International Journal of Ophthalmology & Visual Science
2020; 5(4): 101-105
http://www.sciencepublishinggroup.com/j/ijovs
doi: 10.11648/j.ijovs.20200504.13
ISSN: 2637-384X (Print); ISSN: 2637-3858 (Online)

Case Report

Papillophlebitis with Uveitis in MPO ANCA Associated Pregnancy

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To cite this article:

Deepesh Arora, Kanika Gupta, Surabhi Verma, Dinesh Sharma. Papillophlebitis with Uveitis in MPO ANCA Associated Pregnancy. *International Journal of Ophthalmology & Visual Science*. Vol. 5, No. 4, 2020, pp. 101-105. doi: 10.11648/j.ijovs.20200504.13

Received: November 22, 2020; **Accepted**: December 14, 2020; **Published**: December 22, 2020

Abstract: *Purpose:* We aim to describe first case of papillophlebitis with uveitis and vasculitis in perinuclear-anti-neutrophilic-cytoplasmic antibody myeloperoxidase (p-ANCA-MPO) positive term pregnancy reported in INDIA and to underline the importance of disease which should be better known among ophthalmologist. *Methods:* A 32 years old women visited our outpatient with unilateral defective vision, running nose, multiple joint ache in 3rd trimester pregnancy. Slit lamp examination revealed unilateral non-granulomatous uveitis, papillophlebitis with vasculitis. She had a positive nasal necrotizing lesion confirmed on biopsy by pathologist and p-ANCA-MPO serology positive. In view of above she was referred to rheumatologist. *Results:* She was diagnosed with Wegener's granulomatosis (WG) and advised immunosuppresive therapy. She was started on 15mgm/kg/pulse of cyclophosphamide as induction therapy along with steroids and azathioprine 50mgm which were continued for a year postpartum. Anterior uveitis was treated with topical steroids with good effect. The side effects were transitory cushingoid change in mother and growth retardation in the infant. *Conclusion:* Pappilophlebitis, uveitis and vasulitis may be so mild that they may not cause troubling symptoms and hence in case of term pregnancy with Wegeners granulomatosis as an underlying disease it is commonly underdiagnosed. Great co-operation between ophthalmologist and immunologist is extremely crucial for early diagnosis and initiation of therapy. WG tends to be a multi-organ disease with high rate of recurrences and relapses requiring constant follow up. Early diagnosis would introduce immunosuppressive therapy safeguarding the outcome of pregnancy and lives of mother and foetus.

Keywords: Papillophlebitis, Unilateral, Uveitis, Vasculitis, ANCA, MPO, Immunesuppression

1. Introduction

Papillophlebitis is self-limiting condition characterized by painless unilateral disc edema and hyperemia, retinal venous engorgement, and a variable extent of intraretinal hemorrhage and macular edema in otherwise healthy adults younger than 50 years [1-3]. Papillophlebitis and its association with uveitis presenting as manifestation of post streptococcal uveitic syndrome has been reported previously [4]. Papillophlebitis has also been documented in uncomplicated pregnancy as a selflimiting condition [5]. Vasculitis-like retinal changes with hemorrhage can occur in systemic conditions like Wegener's granulomatosis /granulomatosis with polyangiitis responding well to immunotherapy (WG/GPA) [6]. The overall incidence of WG/GPA is estimated to be 4-8.8 cases / million but this varies depending on location. In U.K the annual incidence of WG/GPA is reported as being at higher end of scale at 8.4 cases/million [7]. Bambery et al. analysed the data of patients with WG/GPA in an institutional based study from North India and felt the incidence to be far lower. They concluded

that WG/GPA in India is apparently similar to that seen elsewhere, but the high incidence of tuberculosis interferes with early diagnosis and treatment [8]. Uveitis is rare manifestation of WG/GPA and is seen only to occur in 3% of patients in one study [9]. Often uveitis in association with WG/GPA occurs concurrently with scleritis and is termed sclero-uveitis and probably carries a poor prognosis [10]. Establishing a diagnosis of WG/GPA in ocular disease in pregnancy may be extremely difficult in large number of cases because of variability in their occurrences. Papillophlebitis is selflimiting and it is rarely recurrent or associated with vitreous haemorrhage [11]. A specific diagnosis cannot be made in substantial number of papillophlebitis and uveitis with vasculitis cases. Recognition of disease such as WG/GPA with uveitis, vasculitis and papillophlebitis helps to place these patients in category of vasculitides making early intervention with immunotherapy and oral steroids possible. The outcome of pregnancy and the risk of maternal and fetal morbidity and mortality would hence depend on early intervention. Presentation of disease in patients could initially be ophthalmological findings or symptoms related to WG/GPA. Ophthalmologist play a crucial role in the initial and early diagnosis of patients with WG/GPA with ANCA positivity. To our knowledge this is the first documented case worldwide.

2. Case Report

2.1. Case History, Clinical Examination and Imaging

A 32 years old Asian Indian women presented at 28 weeks of gestation with complaints of gradual painless progressive dimness of vision in left eye of three weeks duration associated with running nose and multiple small joints, hip and lower back pain. This was her second pregnancy, previous pregnancy was associated with history of preterm delivery of single male live birth via caesarean section. Physical examination revealed a tired breathless pregnant women, afebrile with normal blood pressure, weighing 56 kg and 165 cm in height. Best corrected visual acuity (BCVA) was 20/20 in right eye (RE) and 20/200 in left eye (LE). On slit lamp examination RE anterior segment was normal, LE showed circumcorneal congestion with unilateral anterior non granulomatous uveitis (aqueous flare, one plus cells and fine diffuse pigmented keratic precipitate). Normal intraocular pressure was noted (OU 16mmhg). On fundus examination RE was normal, LE depicted significant optic disc oedema accompanied with mildly dilated tortuous veins with multiple cotton wool spots and flame shape superficial haemorrhages distributed along the veins and four quadrants with presence of macula star [figure 1]. Diagnosis of LE non granulomatous uveitis with vasculitis and papillophlebitis was made. She was started on intensive 1% prednisolone eye drops along with thrice application of homatropine hydrobromide 2% eye drops. Fluorescein angiography was significant for marked leakage and staining seen from the disc, macula and venous circulation in all four quadrants. There was presence of 5-6 disc diopter (DD) of juxtapapillary capillary non perfusion area [figure 2]. Optical coherence tomography (OCT) was normal for RE, and LE showed subfoveal neurosensory detachment and intraretinal odema with presence of hyperreflective spots nasal to fovea [figure 3].

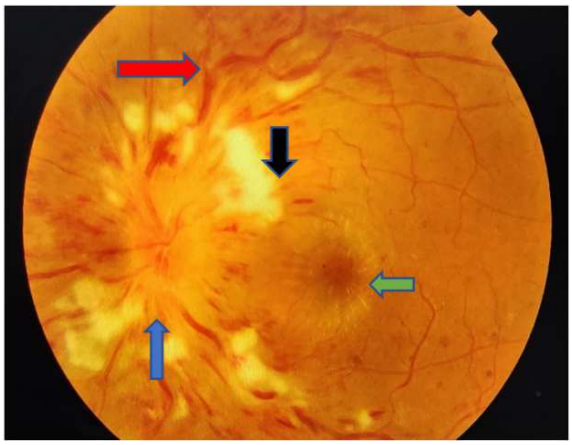

Figure 1. *Fundus photo depicting optic disc oedema (blue arrow), dilated tortuous vessels, flame shape superficial haemorrhages in four quadrant (red arrow), cotton wool spots (black arrow) and macula star (green arrow).*

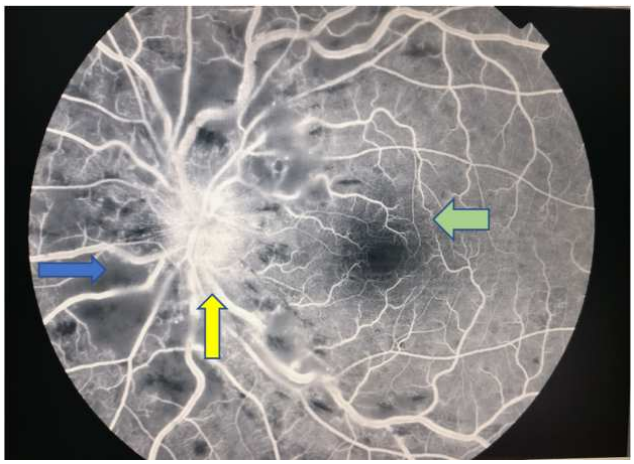

Figure 2. *FFA shows leakage of dye from vessel and disc with staining (yellow vertical arrow) and presence of 5-6 Disc Dioptre size juxtapapillary capillary non-perfusion area (blue arrow) and altered foveal avascular zone (green arrow).*

Figure 3. *OCT Macula shows subfoveal neurosensory detachment (blue vertical arrow), intraretinal odema (green downward vertical arrow) and hypereflective spots (solid horizontal yellow arrow).*

2.2. Laboratory Investigation, Serology and Histopathology

Laboratory tests were advised to determine etiology of disease. Biochemistry revealed microcytic normochromic anemia (hemoglobin =10gm /dl, normal range for women 12.0-15.5 gm/dl), erythrocyte mean cell volume (MCV= 71/ fL, normal range 80-96 fL), erythrocyte sedimentation rate (ESR=54mm/hour, normal range for women < 50 years, 0-20 mm/hr), C- reactive protein (CRP=1.4 mgm/dl, normal range < 10mg/L). Total leucocyte and differential leucocyte count revealed leukocytosis with neutrophilia. (Total leucocyte count= 12800/dl, normal range 4.5-11.0 x 109 /L and absolute neutrophil count=14.0/mm^3, normal range 1.5-8.0/mm^3) and a borderline high platelet count [platelet count=380,000/dl, normal range for women 1.57-3.71/ml). Her prothrombin time was prolonged (PT=68.6 seconds, normal range 11-13.5 seconds). Patients was positive for p-ANCA- MPO test done by indirect immune fluorescence (IIF) microscopy method (levels measured=39AU/ml, normal range <26AU/mL). Myeloperoxidase antibody and serine protease with levels of <19 AU/mL, 20-25AU/mL and >26 AU/mL are considered negative, equivocal and positive respectively for diagnosis of WG. Her renal and liver function test were normal. There was no proteinuria or hematuria. Thyroid profile was normal. Other test included anti-cyclic citrullinated peptide, anti- double stranded DNA, rheumatoid factor (RF), fluorescent treponemal antibody-absorption test (FTA-ABS), HLA B-27 and serum homocysteine levels were nonreactive along with negative tonsillar cultures for Streptococcus pyogenes and other bacteria. An urgent gynaecologist and rheumatologist opinion were sought in view of ANCA positivity and the need for immunosuppression therapy. A fetal ultrasound was advised which showed a single live fetus with adequate liquor and growth. A full thickness nasal biopsy histopathology was advised by rheumatologist showed acute non-specific necrotizing inflammation with infiltration of neutrophils and monocytes. Chest CT was done to rule out systemic involvement of WG revealed no pulmonary abnormality. With nasal biopsy and p-ANCA-MPO positivity along with clinical symptoms a diagnosis of early systemic Wegener's granulomatosis /granulomatosis with polyangiitis (WG/GPA) was confirmed as per EULAR classification.

2.3. Treatment and Outcome

The patient received intravenous methylprednisolone infusion 1 gm per day for 3 consecutive days followed by prednisolone and induction of cyclophosphamide therapy 15/mg/pulse daily for five days. Azathioprine 50 mg tid induction with oral steroids 40 mg were started thereafter and maintained postpartum for a year. During term visit around 8.5months the patient noticed poor fetal movements. Ultrasonography showed intrauterine growth retardation (IUGR) with oligohydramnios. She went on to deliver a healthy low weight female foetus weighing 1.89 gm via segment caesarean section (LSCS) at 34 weeks. At 2 months both mother and child were doing well with mother being in remission with normal blood counts. Her vision had at 6 months in the left eye to 20/32, disc oedema had resolved and had been replaced by disc pallor. OCT macula at 6 months follow up showed complete resolution of neurosensory detachment with IS-OS junction disruption (figure 4). Residual complications were cushingoid feature in mother and growth retardation in infant.

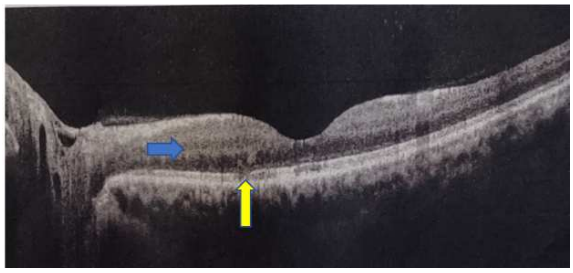

Figure 4. *OCT macula at 1 year follow shows normal retinal contour with altered outer retinal layers with cystoid changes (Blue horizontal arrow) and disruption of IS-OS Junction (yellow vertical arrow).*

3. Discussion

Papillophlebitis is a condition characterized by features of central retinal vein occlusion with no prior history of vascular disease [12]. Although etiopathogenesis of the condition may not be clear central retinal vein inflammation at the optic disc has been suggested as being the cause and the source has been postulated as vasculitis in origin [13]. Vasculitis is a heterogenous group of diseases characterized by necrosis and inflammation in the walls of the vessels [14]. GPA/WG is a multisystemic autoimmune disease in which presence of ANCA positive vasculitis is often characterized by necrotizing vasculitis with or without minimum immune deposits. ANCA positive vasculitis primarily affects small vessels such as capillaries, venules, arterioles, or small arteries [15]. Ocular manifestations occur in 30% to 60% of patients with retinal vasculature involvement in 7% to 18% of patients with WG [16]. The disease affects men more frequently than women with high percentage of patients being positive for anti-neutrophilic cytoplasmic antibody [17]. In 1985, a major breakthrough was made by Woude et al. who reported autoantibodies sensitive and specific for WG with local disease. These autoantibodies reacted with the cytoplasm of ethanol-fixed neutrophils and monocytes and were called anti-neutrophil cytoplasmic autoantibodies (ANCA) [18]. ANCA are predominantly IgG antibodies that were first described in the 1980s in patients with necrotizing glomerulonephritis [19]. Indirect immunofluorescence (IIF) of ethanol fixed neutrophils reveals cytoplasmic (c ANCA) or perinuclear (p ANCA) staining. c ANCA staining correlates with proteinase-3 (PR3) reactivity and mainly detected in patients with WG/GPA, while p ANCA staining correlates with reactivity towards myeloperoxidase (MPO) are seen in patients with microscopic polyangitis (MPA) and churg strauss syndrome (CSS) with relative chances of overlap being a possibility [20]. The diagnosis of WG/GPA, particularly the limited form of disease is based on clinical presentation and pathological criteria based on disease

severity ranging from nonspecific inflammatory picture involving only one site or organ to fulminant multi organ vasculitis [21]. In systemic WG/GPA, c ANCA were found to be positive in 74% of patients; with anti-PR3 detected in 87% [22, 23]. In current clinical practice we use ANCA detection for diagnosis of WG/GPA and as an indicator of disease activity [15]. MPO- ANCA is found in fewer than 5% of WG patients. The c-ANCA is found with lower frequency in localized WG (39%) as compared to generalized WG (86%). The sensitivity and specificity of combined testing for c-ANCA and p-ANCA were 85% and 93% respectively for WG. p-ANCA/MPO–ANCA positive patients have been found to have fewer organ involvement than those with c ANCA/ PR3 ANCA [24]. Our patient had fewer organ involvement and had p-ANCA vasculitis with c-ANCA-ve which was in concurrence with literature hence falling under category of early systemic WG. GPA/WG have an associated nonspecific unilateral or bilateral anterior, intermediate, or posterior uveitis, with varying degrees of vitritis. The retinal vascular manifestations may present as branch or central retinal artery or vein occlusion [25]. The origin of thrombosis in anti-neutrophilic cytoplasmic antibodies associated vasculitis (AAV) is linked to detachment of endothelial cells from their basement membrane and the circulating cells secreting TF (Tumour necrosis factor) which cause thrombi at sites distant from areas of active vasculitis. It is also possible that circulating cytokines induce TF expression on endothelial cells and monocytes in the setting of intact endothelium [26, 27]. It has been postulated that in vasculitis upon activation platelets release multiple cytokines including CD40 ligand (CD40L) and vascular endothelial growth factor (VEGF), which further stimulate coagulation by induction of TF expression on both monocytes and endothelial cells. Hence it is strongly possible our patient with high platelet count, prolonged PTT and elevated neutrophils developed thrombosis in similar mechanism [28, 29]. It is unclear whether AAV symptoms are affected by pregnancy. The literature reports risk of flares up of GPA during pregnancy in women with pre-existing eosinophilic granulomatosis with polyangiitis or GPA to be in range of 36.4% and 40% respectively [30]. The risk of relapse during pregnancy is unpredictable, bimodal and highest in the first / second trimester of pregnancy and one month postpartum [31]. The prognosis of patients with AAV has improved significantly over the past few decades, reflecting in terms of lower mortality and improved disease free survival [32, 33]. However studies have documented that women with systemic vasculitis were more likely to have shortened gestation periods and lower birth weight infants as compared to controls [33]. The management of pregnancy in AAV patient needs continued immunosuppression and also managing the effects of these drugs on maternal and fetal outcomes. In a systematic review of literature assessing successful treatment outcomes in pregnant patients with ANCA−associated vasculitides, the use of systemic steroids, cyclophosphamide, azathioprine with IVGA and plasma exchange have been reported amongst the most commonly used drugs and therapies. The article documented 82.5% live births associated with cyclophosphamide use and consistent success was seen with pulse cyclophosphamide therapy use in third trimester of pregnancy [34]. This provides extremely useful evidence to support the use of cyclophosphamide in life threatening events during pregnancy. Cyclophosphamide is traditionally one of the mainstays of induction therapy in AAV, however it is mutagenic, teratogenic and embryo lethal, especially in the first trimester of pregnancy and its use is done with extreme caution [35]. As per our knowledge this is the first documented case of papillophlebitis with uveitis and vasculitis in a p-ANCA MPO positive pregnancy in third trimester.

4. Conclusion

Papillophlebitis is rare in pregnancy, hence needs to be considered as differential diagnosis and investigated in patients presenting with variable symptoms' as breathlessness, polyarthralgia and otolaryngological symptoms for underlying disease such as granulomatosis with polyangitis. Early diagnosis of systemic disease would lead to early initiation of treatment with immunosuppresive therapy safeguarding the outcome of pregnancy and lives of mother and fetus. Greater and better medical outcome to be expected with reduced maternal and fetal morbidity and mortality.

Financial Interest

Nil

References

[1] Lonn LI and Hoyt WF. Papillophlebitis: a cause of protracted benign optic disc edema. Eye Ear Nose Throat Mon 1996; 45: 62-68.

[2] Fong AC, Schatz H, McDonald HR, et al. Central retinal vein occlusion in young adults (papillophlebitis) Retina 1992; 12: 3-11.

[3] Ellenberger Jr C and Messner K. Papillophlebitis: benign retinopathy resembling papilledema or papillitis. Ann Neurol 1978; 3: 438-440.

[4] Smet de M D. Papillophlebitis and Uveitis as a Manifestation of Post-Streptococcal Uveitis Syndrome. Eye 2009; 23: 985–987.

[5] Mcloone EM and Best RM. Pregnancy related Papillophlebitis. Eur J Ophthalmol 2004; 14: 65-6.

[6] Matlach J, Freiberg FJ, Gadeholt O and Göbel W. Vasculitis-like Hemorrhagic Retinal Angiopathy in Wegener's Granulomatosis. BMC Res Notes 2013; 6: 364.

[7] Watts RA, Al-Taiar A, Scott DG and Macgregor AJ. Prevalence and Incidence of Wegener's Granulomatosis in the UK General Practice Research Database. Arthritis Rheum 2009; 61: 1412-6.

[8] Bambery P, Sakhuja V, Gupta V, et al. Wegener's Granulomatosis in North India. An Analysis of Eleven Patients. Rheumatol Int 1987; 7: 243-7.

[9] Taylor SRT, Salama AD, Pusey CD and Lightman S. Ocular manifestations of wegners granulomatisis. Expert rev. Ophthalmol 2007; 2: 91-103.

[10] Pakrou N, Selva D and Leibatch I. Wegners granulomatosis: Ophthalmic manifestation and management. Semin Arthritis Rheum 2006; 35: 284-292.

[11] Hayreh SS. Optic disc vasculitis. Brit J Ophthalmol 1972; 56: 652-670.

[12] Grosso A, Calzada AI, Randolph J and Sigler. Pappilophlebitis: A closer look. Retina today. Medical Retina. July/August 2017; 32-38.

[13] Heir JS and Morley MG. Venous obstructive disease of the retina. In: Yanoff M, Duker JS, editors. Ophthalmology 1998; London: Mosby International: 8/18. 1-8/ 18.8.

[14] Jennette JC, Falk RJ, Bacon PA, et al. 2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. Arthritis Rheum 2013; 65: 1–11.

[15] Finkielman JD, Merkel PA, Schroeder D, et al. Antiproteinase antineutrophil cytoplasmic antibodies and disease activity in Wegeners granulomatosis. Ann Intern Med 2007; 147: 611-9.

[16] Robin JB, Schanzlin DJ, Meisler DM, deLuise VP and Clough JD. Ocular Involvement in the Respiratory Vasculitides. Surv Ophthalmol 1985; 30: 127-40.

[17] Rao JK, Weinberger M, Oddone EZ, Allen NB, Landsman P and Feussner JR. The role of antineutrophil cytoplasmic antibody (c-ANCA) testing in the diagnosis of Wegener granulomatosis. A literature review and meta-analysis. Ann Intern Med 1995; 123: 925-32.

[18] Woude van der FJ, Rasmussen N, Lobatto S, et al. Autoantibodies Against Neutrophil and Monocytes: Tool for Diagnosis and Marker of Disease Activity in Wegener's Granulomatosis. Lancet 1985; 1: 425-9.

[19] Davies DJ, Moran JE, Niall JF & Ryan GB. Segmental necrotising glomerulonephritis with antineutrophil antibody: possible arbovirus aetiology? Br Med J 1982 (Clin Res Ed); 285 (6342): 606.

[20] Savage CO, Harper L and Adu D. Primary systemic vasculitis. Lancet 1997; 349 (9051): 553-558.

[21] White ES and Lynch JP. Pharmacological Therapy for Wegener's Granulomatosis. Drugs 2006; 66 (9): 1209-28.

[22] Tsiveriotis K, Tsirogianni A, Pipi E, Soufleros K and Papasteriades C. Antineutrophil Cytoplasmic Antibodies Testing in a Large Cohort of Unselected Greek Patients. Autoimmune Dis 2011; 2011: 626495.

[23] Wiik A. Rational use of ANCA in Diagnosis of vasculitis. Rheumatology 2002; 41: 481-3.

[24] Schonemarck U. Lamprecht P, Csemok E and Gross WL. Prevalence and spectrum of rheumatic disease associated with protinase 3-antineutrophil cytoplasmic antibodies (ANCA) and myeloperoxidase-ANCA. Rheumatology 2001; 40: 178-84.

[25] Takanashi T, Uchida S, Arita M, Okada M and Kashii S. Orbital inflammatory pseudotumor and ischemic vasculitis in Churg-Strauss syndrome: report of two cases and review of the literature. Ophthalmology 2001; 108: 1129–1133.

[26] Woywodt A, Streiber F, Groot de K, Regelsberger H, Haller H and Haubitz M, et al. Circulating endothelial cells as markers for ANCA-associated small-vessel vasculitis. Lancet 2003; 361: 206–210.

[27] WGET -research group. Design of the Wegener's Granulomatosis Etarnercept Trial (WGET). Control Clin Trials 2002; 23: 450-468.

[28] Henn V, Slupsky JR, Grafe M, Anagnostoppoulos I, Forster R, Müller-Berghaus G, Kroczek RA, et al. CD40 ligand on activated platelets triggers an inflammatory reaction of endothelial cells. Nature 1998; 391: 591–594.

[29] Slupsky JR, Kalbas M, Willuweit A, et al. Activated platelets induce tissue factor expression on human umbilical vein endothelial cells by ligation of CD40. Thromb Haemost 1998; 80: 1008–1014.

[30] Fredi M, Lazzaroni MG, Tani C, et al. Systemic vasculitis and pregnancy: a multicenter study on maternal and neonatal outcome of 65 prospectively followed pregnancies. Autoimmun Rev 2015; 14: 686–691.

[31] Harber MA, Tso A, Taheri S, Tuck SM and Burns A. Wegener's granulomatosis in pregnancy–the therapeutic dilemma. Nephrol Dial Transplant 1999; 14: 1789-91.

[32] Westman K, Flossmann O and Gregorini G. The long-term outcomes of systemic vasculitis. Nephrol Dial Transplant 2015; 30 Suppl 1: i60-6.

[33] Sangle SR, Vounotrypidis P, Briley A, et al. Pregnancy outcome in patients with systemic vasculitis: a single-centre matched case-control study. Rheumatology (Oxford) 2015; 54: 1582-1586.

[34] Singh P, Dhooria A, Manish Rathi M, et al. Successful Treatment Outcomes in Pregnant Patients With ANCA-associated Vasculitides: A Systematic Review of Literature. Int J Rheum Dis 2018; 21: 1734-1740.

[35] Leroy C, Rigot J-M, Leroy M. et al. Immunosuppressive drugs and fertility. Orphanet J Rare Dis 2015; 10: 136.