI was diagnosed according to the criteria established in the management guidelines of the European Society of Human Reproduction and Embryology: primary or secondary amenorrhea lasting for at least 4 months before 40 years old, with at least two measurements of serum follicle-stimulating hormone levels exceeding 25 IU/L with an interval of 4-6 weeks [9]. Patients with karyotype abnormalities, genetic defects (such as Turner syndrome), hypothalamic amenorrhea, POI with autoimmune symptoms, infectious or iatrogenic etiologies or abnormal liver function were excluded. In order to exclude the cardiovascular disease which may influence the retinal vessel, patients with diabetes, hypertension, dyslipidemia, inflammatory disorders were also excluded in this study. 48 normal group with regular menstrual cycles and no POI diagnosis history was selected. All participants provided written consent for their participation in the study. The age, height, weight, infertility duration of both the POI group and control group were recorded. The body mass index (BMI) was calculated. The level of follicle-stimulating hormone (FSH), level of luteinizing hormone (LH) and level of estradiol (E2) and level of anti-Mullerian hormone (AMH) of all participants were measured. The FSH/LH ratio was calculated (Figure1).

Retinal Characteristics

Retinal images were taken by a digital retinal camera (CR-2 AF, Canon, Japan). To ensure the compatibility of image parameters, retinal images were scaled to 1365*1024 pixels and saved in jpg format. A fully automatic retinal image analysis (ARIA) system [11] using R and MATLAB was used to measure retinal characteristics. Retinal characteristics of retinal vessel in this study are arteriole-venous nipping (Nipping), arteriole occlusion (Aocclusion), tortuosity (Tortuosity), hemorrhages (Hemorrhage), exudates (Exudates), asymmetry index of arterioles (Aasym), bifurcation coefficient of venule (BCV), bifurcation coefficient of arterioles (BCA), and bifurcation angles of venule (Vangle). According to a method developed by Knudtson *et al* , the retinal vessel measurements were summarized as central retinal artery equivalent (CRAE) and central retinal vein equivalent (CRVE), representing the diameters of arterioles and venules, respectively[12]. The arteriole-to-venule ratio (AVR) was calculated as the ratio of CRAE to CRVE. Vessel tortuosity provides both qualitative and quantitative information by visual grading of one fovea-center and one disc-centered fundus image. Arteriole venous nipping causes narrowing of the venule when crossed by an arteriole. The arteriole occlusions refer to the blockage of blood flow inside the arterioles when obstructed by an emboli. The branching pattern of retinal vessels, such as BCV, the ratio of the widths of branching vessels to trunk vessels, the angle between two branching vessels and index of venules asymmetry (Vasym), the ratio of diameters of two branching vessels represents the relationship between the trunk and the branching vessels. The fractal dimension of the retinal vasculature (FDv) and arterioles (FDa) measured the complexity of branching patterns. The bifurcation angles of arterioles (Aangle) represent the mean of three sets of vessels in one retinal image. The analysis was performed using three sets of vessels in a single retinal image. Hemorrhage and Exudates were recorded as present or absent and their probabilities (0 to 1) were calculated (Figure 2).

Statistical Analysis

Chi-square tests, and two-tailed independent samples t-tests were used to compare the demographics and retinal characteristics between the POI group and the control group. Retinal characteristics of patients with POI were identified using a univariate analysis. A *p*-value <0.05 was considered as statistically significant. The binary logistic regression with backward stepwise selection was used to select the best model. The classification accuracy and the area under the curve of the receiver operating characteristic (ROC) were measured. All the data were analyzed using the Statistical Package for Social Science software Stata 15.0 (Stata Corp., College Station, TX, USA).

Results

The general characteristics of the study participants were summarized in Table 1. The average age was 34.53(SD: ±4.11) years, the average BMI was 21.8(SD: ±1.13). In the univariate analysis, clinical characteristics such as age, height, weight, BMI showed no statistical significance between the two groups(*P*>0.05). Compared to the control group, the POI group had significantly higher levels of infertility duration, FSH, LH and FSH/LH ratio, and significantly lower levels of E2 and AMH.

Compared the retinal characteristics of the two groups, the POI group had higher CRAE ($P=0.006$), CRVE ($P=0.001$), and Vasym ($P=0.000$); larger Aangle ($P=0.001$) and BCV ($P=0.001$); more obvious Nipping ($P=0.005$), and lower AVR ($P=0.012$) (Figure 3).

The multivariate logistic regression model was built for POI identification. In the POI group, the OR of Vasym was $6.72e-32$ (95% C.I. $4.62e-49-9.79e-15$, $P=0.000$), the OR of BCV was $5.66e-20$ (95% C.I. $1.93e-34-.0000$, $P=5.66e-20$) and the OR of Nipping was $6.65e-06$ (95% C.I. $6.33e-10-.0698$, $P=0.012$) (Table 2). Diagnostic testing was performed to evaluate the prediction accuracy of the model. The area under the ROC curve for the binary logistic regression with retinal characteristics was 0.8582, and the goodness of fit test was 60.48% (Prob=0.6048, Prob>chi-square) (Figure 4).

Discussion

Luteinizing hormone, follicle-stimulating hormone and estradiol are the common markers in POI patients. POI indicates an early menopause and it can be diagnosed when the levels of blood LH and FSH increase substantially. One of the most sensitive hormones to diagnosis POI is FSH, which negatively correlated with ovarian function. Therefore, monitoring of elevated FSH for several months is helpful for women to be diagnosed of early-onset ovarian insufficiency. The ovaries occasionally experience a stage of low activity, and then return to normal function. For this reason, to diagnosis POI, at least two hormone measurements from two menstrual cycles are required. Furthermore, time limit to blood test is important, considering that the FSH and LH levels in women vary greatly in each menstrual cycle, requiring blood samples to be drawn within 3-5 days after menstruation. In a word, the diagnosis using blood examinations is invasive and inconvenient. It is very important to propose an effective, noninvasive diagnostic method for patients with POI in clinical application.

POI not only causes menstrual changes, but also affects blood vessels. E2 has a direct stimulatory effect on vascular endothelial cells via the estrogen receptor [13]. It was reported that the endocrine changes in female patients, especially the decrease of E2, were associated some abnormalities of the microvascular system [15]. Retina is a small part of the vascular system in human body which can be observed directly. It is not only an important sign of retinopathy, but also a direct evidence of vessels injury in human body. Some endocrine diseases, induced by hormone changes, can affect the vascular system, and can be reflected in the fundus blood vessels. Raizada[16] found that the change in sex hormones can cause the retinal capillaries, arterioles and venues to develop mild per phlebitis. E2 have been linked with alterations in the ocular and retinal circulation, Estrogen-replacement therapy in postmenopausal women can substantially reduce vascular resistance distal of the ophthalmic artery to levels matching those of young women [17]. LH plays a physiologic role in VEGF regulation and retinal vascularization in the development of eyes but it is not required for the development of various components of retina in mouse [18]. In the vasculature of nonmalignant tissues, FSHR is only expressed in placental endothelial cells [14] and to a lesser extent, in the endothelium of ovaries[19] and testis [20]. Estrogen has dual effects on the inflammatory system, with anti-inflammatory and pro-inflammatory effects, which increase after menopause [21-22]. Inflammatory aging plays an important role in the pathogenesis of POI, leading

to the imbalance of inflammatory cytokine network [23], so it can be inferred that POI has a close relationship with vascular endothelial dysfunction and vascular inflammation due to low estrogen level, and this result can be confirmed that there is no sign of accelerated vascular aging in POI women receiving timely and sufficient HRT. Therefore, endothelial function is a barometer of vascular health and a predictor of atherosclerosis, which may begin earlier than usual in female patients with POI [24-25]. Kalantaridou et al. [26] found that after receiving HRT 6 months, the blood flow mediated diastolic function in POI patients increased more than twice and returned to the normal value similar to that in the control group. It can be inferred that the vascular endothelial function can be effectively reflected by the vascular diastolic function. In our study, we found that POI is related to the increase of risk factors or markers reflecting vasodilation function in retinal fundus vascular analysis, such as Vasym, BCV and Nipping, which is consistent with the author's purpose to distinguish POI from healthy people by observing retinal fundus vessels.

Ocular blood flow velocity was positively correlated with levels of LH, FSH and total cholesterol. Therefore, the characteristics of retinal image can provide useful information for the diagnosis of POI. In our study, we found that the characteristics of retinal image of POI were mainly focus on the vein vessels. The increased branching coefficients of arteries and venules were associated with a higher risk of POI, indicating changes in retinal vascular branching patterns. In healthy individuals, retinal vessels provide optimal pathways for blood flow, and thus the energy consumption is minimal. Therefore, we hypothesized that the retinal microcirculation abnormalities in POI patients were associated with chronic and lower levels of E2.

So far, there was no literature supporting the finding that the protective effect of estrogen on cardiovascular system is mainly through the influence of coagulation and fibrinolysis system, inflammatory factors and vascular endothelial cells [27-30], which may reflect that microvascular injury is caused by POI and can be identified by retinal bifurcation coefficient. Since biological effects are considered to be more complex, we explored the interaction between retinal features. This study found that the risk of POI increased as the levels of a series of retinal components (CRAE, CRVE, BCA, venous angle, arterial angle, FDA) increased.

This study has some limitations. All participants in the study were recruited from the same hospital, which may lead to potential selection bias. Therefore, multicenter clinical studies is necessary in further research. In addition, cross-sectional design resulted in difficulties in causal inference. A larger sample size is needed in further research.

In summary, this study provided evidence for correlation of vascular abnormalities and POI. Micro-circulation abnormalities may occur at the earliest stages in many diseases and the ocular circulation is a preferred target for disease processes. Meanwhile, it is unclear how these findings may be applied to individual patients and it is also not clear yet whether retinal characteristic analysis in POI management would change the course of the comorbidities. The ability to directly monitor the status of specific

microvascular beds may have a potential therapeutic and prognostic value, requiring prospective follow-up studies with larger sample size.

Declarations

The EXCEL data used to support the findings of this study are available from the corresponding author upon request.

Ethical Approval

This study was approved by the Ethics Committee of the Maternity & Child Healthcare Hospital, Southern Medical University and carried out in accordance with the guidelines of the Declaration of Helsinki (Approval number: SFYLS2020-012).

Consent

All patients provided written informed consent prior to participation in any study-related procedures.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

Authors' Contributions

J.M. Wu and L.Y. Tan contributed equally to this paper. J. M.Wu and Y.Y.Zhuo conceived of the presented idea and planned the experiments. Y. Y. Zhuo and E.F.Wang conducted the experiments. Z.W. Li, Y. Ning and F.Ma designed the computational framework and analyzed the data. J. M. Wu, L.Y.Tan and Y. Y. Zhuo wrote the manuscript. All authors discussed the results and contributed to the final manuscript.

Acknowledgments

This work was supported by Sanming Project of Medicine in Shenzhen (No. SZSM201612046), Guangdong Provincial Administration of Traditional Chinese Medicine (No.20201294), and internal research project of Shenzhen Maternity & Child Healthcare Hospital (No. FYA2018006);the General project of Shenzhen basic research special (Natural Science Foundation) (No.JCYJ20210324130001004).We would like to thank all the participants of this study for their cooperation and patience.

Supplementary Materials

These are the retinal images of 126 participants recruited in the study. Supplementary for univariate analysis.

References

- [1] J.J. Chae-Kim, L. Gavrilova-Jordan (2018) Premature Ovarian Insufficiency: Procreative Management and Preventive Strategies, *Biomedicines*. 7.<http://10.3390/biomedicines7010002>.
- [2] L. Webber, M. Davies, R. Anderson, J. Bartlett, D. Braat, B. Cartwright, R. Cifkova, S. de Muinck Keizer-Schrama, E. Hogervorst, F. Janse, L. Liao, V. Vlasisavljevic, C. Zillikens, N. Vermeulen (2016) ESHRE Guideline: management of women with premature ovarian insufficiency, *Hum Reprod*. 31: 926-37.<http://10.1093/humrep/dew027>.
- [3] K. Lagergren, M. Hammar, E. Nedstrand, M. Bladh, G. Sydsjö (2018) The prevalence of primary ovarian insufficiency in Sweden; a national register study, *BMC Womens Health*. 18: 175.<http://10.1186/s12905-018-0665-2>.
- [4] E. Løkkegaard, Z. Jovanovic, B.L. Heitmann, N. Keiding, B. Ottesen, A.T. Pedersen (2006) The association between early menopause and risk of ischaemic heart disease: influence of Hormone Therapy, *Maturitas*. 53: 226-33.<http://10.1016/j.maturitas.2005.04.009>.
- [5] Y.J. Jeon, Y. Choi, S.H. Shim, Y.S. Choi, J.J. Ko, T.K. Yoon, S.H. Cha, N.K. Kim (2011) Vascular endothelial growth factor gene polymorphisms in Korean patients with premature ovarian failure, *Eur J Obstet Gynecol Reprod Biol*. 159: 138-42.<http://10.1016/j.ejogrb.2011.07.007>.
- [6] R.J. Baber, N. Panay, A. Fenton (2016) 2016 IMS Recommendations on women's midlife health and menopause hormone therapy, *Climacteric*. 19: 109-50.<http://10.3109/13697137.2015.1129166>.
- [7] S. Dragojević Dikić, M. Vasiljević, A. Jovanović, S. Dikić, A. Jurišić, L. Srbinović, S. Vujović (2020) Premature ovarian insufficiency - novel hormonal approaches in optimizing fertility, *Gynecol Endocrinol*. 36: 162-165.<http://10.1080/09513590.2019.1640203>.
- [8] Z. Yuanyuan, W. Jiaman, Q. Yimin, Y. Haibo, Y. Wei-qu, Y. Zhuoxin (2020) Comparison of Prediction Models based on Risk Factors and Retinal Characteristics Associated with Recurrence One Year after Ischemic Stroke, *J Stroke Cerebrovasc Dis*. 29: 104581.<http://10.1016/j.jstrokecerebrovasdis.2019.104581>.
- [9] Y. Zhuo, J. Wu, Y. Qu, H. Yu, X. Huang, B. Zee, J. Lee, Z. Yang (2020) Clinical risk factors associated with recurrence of ischemic stroke within two years: A cohort study, *Medicine (Baltimore)*. 99: e20830.<http://10.1097/md.00000000000020830>.
- [10] Y.Y. Zhuo, J.M. Wu, L. Kuang, Y.M. Qu, B. Zee, J. Lee, Z.X. Yang (2020) The Discriminative Efficacy of Retinal Characteristics on Two Traditional Chinese Syndromes in Association with Ischemic Stroke, *Evid Based Complement Alternat Med*. 2020: 6051831.<http://10.1155/2020/6051831>.
- [11] C.Y. Zee, J.W. Lee, E.Q. Li (2014) Method and device for retinal image analysis, US.
- [12] M.D. Knudtson, K.E. Lee, L.D. Hubbard, T.Y. Wong, R. Klein, B.E. Klein (2003) Revised formulas for summarizing retinal vessel diameters, *Curr Eye Res*. 27: 143-9.<http://10.1076/ceyr.27.3.143.16049>.

- [13] G.M. Rubanyi, A. Johns, K. Kauser (2002) Effect of estrogen on endothelial function and angiogenesis, *Vascul Pharmacol.* 38: 89-98.[http://10.1016/s0306-3623\(02\)00131-3](http://10.1016/s0306-3623(02)00131-3).
- [14] A. Radu, C. Pichon, P. Camparo, M. Antoine, Y. Allory, A. Couvelard, G. Fromont, M.T. Hai, N. Ghinea (2010) Expression of follicle-stimulating hormone receptor in tumor blood vessels, *N Engl J Med.* 363: 1621-30.<http://10.1056/NEJMoa1001283>.
- [15] F. Naftolin, J. Friedenthal, R. Nachtigall, L. Nachtigall (2019) Cardiovascular health and the menopausal woman: the role of estrogen and when to begin and end hormone treatment, *F1000Res.* 8.<http://10.12688/f1000research.15548.1>.
- [16] K. Raizada, K. Tripathy, Eales Disease, StatPearls, StatPearls Publishing
- Copyright © 2021, StatPearls Publishing LLC., Treasure Island (FL), 2021.
- [17] M. Harris-Yitzhak, A. Harris, Z. Ben-Refael, D. Zarfati, H.J. Garzozi, B.J. Martin (2000) Estrogen-replacement therapy: effects on retrobulbar hemodynamics, *Am J Ophthalmol.* 129: 623-8.[http://10.1016/s0002-9394\(99\)00468-7](http://10.1016/s0002-9394(99)00468-7).
- [18] T.Z. Movsas, R. Sigler, A. Muthusamy (2018) Elimination of Signaling by the Luteinizing Hormone Receptor Reduces Ocular VEGF and Retinal Vascularization during Mouse Eye Development, *Curr Eye Res.* 43: 1286-1289.<http://10.1080/02713683.2018.1495740>.
- [19] B. Vannier, H. Loosfelt, G. Meduri, C. Pichon, E. Milgrom (1996) Anti-human FSH receptor monoclonal antibodies: immunochemical and immunocytochemical characterization of the receptor, *Biochemistry.* 35: 1358-66.<http://10.1021/bi952290f>.
- [20] M.T. Vu Hai, P. Lescop, H. Loosfelt, N. Ghinea (2004) Receptor-mediated transcytosis of follicle-stimulating hormone through the rat testicular microvasculature, *Biol Cell.* 96: 133-44.<http://10.1016/j.biolcel.2003.11.008>.
- [21] Straub RH. The complex role of estrogens in inflammation. *Endocr Rev.* 2007;28(5):521–574 .
<https://doi.org/10.1210/er.2007-0001>.
- [22] Stanhewicz AE, Wenner MM, Stachenfeld NS. Sex differences in endothelial function important to vascular health and overall cardiovascular disease risk across the lifespan. *Am J Physiol Heart Circ Physiol.* 2018;315(6):H1569–H1588. <https://doi.org/10.1152/ajpheart.00396.2018>
- [23] Huang Y, Hu C, Ye H, et al. Inflamm-aging: a new mechanism affecting premature ovarian insufficiency. *J Immunol Res.* 2019; 2019:8069898. <https://doi.org/10.1155/2019/8069898>
- [24] Kok HS, van Asselt KM, van der Schouw YT, et al. Heart disease risk determines menopausal age rather than the reverse. *J Am Coll Cardiol.* 2006;47(10):1976–1983.
<https://doi.org/10.1016/j.jacc.2005.12.066>

- [25] Laven JSE, Visser JA, Uitterlinden AG, et al. Menopause: genome stability as new paradigm. *Maturitas*. 2016;92:15–23. <https://doi.org/10.1016/j.maturitas.2016.07.006>
- [26] Kalantaridou SN, Naka KK, Papanikolaou E, et al. Impaired endothelial function in young women with premature ovarian failure: normalization with hormone therapy. *J Clin Endocrinol Metab*. 2004;89(8):3907–3913. <https://doi.org/10.1210/jc.2004-0015>
- [27] M.H. Errera, A. Pratas, P. Goldschmidt, N. Sedira, J.A. Sahel, J. Benesty (2016) [Eales' disease], *J Fr Ophthalmol*. 39: 474-82.<http://10.1016/j.jfo.2016.03.001>.
- [28] J.K. Shrestha, D. Khadka, G. Lamichhane, S. Khanal (2009) Retinal vasculitis, *Nepal J Ophthalmol*. 1: 66-71.<http://10.3126/nepjoph.v1i1.3675>.
- [29] F. Paneni, C. Diaz Cañestro, P. Libby, T.F. Lüscher, G.G. Camici (2017) The Aging Cardiovascular System: Understanding It at the Cellular and Clinical Levels, *J Am Coll Cardiol*. 69: 1952-1967.<http://10.1016/j.jacc.2017.01.064>.
- [30] A. de Almeida, T.P. Ribeiro, I.A. de Medeiros (2017) Aging: Molecular Pathways and Implications on the Cardiovascular System, *Oxid Med Cell Longev*. 2017: 7941563.<http://10.1155/2017/7941563>.

Tables

Due to technical limitations, table 1-2 is only available as a download in the Supplemental Files section.

Figures

Figure 1

Flow chart of retinal images control study between POI patients and normal women, POI represents women with premature ovarian insufficiency.

Figure 2

Characterization of retinal vessel in the POI and control groups. Nipping, arteriole-venous nipping; Aocclusion, arteriole occlusion; Tortuosity, tortuosity; Hemorrhage, hemorrhages; Exudates, exudates; Aasym, asymmetry index of arterioles; Vasym, asymmetry index of venules; BCV, bifurcation coefficient of venule; BCA, bifurcation coefficient of arterioles; Vangle, bifurcation angles of venule; Aangle, bifurcation angles of arterioles; CRAE, central retinal artery equivalent; CRVE, central retinal vein equivalent. AVR, CRAE to CRVE ratio; FDv, the fractal dimension of the retinal vasculature; arterioles FDa, the fractal dimension of the retinal arterioles.

Figure 3

The retinal characteristics that differed significantly between the POI and control groups. POI represents women with premature ovarian insufficiency.

Note:

The p-value with a * represents nonparametric test of matched pair data (Wilcoxon Signed-Rank Test), others use paired t-test. **** represents $P \leq 0.000$, ** represents $P \leq 0.01$, * represents $P \leq 0.05$.

Figure 4

The area under the ROC curve for the binary logistic regression with retinal characteristics, and the fitting degree of regression models was 60.48% (Prob > chi-square = 0.6048).

Note: Area under ROC curve = 0.8582, Prob > chi2 = 0.6048

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Table1.pdf](#)
- [Table2.pdf](#)