Oral contraceptive pills: A risk factor for retinal vascular occlusion in *in-vitro* fertilization patients

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ABSTRACT

Retinal vascular occlusion is the most common cause of retinopathy leading to severe visual loss in all age groups. Central retinal vein occlusion (CRVO) is usually seen in older age group and is often associated with systemic vascular diseases. Although the exact cause and effect relationship has not been proven, central retinal vein occlusion has been associated with various systemic pathological conditions, hence a direct review of systems toward the various systemic and local factors predisposing the central retinal vein occlusion is advocated. We describe the development of central retinal venous occlusion with associated cystoid macular edema (CME) in two healthy infertile women who were recruited for *in vitro* fertilization cycle for infertility. Predisposing risk factors associated with central retinal vein occlusion are obesity, sedentary life style, smoking, and some systemic diseases such as hyperlipidemia, hypertension, associated autoimmune disorders e.g., antiphospholipid antibody syndrome, lupus, diabetes mellitus, cardiovascular disorders, bleeding or clotting disorders, vasculitis, closed-head trauma, alcohol consumption, primary open-angle glaucoma or angle-closure glaucoma.In our patients, they were ruled out afterdoing allpertaining investigations. The cases were managed with further avoidance of oral contraceptives and intra-vitreal injections of Bevacizumab (Avastin), an anti-vascular endothelial growth factor (anti-VEGF drug) and Triamcinolone acetonide (a long acting synthetic steroid). Hence, even if no systemic diseases are detected. Physical examinations are recommended periodically for young women on oral contraceptive pills.

KEY WORDS: *In vitro* fertilization, retinal vascular occlusion, oral contraceptive pills

INTRODUCTION

An ophthalmologist may see many cases of vascular occlusions and majority of the cases are due to the thromboembolic phenomena. Apart from hypertension, diabetes, advancing age, and hyper-lipidemia or genetic predisposition, the next most common predisposing factor, amongst the systemic factors, is the use of oral contraceptive pills.[1-10] Other risk factors associated with central retinal vein occlusion are obesity, sedentary life style, smoking, dehydration, cardiovascular disorders, bleeding or clotting disorders, vasculitis, closed-head trauma, alcohol consumption, primary open-angle glaucoma or angle-closure glaucoma and autoimmune disorders e.g., antiphospholipid antibody syndrome, lupus, sarcoidosis, dysproteinemia. Majority of gynecologists advocate the use of oral contraceptive pills (OCP) for contraception in females of reproductive age group, but nowadays, there is extended use of these drugs in regulating the menstrual cycles for the patients undergoing *in vitro* fertilization (IVF), resulting ina rise in the usage of these drugs. Therefore, its role in causing various problems like retinal vascular occlusions is of concern. Here we present a two such cases that were given OCP undergoing IVF cycles in a tertiary center of western India. In these patients, after ruling out any family history of thromboembolic disorders, laboratory testing was directed towards identifying various systemic vascular problems.The basic workup included complete blood cell count (CBC), glucose tolerance test, lipid profile, coagulation profile, activated partial thromboplastin time (aPTT), Venereal Disease Research Laboratory (VDRL),

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thrombophilia screening, testing for lupus anticoagulant and anticardiolipin antibodies.

CASE REPORTS

In a tertiary center in western India, 987 patients underwent IVF cycles in two years (from December 2009 to December 2011). As a routine, these patients were recruited in the long protocol for IVF and started with third generation monophasic combined OCP containing Ethinylestradiol 0.03 mg and Desogestrel 0.15 mg on Day 2 of menstrual cycle, till midluteal phase (Day 21) along with Folic acid. From Day 21 of menstrual cycle, they were started on gonadotropic releasing hormone (GnRH) analogue inj. Luprolide acetate 0.5 mg subcutaneously daily for initial down regulation of ovaries. Out of these 987 cases, two cases had developed central retinal vein occlusion (CRVO).

Case 1

A 31-year-old female having primary infertility was recruited for *in vitro* fertilization-intracytoplasmic sperm injection cycle (IVF-ICSI). The cause for infertility was male factor. She was given oral contraceptive pills for persistent functional ovarian cyst of 3.5 cm × 3.5 cm which persisted for two menstrual cycles prior to starting her IVF cycle. After few weeks of treatment, she started complaining of painless blurring of vision in right eye associated with metamorphopsia without redness, discharge, or colored halos. On examination, her visual acuity in left eye was found to be 6/6 without glasses but in right eye it was 6/18 with correction and was not improving with pinhole. All the anterior segment findings were found to be within normal limits in both eyes. On fundus examination, left eye was found to be within normal limits, but right eye showed dilated tortuous central vein with multiple dots and blot hemorrhages all over the fundus, along with macular edema which was confirmed on optical coherence tomogram [Figure 1]. In both the eyes, intraocular pressure was found to be within normal limits. The systemic investigations undertaken were within normal limits. Since all the work up done was within normal limits, it was diagnosed to be a case of CRVO in right eye secondary to the OCP. The patient was given intra-vitreal injection of Bevacizumab (Avastin) and was meticulously followed up for 6 months. After 6 months, her vision in right eye improved to 6/6 partial and the macular edema regressed as seen on optical coherence tomogram, but the patient is still complaining of metamorphopsia till her last follow up.

Case 2

A female patient aged 38 years who was a case of primary infertility was recruited for her fourth consecutive IVF cycle. She was started on monophasic OCP on Day 2 of her periods. Tubal factor was the cause of infertility. Her three consecutive cycles of IVF had failed earlier prior to initiation of this fourth IVF cycle. At that time also, she was given monophasic OCP for down regulation of ovaries as well as to make the ovaries silent after the failure of cycle. After a few months of treatment, she complained of painless diminution of vision in right eye, which was not associated with any other complaint. On examination, her best corrected visual acuity was found to be 6/12 partial in right eye and 6/6 in left eye. The anterior segment findings were within normal limits. On fundus examination, the upper temporal vein was found to be dilated and congested, with cotton wool spots and dot and blot hemorrhages along the upper temporal branch of retinal vein. Associated macular edema was confirmed on optical coherence tomogram [Figure 2]. All the systemic and local causes investigated were within normal limits. It was diagnosed to be secondary to OCP. Patient was given an intra-vitreal injection of triamcinolone acetonide a steroid compound. The edema and hemorrhages resolved within 3 months and the visual acuity improved to 6/6 after 3 months.

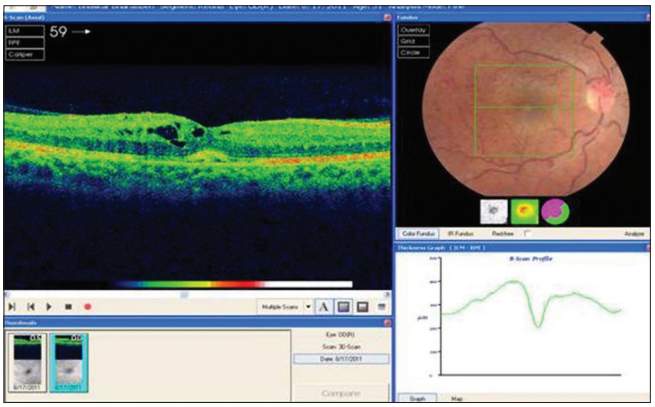

Figure 1: Fundus photograph of right eye showing central retinal vein occlusion and optical coherence tomography showing macular edema

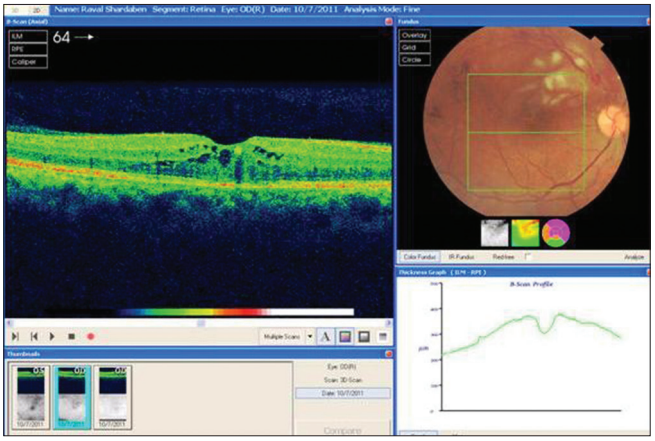

Figure 2: Fundus photograph showing right eye having upper temporal branch retinal vein occlusion with optical coherence tomography showing macular edema

DISCUSSION

Central retinal vein occlusion is a common sight-threatening retinal vascular disease. The exact pathogenesis of the thrombotic occlusion of the central retinal vein is not known. Various local and systemic factors play a role in the pathological closure of the central retinal vein.[11] Thrombotic occlusion of the central retinal vein can occur as a result of various pathologic insults, including compression of the vein (mechanical pressure due to structural changes in lamina cribrosa, e.g., glaucomatous cupping, inflammatory swelling in optic nerve, orbital disorders), hemodynamic disturbances (associated with hyperdynamic or sluggish circulation), vessel wall changes (e.g., vasculitis), and changes in the blood (e.g., deficiency of thrombolytic factors, increase in clotting factors).

Occlusion of the central retinal vein leads to the backup of the blood in the retinal venous system and increased resistance to venous blood flow. This increased resistance causes stagnation of the blood and ischemic damage to the retina. It has been postulated that ischemic damage to the retina stimulates increased production of vascular endothelial growth factor (VEGF) in the vitreous cavity. Increased levels of VEGF stimulate neovascularization of the posterior and anterior segment (responsible for secondary complications due to central retinal vein occlusion). Also, it has been shown that VEGF causes capillary leakage leading to macular edema (which is the leading cause of visual loss in both ischemic central retinal vein occlusion and non-ischemic central retinal vein occlusion).

The OCP are used for down regulation of IVF cycles, treatment of functional ovarian cysts, and regularization of periods in polycystic ovarian syndrome, dysfunctional uterine bleeding, and puberty menorrhagia and to schedule/postpone menstrual cycle. Besides their main effect on cardiovascular system that can lead to increased mortality,[2] oral contraceptives have been previously implicated in central retinal vein occlusion.[12] The mechanisms for retinal vascular occlusion development, symptomatology, clinical features, and treatment modalities remain the same as with other predisposing factors for central retinal vein occlusion.

In a cohort study by Vessev *et al*.,[13] the only eye disease for which there was consistent evidence of a notable increase in risk in oral contraceptives users was a retinal vascular problem. Similarly, the prevalence of retinal vein occlusion in female patients less than 35 years taking the OCP was 66.0% in a large series by Kirwan *et al*.[14] In apopulation based study by Scoditti *et al*.,[15] reported that the use of low estrogen oral contraceptives was associated with an increased risk of cerebral venous thrombosis and ischemic stroke, but not of retinal vein/artery thrombosis.

CONCLUSION

Because of the rise in infertile population and advances in treatment modalities like IVF, there is rise in usage of the OCP, hence, the risk for retinal vascular catastrophes is also rising. So the treating doctor should be aware and more conscious of this situation and should refer the cases for screening at the earliest.

REFERENCES

1. Thapa R, Paudyal G. Central retinal vein occlusion in young women: Rare cases with oral contraceptive pills as a risk factor. Nepal Med Coll J 2009;11:209-11.
2. Klein R, Klein BE, Moss SE, Meuer SM. The epidemiology of retinal vein occlusion: The Beaver Dam Eye Study. American Academy of Ophthalmology. Retina and vitreous: Basic and clinical science course, Sec. 12. Singapore: 2007-2008:136-45.
3. Klein R, Klein BE, Moss SE, Meuer SM. The epidemiology of retinal vein occlusion: The beaver dam eye study. Trans Am Ophthalmol Soc 2000;98:133-41.
4. Cugati S, Wang JJ, Rochtchina E, Mitchell P. Ten year incidence of retinal vein occlusion in an older population: The blue mountainseye study. Arch Ophthalmol 2006;124:726-32.
5. Lim LL, Cheung N, Wang JJ, Islam FM, Mitchell P, Saw SM, *et al*. Prevalence and risk factors of retinal vein occlusion in an Asian population. Br J Ophthalmol 2008;92:1316-9.
6. Shrestha RK, Shrestha JK, Koirala S, Shah DN. Association of systemic diseases with retinal vein occlusive disease. JNMA J Nepal Med Assoc 2006;45:244-8.
7. Klein R, Moss SE, Meuer SM, Klein BE. The 15 year cumulative incidence of retinal vein occlusion: The beaver dam eye study. Arch Ophthalmol 2008;126:513-8.
8. O'Mahoney PR, Wong DT, Ray JG. Retinal vein occlusion and traditional risk factors for atherosclerosis. Arch Ophthalmol 2008;126:692-9.
9. Hayreh SS, Zimmerman B, McCarthy MJ, Podhajsky P. Systemic diseases associated with various types of retinal vein occlusion. Am J Ophthalmol 2001;131:61-77.
10. Teoh SL, Amarjeet K. A comparative study of branch retinal vein occlusion and central retinal vein occlusion amongst Malaysian patients. Med J Malaysia 1993;48:410-5.
11. Hayreh SS. Retinal vein occlusion. Indian J Ophthalmol 1994;42:109-32.
12. Beral V, Hermon C, Kay C, Hannaford P, Darby S, Reeves G. Mortality associated with oral contraceptive use: 25 year follow up of cohort of 46, 000 women from Royal College of General Practitioners' oral contraception study. BMJ 1999;318:96-100.
13. Vessev MP, Hannaford P, Mant J, Painter R, Frith P, Chappel D. Oral contraception and eye disease: Findings in two large cohort studies. Br J Ophthalmol 1998;82:538-42.
14. Kirwan JF, Tsaloumas MD, Vinall H, Prior P, Kritzinger EE, Dodson PM. Sex hormone preparations and retinal vein occlusion. Eye (Lond) 1997;11:53-6.
15. Scoditti U, Buccino GP, Pini M, Pattacini C, Mancia D. Risk of acute cerebrovascular events related to low oestrogen oral contraceptive treatment. Ital J NeurolSci 1998;19:15-9.

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