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SHORT COMMUNICATION

Protein S deficiency and retinal arteriolar occlusion in pregnancy

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PURPOSE. *To report two cases of retinal arteriolar occlusion in pregnant women with transient protein S (PS) deficiency.*
METHODS. *Observational case reports.*
RESULTS. *Two pregnant women in their 30s presented with a paracentral scotoma in their right and left eye, respectively. In both cases the only risk factor for vascular occlusion was pregnancy. Systemic diseases were excluded. Free and functional PS activity was physiologically reduced in both patients. In Case 1, free PS was 47% and functional PS was 22%. In Case 2, free PS was 43% and functional PS was 25%. These levels of PS seem to be lower than those published for normal pregnancy.*
CONCLUSIONS. *There might be a special relationship between PS deficiency and the development of arterial occlusion in pregnant women. A direct effect may be possible. Although the prevalence and incidence of vasoocclusive disease in these patients are low, PS deficiency should be considered as another risk factor. Further studies are necessary to evaluate changes in PS and to assess its relationship with thromboembolic events during pregnancy. (Eur J Ophthalmol 2007; 17: 1004-6)*

KEY WORDS. *Protein S deficiency, Retinal arteriolar occlusion, Pregnancy*

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INTRODUCTION

Pregnancy is associated with a hypercoagulable state and quantitative changes in platelets and clotting factors occur.
Protein S (PS) is a vitamin K-dependent plasma protein that modulates coagulation. It serves as a cofactor with protein C to inhibit the clotting cascade at the levels of factors V and VIII. PS deficiency may be hereditary or acquired; the latter is usually due to hepatic diseases or a vitamin K deficiency. It is known that during pregnancy a transient decrease in levels of PS exists.
We describe two pregnant patients with transient PS deficiency who developed a retinal arteriole obstruction.

Case 1

A 30-year-old pregnant woman was referred at 27 weeks gestation with a sudden paracentral scotoma in her right eye. Funduscopic examination of the right eye revealed a single cotton-wool spot in the papillomacular bundle locating the arteriolar occlusion in the optic disc (Fig. 1). The retinal opacity resolved within 3 months but her paracentral scotoma remained unchanged. Nerve fiber layer field defects persisted.
Free PS activity was reduced (47%). Functional (22%) PS was also decreased. PS raised to normal levels 6 months after childbirth (free PS: 99%, functional PS: 80%).

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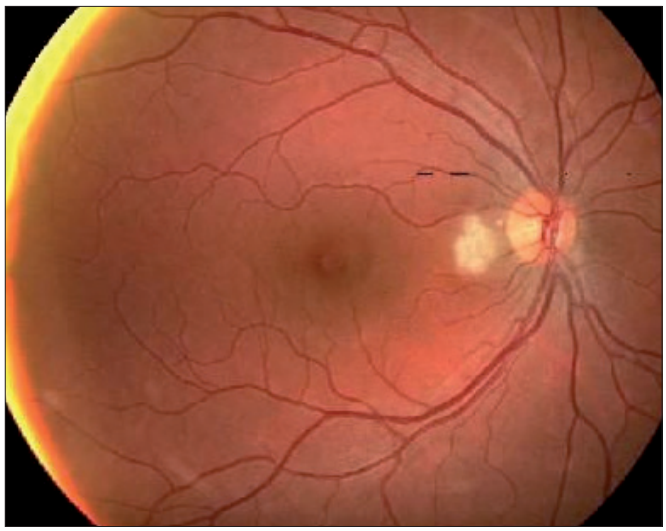

Fig. 1 - *Case 1. Fundus photograph shows a single cotton-wool spot in the papillomacular bundle that measured 2/3 of the optic disc.*

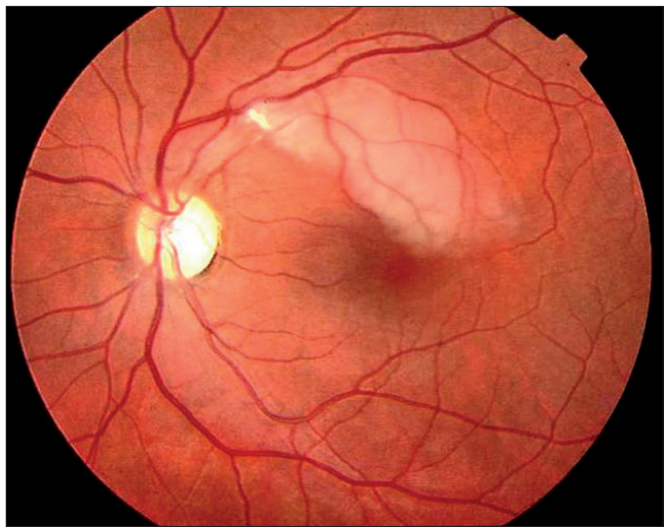

Fig. 2 - *Case 2. A large geographic area of retinal opacity and macular edema in the left fundus superiorly to the macula is present.*

Case 2

A 31-year-old woman in the 11th week of pregnancy with an inferior scotoma in her left eye was referred to us. On presentation, best-corrected visual acuity was 20/20 in the right eye and 20/30 in the left eye. Slit-lamp examination was normal in both eyes, but a branch arteriolar obstruction associated with a large whitening area of retinal opacity and macular edema was visible in her left fundus, superiorly to the macula (Fig. 2).

Macular edema and soft exudates resolved within 6 months and her left visual acuity improved to 20/25. A superior scotoma persisted.

Free (43%) and functional (25%) PS activity were low on presentation. A new laboratory workup was done 6 months after delivery to confirm physiologic PS levels (free PS: 96%, functional PS: 83%).

RESULTS

Free PS antigen was measured by enzyme-linked immunosorbent assay and functional PS by a clot-based test.

Results of laboratory workup showed a complete blood count, prothrombin time, partial thromboplastin time, lipid profile, antithrombin III, protein C, factor V Leiden, plasminogen level, antinuclear antibody, rheumatoid factor, anticardiolipin antibody, and a Von Willebrand factor antigen level within normal limits in both patients. Blood pressure and carotid echo color Doppler and echocardiography tests were normal.

DISCUSSION

Retinal artery obstruction in children and young adults is relatively rare (1). In this period, vasoocclusive disease is present during pregnancy. Cases of retinal arterial occlusions in the absence of additional risk factors have been reported. The majority of cases occurred within 24 hours after childbirth (2).

Embolic events are rare during the first and second trimester of gestation, as occurred in our two patients, and may be related to abnormal levels of clotting and clot-inhibiting factors. The level of plasminogen activator inhibitor increases threefold during pregnancy. Also, there is an increase in levels of fibrinogen. Only two similar cases of branch retinal artery occlusion associated with hypercoagulability from PS deficiency have been reported (3, 4). However, they were related to congenital deficiency of protein and occurred after delivery. A direct effect of PS deficiency in development of arterial occlusion may be possible since both endothelial cells and platelets are

sites of PS synthesis and action in vivo.

Pregnancy is associated with a decrease in PS. Sixty percent of PS circulates in a protein bound form and the remaining 40% free form is biologically active. Pregnancy leads to increased levels of the complement 4b-binding protein, which binds to PS, and thereby decreases PS activity.

Level of PS is reduced to 40 to 50% of normal levels (free PS: 50 to 130%; functional PS: 60 to 110%) but it varies from study to study (5) and depends on the method used to measure PS. Lockwood suggested that PS deficiency may only be able to be diagnosed during pregnancy when a value is obtained that is <35% of the expected level (6). Referral range values of free and functional PS have not been established, and levels of PS change from the first to the third trimester.

Levels of free and functional PS in our patients seem to be lower than those published for normal pregnancy, or at least, in the lower range limit. This could increase the risk of developing thromboembolism. Therefore the degree of PS decrease would be important. This relationship is difficult to prove since pregnancy is very common and retinal vascular occlusions are rare complications of this condition, especially out of delivery period.

We believe that PS deficiency could play a role in these patients and could be considered in young patients with unexplained retinal vascular occlusions, particularly when occurring during pregnancy. Further studies are necessary to establish levels of PS in normal pregnancy and evaluate the relationship between low levels of PS and retinal vascular occlusion.

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