Association between Clomiphene Citrate and Visual Disturbances with Special Emphasis on Central Retinal Vein Occlusion: A Review

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Introduction

Retinal vein occlusions are the second most common type of retinal vascular disorder after diabetic retinal disease [1], with an incidence of approximately 2 per 1,000 in the >40 years age group and 5.4 cases per 1,000 in the >64 years age group with equal gender distribution [2].

Retinal vein occlusion is due to thrombosis of retinal veins (central, hemi or branch) and has been associated with cardiovascular risk factors [2]. However, the pathogenesis and management of this disorder remains somewhat of an enigma [3]. It is a complication not commonly seen by the gynecologists, but they should be aware of the condition in fertility patients undergoing ovulation induction with clomiphene citrate (CC). Other CC adverse effects are [4–6]: ovarian enlargement, vasomotor flashes, nausea, vomiting, breast discomfort, headache, abnormal vaginal bleeding, visual symptoms, weight gain, shortness of breath; long term use may increase the risk of ovarian cancer and multiple pregnancy [7]. Other less common side effects have been described: acute pancreatitis without hypertriglyceridemia [8], myocardial infarction [9], hypertriglyceridemia [10], deep vein thrombosis [11], pulmonary embolism [12].

The purpose of this article is to firstly review the relationship between CC and central retinal vein occlusion (CRVO) in infertility patients, and secondly other related visual disturbances.
Central Retinal Vein Occlusion

CRVO is a common retinal vascular disorder. Clinically it presents with painless, but variable visual loss. The exact pathogenesis is uncertain. Various local and systemic factors play a role in the pathological closure of the central retinal vein such as [2]: hypertension, hyperlipidemia, diabetes mellitus, glaucoma, thrombophilia and myeloproliferative disorders. Other rare associations with CRVO include: chronic renal failure, oral contraceptives, inflammatory diseases that are associated with retinal vasculitis, such as Behçet’s disease, polyarteritis nodosa, sarcoidosis, Wegener’s granulomatosis and Good-pasture syndrome. Some other nonspecific associations like closed head trauma, optic disc drusen and arteriovenous malformations of the retina have been described.

Hypertension is the predominant risk factor with up to 64% of patients suffering from hypertension in the older age group (more than 50 years), while thrombophilia assume greater importance in the younger patients (<50 years). The two aims in the management of CRVO are the identification of modifiable risks factors and their medical management and the recognition and management of sight-threatening complications to prevent further non-ocular target organ damage, as well as to prevent recurrence of venous occlusion particularly in the fellow eye [2]. There is no proven risk of increased long-term mortality in patients with CRVO in contrast to patients with retinal artery occlusion. However, there is a 7% risk of developing CRVO in the fellow eye within 2 years [13].

Ovulation Induction and Selective Estrogen Receptor Modulators

Infertility due to anovulation is one of the most common causes for reproductive difficulty in otherwise fertile couples. Once successful ovulation is achieved, fertility is often restored. Anovulation and oligo-ovulation are estimated to cause 21% of female infertility [14, 15].

The group of interest in this review is the eugonadotropic, hypothalamic pituitary dysfunction group (group 2) and consists predominantly of women with polycystic ovary syndrome but may also include hyperprolactinemia and women with unexplained infertility [15].

Selective estrogen receptor modulators (SERMs) are structurally diverse nonsteroidal compounds that bind to estrogen receptors and show tissue-dependent agonistic and antagonistic effects. For many years, the first line of pharmacologic ovulation induction has involved the use of SERMs, of which CC has been most extensively studied. CC is characterized by agonistic properties when endogenous estrogen levels are low, and acts as a competitive antagonist when levels are high. Depletion of estrogen receptors in the hypothalamus results in normalization of gonadotropin-releasing hormone secretion, and hence secretion of pituitary follicle stimulating hormone levels are optimized and follicular development will occur, followed by ovulation [14].

Tamoxifen (TMX), another SERM, is the standard hormonal therapy treatment for premenopausal women diagnosed with hormone receptor-positive breast cancer. A prospective controlled trial compared the efficacy of TMX with CC in anovulatory women, and the overall rates of ovulation and pregnancy were similar in both groups [16]. Other studies have suggested that TMX may be superior to CC because it does not appear to produce an adverse impact on the endometrium [14, 17]. A recent systematic review shows evidence supporting the effectiveness of the current first-line treatment CC. There was no evidence of a difference in effect between CC and TMX [4, 7, 15].

Methods

In this review, articles were located by means of a computerized PubMed search using the key words clomiphene citrate, retinal vein occlusion, thrombus, visual disturbances, adverse effects, visual problems, SERMs. Limitations were English, human and 1976 to November 2009. Other databases searched were: Medline Plus 2009, Google and Google Scholar from 1996 to November 2009, and Cochrane Library from 1996 to November 2009 following the same criteria.

The searches were carried out by two authors (M.I.V and T.K.) independently, and the results compared. References of all relevant articles were hand-searched for additional citations. Only 35 relevant titles were identified, 25 full text and 10 abstracts read by authors.

No review describing adverse effects of CC in infertility patients has been published in the literature. Only four articles described visual problems with CC in fertility patients and were published as case reports. The only two systematic reviews found published adverse effects with clomid in anovulatory patients as a secondary outcome of the study, and no visual changes were described.

Results

The incidence of visual adverse events with the use of CC in clinical studies was reported as 1.5%. These include blurred vision, photophobia, diplopia, scotomata, phosphenes [6] and periphlebitis [18].

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An acute form of toxicity with TMX has been described. Symptoms include an acute loss of vision, retinal edema, retinal hemorrhage and optic disc swelling. These findings may be due to TMX’s estrogenic activity, which may cause venous thromboembolism, but are reversible on discontinuation of the drug [19–21]. Due to the similar estrogen receptor action of CC, professionals should be aware of this danger.

Brief episodes of shimmering after images (palinopsias) especially of moving targets and photophobia have been described as clinical findings in 3 women aged 32–36 years treated for infertility with CC for 4–15 months. Despite cessation of treatment, these women remained symptomatic 2, 3 and 7 years later [22].

Single case reports of CRVOs in patients using CC are available. A 36-year-old woman, after eight courses of CC, experienced amaurosis fugax with central scotoma, which subsided spontaneously, but 2 weeks later after completing the last course of CC she had persistent loss of vision and the diagnosis of CRVO was confirmed [23].

Another case of CRVO was reported due to CC in a 35-year-old man treated for infertility. The patient was heterozygous for the factor V Leiden mutation and the MTHFR polymorphism, but probably the event was precipitated due to the presence of CC [24].

In our clinic, we also experienced CRVO in a 38-year-old woman who was a known hypertensive and dyslipidemic on treatment for the conditions. She experienced black spots and flashes initially followed by moderate loss of acuity. CRVO was confirmed ophthalmologically (table 1) [25].

A recent observational study was performed to evaluate visual disturbances experienced during CC therapy, and a reversible change in foveal flicker sensitivity was the only statistically significant finding, suggesting that the visual disturbances are more likely due to a transient effect of CC on the visual cortex than to a toxic effect on the retina. Unfortunately, only 8 patients were tested, limiting the power of the study [26].

**Conclusion**

CRVO is a common retinal vascular disorder and has been associated with various systemic and pathological conditions. The first endocrine event in response to a course of clomiphene therapy is an increase in the release of pituitary gonadotropins followed by an increase in thrombogenic estradiol. Therefore CC may predispose to CRVO, especially in patients with underlying conditions.

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**Table 1. Case reports**

<table>
<thead>
<tr>
<th>First author, year</th>
<th>Age/sex/indication</th>
<th>CC dose, mg/days</th>
<th>Duration, months</th>
<th>Visual effects</th>
<th>Symptom persistence</th>
<th>Medical history</th>
</tr>
</thead>
<tbody>
<tr>
<td>Purvin, 1995</td>
<td>32 female infertility</td>
<td>50/5 5</td>
<td>5</td>
<td>shimmering, afterimages, sensitivity to light</td>
<td>2.5 years</td>
<td>unremarkable</td>
</tr>
<tr>
<td>Purvin, 1995</td>
<td>32 female infertility</td>
<td>100/5 5</td>
<td>5</td>
<td>vibrating and shimmering, flickering, afterimages, sensitivity to light</td>
<td>4 years</td>
<td>unremarkable</td>
</tr>
<tr>
<td>Purvin, 1995</td>
<td>36 female infertility</td>
<td>50/5 1</td>
<td>1</td>
<td>blurred vision, flickering, sensitivity to light, symptoms increase</td>
<td>7 years</td>
<td>unremarkable</td>
</tr>
<tr>
<td>Purvin, 1995</td>
<td>36 female infertility</td>
<td>100/5 5</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>100/5 &gt;4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lee, 2008</td>
<td>36 female infertility</td>
<td>50/5 8</td>
<td>CRVO</td>
<td>marked regression after 5 months</td>
<td>unremarkable</td>
<td></td>
</tr>
<tr>
<td>Politou, 2009</td>
<td>35 male infertility</td>
<td>50/1 8</td>
<td>CRVO</td>
<td>7 months later angiography was normal</td>
<td>unremarkable, factor V Leiden detected later</td>
<td></td>
</tr>
<tr>
<td>Viola, 2008</td>
<td>38 female infertility</td>
<td>100/5 1</td>
<td>CRVO</td>
<td>minimally improved</td>
<td>hypertensive, dyslipidemic</td>
<td></td>
</tr>
</tbody>
</table>

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risk factors. This needs to be confirmed by further investigation.

Candidates for CC therapy should be carefully selected and supervised by physicians experienced in management of gynecological or endocrine disorders [18]. Patients should be instructed to inform the physician about any unusual visual symptoms such as blurring, spots or flashes. These visual symptoms are total drug dose and duration of exposure dependent and generally disappear within a few days or weeks after CC is discontinued [6].

Physicians should be aware of the potential risk of CC and if visual disturbances occur, therapy should be terminated and the patient referred for specialist ophthalmic care.

References