

# Retinal vascular occlusion: a window to diagnosis of familial and acquired thrombophilia and hypofibrinolysis, with important ramifications for pregnancy outcomes

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**Aim:** Our specific aim was to document the pathoetiologic importance of thrombophilia among females presenting with severe ischemic retinal vein (RVO) or retinal artery (RAO) occlusion, without typical risk factors, and to emphasize that the ophthalmologists' diagnosis of thrombophilia has important diagnostic and therapeutic downstream ramifications for nonocular thrombosis, including reproductive outcomes.

**Methods:** We evaluated familial and acquired thrombophilia in 60 females with RVO (central RVO, n=52; branch RVO, n=8) and 16 with RAO (central RAO, n=11; branch RAO, n=5). They were referred by retinologists, without typical risk factors for RVO/RAO and/or severe ocular ischemic presentation. We focused on extraocular thrombotic events, particularly pregnancy complications, including unexplained spontaneous abortion, pre-eclampsia–eclampsia. Thrombophilia measurements in the 76 females were compared with 62 healthy normal females without ocular vascular occlusions (OVOs).

**Results:** The 76 females with OVO were more likely than 62 normal female controls to have high homocysteine (24% vs 0%,  $P<0.0001$ ), high anticardiolipin antibody (immunoglobulin M, 17% vs 3%,  $P=0.012$ ), high (>150%) factor VIII (42% vs 11%,  $P<0.0001$ ), and high (>150%) factor XI (22% vs 4%,  $P=0.004$ ). Of the 76 females, 26 (34%) had  $\geq 1$  spontaneous abortion; 17 (22%) had  $\geq 2$  spontaneous abortions and/or pre-eclampsia–eclampsia. Compared to 62 healthy female controls, these 17 females with pregnancy complications had high homocysteine (29% vs 0%,  $P=0.0003$ ), high anticardiolipin antibody immunoglobulin M (24% vs 3%,  $P=0.02$ ), high factor VIII (38% vs 11%,  $P=0.02$ ), and were marginally more likely to be heterozygous for the factor V Leiden mutation (19% vs 3%,  $P=0.058$ ).

**Conclusion:** In females lacking typical risk factors for retinal vascular occlusion or severely ischemic presentation, by diagnosing thrombophilia as an etiology for OVO, the ophthalmologist opens a window to family screening and preventive therapy, with particular relevance to pregnancy outcomes and venous thromboembolism.

**Keywords:** thrombophilia, retinal vascular occlusion, retinal vein occlusion, retinal artery occlusion

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## Introduction

Widely recognized, but neither sensitive nor specific risk factors for ocular vascular occlusion (OVO) include age, history of smoking, hypertension, hyperlipidemia, and diabetes mellitus.<sup>1–11</sup> Rare systemic risk factors for OVO include hyperviscosity, myeloproliferative disorders, retro-orbital mass effect, and vasculitis such as Behcet's.<sup>12,13</sup>

Open-angle glaucoma decreases venous outflow via increased intraocular pressure, thus creating vascular stasis and increased risk of OVO.<sup>2,14-16</sup> In the absence of a cardioembolic etiology for OVO, thrombophilia is a common, major cause of ocular thrombotic events.<sup>12,17-25</sup> In particular, thrombophilia should be carefully assessed in younger patients, <65 years old, or in patients with a personal or family history of thrombosis.<sup>25</sup>

Thrombophilia<sup>20</sup> can be heritable – such as hyperhomocysteinemia, factor V Leiden (FVL), prothrombin G20210A (PTG) mutation,<sup>18</sup> antithrombin III deficiency, protein C deficiency or protein S deficiency – or acquired, particularly the antiphospholipid syndrome-lupus anticoagulant.<sup>26</sup> Of the thrombophilias that are risk factors for OVO,<sup>4,8,9,13,17,24,27-37</sup> hyperhomocysteinemia is the most common disorder.<sup>8,13,17,24,33-37</sup> Homocysteine is also a risk factor for systemic vascular thrombosis, including ischemic heart disease and deep venous thrombosis.<sup>38,39</sup> In addition to hyperhomocysteinemia, FVL and PTG heterozygosity have been shown to be major risk factors for both OVO<sup>18</sup> and large vein thrombosis.<sup>33,40-43</sup>

Thrombophilia is only one of many causes of spontaneous abortion.<sup>44-47</sup> Familial and acquired thrombophilia are important risk factors for spontaneous pregnancy loss,<sup>48,49</sup> interacting with the physiologic thrombophilia of pregnancy<sup>50,51</sup> or the postpartum period<sup>52</sup> to promote thrombosis of the spiral arteries of the placenta, facilitating development of placental insufficiency, with resultant spontaneous abortion; pre-eclampsia, eclampsia; and hemolysis, elevated liver enzymes, and low platelet count syndrome.<sup>51</sup>

Our specific aim was to document the pathoetiologic importance of thrombophilia among females presenting with severe ischemic retinal vein (RVO) or retinal artery (RAO) occlusion, without typical risk factors, and to emphasize that the ophthalmologists' diagnosis of thrombophilia has important diagnostic and therapeutic downstream ramifications for nonocular thrombosis, including reproductive outcomes.

## Methods

The study was approved by the Jewish Hospital Institutional Review Board (ID 12-03), Cincinnati, OH, USA. Written informed consent was obtained from patients after the nature of the study was fully explained. The study was conducted in accordance with the principles of the Declaration of Helsinki.

In a consecutive case series of females referred to vitreoretinal specialists at the Cincinnati Eye Institute with severe ischemia<sup>18,53</sup> (OVO without typical risk factors), studies of thrombophilia were carried out in parallel with assessment

of other organ systems affected by thrombosis, with special focus on reproductive outcomes, known to be affected by thrombophilia.

The analysis cohort was divided into patients with RVO (low pressure, low velocity), including branch and central RVO (BRVO and CRVO), and those with RAO (high pressure and velocity), including central RAO (CRAO) and branch RAO. Patients were referred and evaluated by vitreoretinal specialists at the Cincinnati Eye Institute. The ocular diagnoses were established by complete ophthalmological evaluations during which the patients' histories, visual deficits, and fundus abnormalities were ascertained. Patients were referred to our outpatient thrombosis research center between January 1, 2014 and January 1, 2016, for thrombophilia/hypofibrinolysis evaluation based on lack of typical risk factors for OVO, or severely ischemic presentation. The 16 patients referred with RAO had normal carotid ultrasound and cardiac echocardiograms without any evidence for emboli causing RAO.

Patients with RVO showed dilation of retinal veins (all veins if a CRVO, and not all the veins if a BRVO) associated with intraretinal hemorrhages, retinal edema, and cotton wool spots limited in area by the drainage bed of the affected veins.<sup>18</sup> Patients with RAO demonstrated retinal arterial narrowing, segmentation of the arterial blood column in some cases, and whitening of the retina due to opacification and thickening of the inner retina.<sup>18</sup> In CRAO cases, a cherry-red spot was seen in the macula. Fluorescein angiography and optical coherence tomography were performed to corroborate the diagnosis depending on the preference of the referring ophthalmologist.

During the patients' initial visit to our center, a detailed history, obstetrical–gynecological history, and physical examination were completed. The number of pregnancies, live births, spontaneous abortions, and elective abortions were recorded. When there was a history of spontaneous abortion, information was systematically obtained on maternal age, gravidity, smoking, alcohol, and cocaine use, in addition to whether there had been prior investigations of risk factors<sup>54,55</sup> for spontaneous abortion. Information was gathered regarding any studies for chromosomal abnormalities,<sup>44</sup> uterine structural issues (including septate uterus),<sup>47</sup> maternal thyroid status, and maternal trauma. Maternal and family histories of previous thrombotic events were obtained. Serologic coagulation assays were done and polymerase chain reaction (PCR) analyses for thrombophilia and hypofibrinolysis were performed. Atherosclerotic risk factors were measured, including age, body mass index (BMI), smoking

history, blood pressure, hemoglobin A1c, glucose, homocysteine, and triglyceride and cholesterol levels, including high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol.<sup>17</sup>

PCR measures<sup>56</sup> were used to measure G1691A FVL, PTG, methylene tetrahydrofolate reductase C677T and A1298C mutations, and the plasminogen activator inhibitor-1 4G4G mutation. PCR measures for the thrombomodulin gene mutation were not obtained. In addition, serologic measures of thrombophilia<sup>20</sup> were done, including anticardiolipin antibodies (ACLA) IgG and IgM, antigenic protein C, total and free protein S, antithrombin III, lupus anticoagulant, factors VIII and XI, and homocysteine. All PCR and serologic measures were done as previously described.<sup>17,18</sup>

After signed informed consent was obtained, healthy normal female volunteers (n=62) served as controls. They were documented by interview and physical examination to be free of acute and chronic disease, including any history or evidence of OVO.

## Statistical methods

All statistical analyses were performed using SAS V9.4 (SAS institute Inc., Cary, NC, USA). Cases were compared to controls by Fisher's exact test. Sample size was estimated based on our recent studies of 265 patients, 191 with ocular vein occlusion, and 74 with ocular artery occlusion, with comparison to 110 normal controls,<sup>20</sup> where 50% of RVO patients had at least one of seven thrombophilias (FVL, prothrombin gene heterozygosity, low free protein S, high homocysteine, high factor VIII, factor XI, ACLA IgM high) vs 20% in controls. At least 39 subjects were required in each group to detect the difference at significance level  $\alpha = 0.05$  with power 80%.

## Results

As an entire cohort, the 76 females with RVO were more likely than the 62 normal female controls to have high homocysteine (24% vs 0%,  $P < 0.0001$ ), ACLA IgM (17% vs 3%,  $P = 0.012$ ), high factor VIII (>150%) (42% vs 11%,  $P < 0.0001$ ), and high factor XI (>150%) (22% vs 4%,  $P = 0.004$ ) (Figures 1 and 2).

Of the 76 females, 16 presented with RAO (eleven CRAO and five branch RAO), and 60 presented with RVO (52 CRVO and eight BRVO). Of the 76 women, 37 (49%) were  $\leq 60$  years of age and 48 (63%)  $\leq 65$  years of age. Homocysteine was high in 13% with RAO ( $P = 0.04$ ) and 27% with RVO ( $P < 0.0001$ ) compared to 0% in 62 healthy normal female controls (Figure 1). Factors VIII and XI were higher in 16 females with RAO (38% and 25%, respectively, [ $P = 0.019$ ,

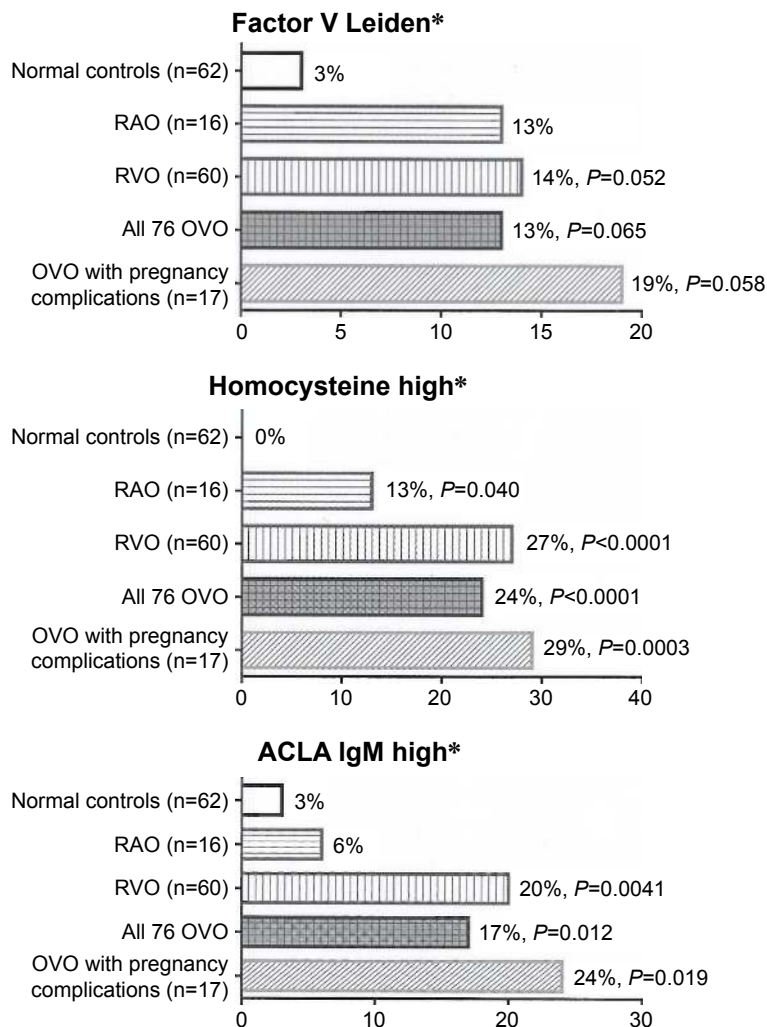
0.021]) and in 60 RVO females (44% and 21%, respectively, [ $P = < 0.0001$ , 0.0074]) than in normal female controls (11% and 4%, respectively) (Figure 2). The 16 females with RAO were more likely than normal female controls (27% vs 4%,  $P = 0.019$ ) to have low free protein S (<66%) (Figures 1 and 2). The 60 females with RVO were more likely to have high ACLA IgM than normal female controls (20% vs 3%,  $P = 0.0041$ ) (Figures 1 and 2).

Of the 76 females, 73 had a total of 244 pregnancies, 180 live births, and 57 spontaneous abortions. Five females (6.8%) had  $\geq 3$  consecutive pregnancy losses before 20 weeks (recurrent pregnancy loss<sup>57,58</sup>), ten (13.9%) experienced two consecutive pregnancy losses, and 26 (35.6%) had  $\geq 1$  pregnancy loss. None of the 57 spontaneous miscarriages in the 73 females could be attributed to alcohol or cocaine use, maternal infection or endocrine abnormalities, uterine structural abnormalities, poorly controlled maternal diabetes, maternal thyroid disorders, or maternal trauma. Cytogenetic studies of the postmiscarriage products of conception samples were done in only three cases, where eight, six, and four spontaneous unexplained abortions had occurred, without demonstration of cytogenetic abnormalities.<sup>54,55</sup>

Of the 76 females, 17 (23%) had  $\geq 2$  spontaneous abortions or eclampsia. Of these 17 females, ten had two spontaneous abortions, three had four, one had six, one had eight spontaneous abortions, and two had eclampsia. Compared to 62 normal female controls, these 17 females had high factor VIII (38% vs 11%,  $P = 0.02$ ), high homocysteine (29% vs 0%,  $P = 0.0003$ ), high ACLA IgM (24% vs 3%,  $P = 0.02$ ), and were marginally more likely to be heterozygous for the FVL mutation (19% vs 3%,  $P = 0.058$ ) (Figures 1 and 2).

## Discussion

Since thrombophilia plays a significant role in the development of OVO,<sup>18,20,24,59,60</sup> particularly in younger patients, and in patients without atherosclerosis but with insulin resistance syndrome risk factors, the ophthalmologist is often the first medical diagnostician to initiate steps to diagnose thrombophilia.<sup>8,12,20,21,24,30,53,61-69</sup> Although all 76 females in the current study were referred to retinologists because of OVO, subsequent thrombophilia studies revealed not only an enrichment of familial thrombophilia in an OVO cohort but also emphasized the potential diagnostic and therapeutic payoffs obtained when the retinologist looks for thrombophilia in otherwise unexplained OVO. In the current study, congruent with our recent evaluation of 191 patients with RVO and 74 with RAO,<sup>20</sup> the group of 76 females (16 with RAO, 60 with RVO) differed from 62 healthy female controls by having



**Figure 1** Factor V Leiden heterozygosity, high homocysteine,<sup>a</sup> and high ACLA IgM<sup>b</sup> in 16 patients with RAO (five branch, eleven central), 60 with RVO (eight branch, 52 central), all 76 patients with OVO, and 17 of the OVO patients with  $\geq 2$  spontaneous abortions or eclampsia, compared with 62 healthy normal females.

**Notes:** <sup>a</sup>Dated cut point for homocysteine high:  $\geq 15$  (November 15, 2008 to December 2, 2014);  $\geq 10.4$  (after December 3, 2014). <sup>b</sup>Dated cut point for IgM high:  $\geq 10$  MPL (before April 30, 2012);  $\geq 13$  (after May 1, 2012). \*P-values are comparisons to controls.

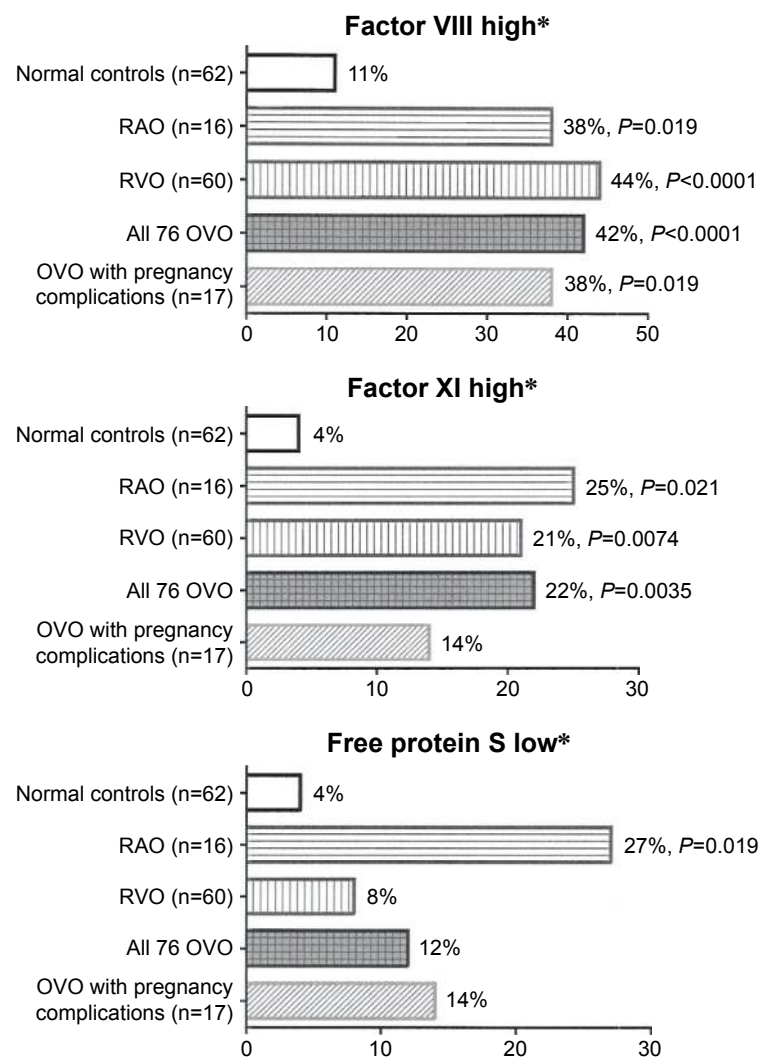
**Abbreviations:** ACLA, anticardiolipin antibody; IgM, immunoglobulin M; MPL, IgM phospholipid units; OVO, ocular vascular occlusion; RAO, retinal artery occlusion; RVO, retinal vein occlusion.

high homocysteine, high ACLA IgM, and high factors VIII and XI. RAO and RVO patients both were more likely than healthy normal controls to have high homocysteine, high factor VIII and XI.

Thrombophilia has been reported to play an important pathoetiologic role in RAO and RVO,<sup>18</sup> as previously documented in this article, which is congruent with findings in our's<sup>18,21,53</sup> and other's<sup>70-74</sup> studies. Thrombophilia is a known pathoetiology for adverse obstetrical outcomes, including, as in the current study, miscarriage,<sup>75-80</sup> recurrent miscarriage,<sup>48,49,57,81</sup> pre-eclampsia,<sup>82,83</sup> and eclampsia.<sup>84,85</sup> Unique to this article is our emphasis on the often central diagnostic role of the ophthalmologist, who, by revealing the pathologic importance of thrombophilia in OVO, opens the gates to primary and secondary prevention and therapy of

thrombosis in other vascular beds, including the uterus and placenta, as in this report.

A growing body of evidence highlights thrombophilia as an important cause for spontaneous miscarriage.<sup>48,49,75-80,86</sup> Thrombophilia should be assessed in all females with recurrent fetal death,<sup>87</sup> but thrombophilia is only one of multiple causes<sup>54,55</sup> for spontaneous abortion, including fetal cytogenetic abnormalities,<sup>44</sup> congenital abnormalities, illicit drug use, teratogens, maternal trauma, infection, uterine structural issues,<sup>45-47</sup> maternal disease, including infection and endocrinopathies. In our cohort, where 73 females had one or more pregnancies with 57 spontaneous abortions, excepting a thrombophilic etiology in 12% to 42% of females, the varied other causes of spontaneous abortion<sup>44,54,55</sup> were not identified.



**Figure 2** High factors VIII,<sup>a</sup> XI,<sup>b</sup> and low free protein S<sup>c</sup> in 16 patients with RAO (five branch, eleven central), 60 with RVO (eight branch, 52 central), all 76 patients with OVO, and 17 of the OVO patients with  $\geq 2$  spontaneous abortions or eclampsia, compared with 62 healthy normal females.

**Notes:** <sup>a</sup>Cut point for high factor VIII (>150%), <sup>b</sup>cut point for high factor XI (>150%), <sup>c</sup>cut point for low free protein S (<66%). \*P-values are comparisons to controls.

**Abbreviations:** OVO, ocular vascular occlusion; RAO, retinal artery occlusion; RVO, retinal vein occlusion.

In our cohort, referred solely by OVO, pregnancy loss was much greater than in the general population,<sup>57</sup> recurrent pregnancy loss (three or more spontaneous unexplained abortions before 20 weeks' gestation) occurred in 6.8% vs 0.4% to 1% in general populations, two consecutive losses in 12.3% vs 2% in general population, and 35.6% had  $\geq 1$  spontaneous pregnancy losses vs 15% in general population.

Normal pregnancy is characterized by an increase in thrombophilia,<sup>88</sup> where a physiologic hyperestrogenic hypercoagulable state appears to be a physiological adaptive mechanism<sup>51</sup> to prevent postpartum hemorrhage.<sup>50</sup> Thrombophilia,<sup>89-94</sup> producing placental insufficiency via thrombosis of the placental spiral arteries, causes spontaneous abortion; pre-eclampsia; eclampsia; and hemolysis, elevated liver enzymes, and low platelet count syndrome.<sup>95-100</sup>

Within this frame of reference, our current study revealed the 17 females, originally evaluated for RVOs and with two or more unexplained spontaneous pregnancy losses or eclampsia, as a group had high homocysteine, high factor VIII, high ACLA IgM, and increased FVL rates compared with normal female controls. We speculate that thrombophilia associated with RAO and RVO, amplified by the thrombophilia of pregnancy, contributes to placental insufficiency and spontaneous abortion. This finding is congruent with our recent report<sup>18</sup> that, of 17 females with FVL or PTG mutations, seven (41%) experienced at least one unexplained spontaneous abortion.

Although prospective with regard to the study of the etiology of OVO, our study is limited by being retrospective with regard to assessment of adverse pregnancy outcomes

(spontaneous abortion, eclampsia). A second limitation of the study involves the expensive nature of laboratory assessment of thrombophilia, which often is not fully covered by private health insurance or Medicare or Medicaid.

## Conclusion

In females lacking typical risk factors for RVO or severe ischemic presentation, by diagnosing thrombophilia as an etiology for OVO, the ophthalmologist opens a window to family screening and preventive therapy, with particular relevance to pregnancy outcomes and venous thromboembolism. The diagnosis of an underlying thrombophilia is important not only for the management of OVO but also for the success of the pregnancy, allowing timely thromboprophylaxis<sup>101–103</sup> to prevent maternal thrombosis and pregnancy loss.

## Disclosure

The authors report no conflicts of interest in this work.

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