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Granulomatosis with polyangiitis in pregnancy – clinical implications and treatment possibilities

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Abstract. – Granulomatosis with polyangiitis (GPA) is an autoimmune disease which has a variable clinical presentation and usually progresses from a localized to a generalized form over the course of weeks to years. Histopathologically, it is a necrotizing systematic vasculitis that can cause sino-nasal, pulmonary, renal, ocular, and cutaneous manifestations. Diagnostic workup should include serologic, radiologic, endoscopic and histopathological examination. Autoantibody c-ANCA may be used as a marker of disease activity and individual follow-up. An appropriate local and systemic treatment should be implemented, which is particularly important in pregnancy. Comprehensive management should be planned, including the needs of both mother and fetus (particularly if vasculitis is diagnosed de novo during pregnancy). Pregnancy in patients with GPA is burdened with the risk of possible complications and increased mortality and the conception should be delayed until remission of the disease. A flare-up of GPA may be life threatening for both mother and fetus. The immunosuppressants, which are used during pregnancy include glucocorticosteroids (GCS) and azathioprine. Studies of GPA in pregnancy are scarce, and this calls for individualized management. Thus, the approach to care for pregnant women with GPA is interdisciplinary, and firmly places the rheumatologist, gynecologist, pulmonologist, otorhinolaryngologist and nephrologist on the management team.

Key Words:
Granulomatosis with polyangiitis, Pregnancy, Treatment.

Introduction

Granulomatosis with polyangiitis (GPA, previously called Wegener's granulomatosis – WG) is a vasculitic autoimmune disorder affecting small and medium sized arteries (larger vessels are rarely affected)[1]. The etiology of this disease is unknown and it commonly presents with ear, nose and throat, pulmonary, skin and renal manifestations. The symptoms may remain limited to specific regions (e.g. the upper respiratory tract – such as the nose and paranasal sinuses) or they can be multisystemic, affecting many organs and causing damage and failure[2]. The Chapel Hill Nomenclature definitions[3] and the American College of Rheumatology defined the nomenclature and diagnosis of GPA according to two of these four criteria: nephritic urinary sediment, abnormal chest findings, nasal or oral inflammation, and granulomatous inflammation on biopsy[4]. However, the symptoms may vary from local involvement, such as nasal (sinusitis, purulent or bloody rhinorrhea, saddle nose deformity), eye (visual loss, conjunctivitis, uveitis, retrobulbar masses) or ear (hearing loss, purulent or bloody discharge), to multisystemic damage (including kidney, lungs, skin and nervous system changes)[5]. In this disease the IgG autoantibodies against cytoplasmic components of neutrophils, granulocytes, and monocytes are synthesized. Circulating anti-neutrophil cytoplasmic antibodies (cANCA) are present in 82-94% of patients with GPA, primarily directed against proteinase 3 (PR3)[6]. Disease activity can be measured by using the Birmingham Vasculitis Activity Score for GPA (BVAS) – a clinical evaluation tool which has been standardized for the management of patients with systemic vasculitis[7].

Specificity of GPA in Pregnancy

The onset of the GPA is usually in the fourth and fifth decades of life, making an association with pregnancy rare[8]. However, if the active disease is present, this increases the risk to mother and fetus health. In the literature, about 40% of pregnancies end in pre-term deliveries[9,10]. The mother's condition during conception is crucial for future pregnancy course. If the conception is during a period of remission of GPA, complications or vasculitis flares occur in about 1/4th of

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the pregnancies, sometimes post-partum. Unfortunately, 40-100% pregnancies end in miscarriage or therapeutic abortion or even the mother's death, when pregnancies started during active GPA[9-11].

The symptoms in pregnancy may vary from an uneventful course or minor vasculitis manifestation to severe symptoms of pneumonia (reported in the third trimester)[11] and alveolar hemorrhage with acute respiratory distress syndrome (ARDS)[9]. In the literature, a variety of signs presented by pregnant women (such as crusting rhinitis, subglottic stenosis, arthralgias, fever, necrotizing glomerulonephritis, otitis, and skin purpura) have been reported, but the pregnancies have usually finished successfully. Healthy neonates have been born and mothers recovered after deliveries[9,11,12]. However, the pregnancy can be complicated by premature rupture of membranes (PROM), leading to pre-term birth or post-partum complications, such as a flare of the disease or progression from severe renal deterioration during pregnancy to end-stage renal disease[11].

Seo[12] reported the case of a woman with arthralgias, fever, necrotizing glomerulonephritis (creatinine 500 mmol/l), alveolar hemorrhage and the presence of anti-PR3 ANCA. During pregnancy, the remission was entered with creatinine 150 mmol/l, proteinuria 2.5 g/l, lack of circulating ANCA and hypertension (BVAS = 0). In this case, ante-partum hemorrhage at 23 weeks due to posterior placenta previa was described and the pregnancy finished successfully with a caesarean section at 32 weeks because of renal deterioration. The woman was treated with prednisolone at a dose of 12.5 mg/day and azathioprine 125 mg/day.

Koukoura et al[9] have described the case of a woman with otitis, crusting rhinitis, skin purpura, necrotizing glomerulonephritis (creatinine 450 mmol/l), alveolar hemorrhage with acute respiratory distress syndrome (ARDS) and the presence of anti-PR3 c-ANCA. After treatment with prednisone (12.5 mg/day) and rituximab (the last 500 mg infused at week 12 of undiagnosed pregnancy), remission of GPA was observed (BVAS = 0). Additionally, the pregnancy ended with the delivery of a healthy neonate.

GPA de novo During Pregnancy

GPA can be diagnosed *de novo* during pregnancy with the onset usually in the second and third trimesters. In most cases, the condition of the fetus is good and the pregnancy finishes successfully; however, there are also reports of medical termination at seven weeks of gestation[13] or maternal and fetus death due to cranial bleeding[14]. Such severe cases have been reported in the past, but recently many reports have shown positive outcomes of pregnancy, which may be caused by quicker diagnosis and new therapeutic options. Sahni et al[15] reported a limited form of *de novo* GPA in pregnancy, which did not require any treatment and finished with delivery at the 34th week. In another case[16], effective treatment with prednisolone and IVIG was reported and the woman entered remission; however, during pregnancy pre-eclampsia and maternal diabetes mellitus was diagnosed. The pregnancy finished with preterm delivery at the 36th week with a good fetus outcome.

Bessias et al[17] describe a pregnancy with *de novo* diagnosed GPA and acute limb ischemia, which was treated with prednisolone and cyclophosphamide and finished by caesarean section (preterm delivery) with a good fetus outcome. Because of the acute limb ischemia and the failure of thrombectomies to maintain arterial flow in the distal limb due to the development of active vasculitis, the mother finally underwent amputation of the limb (the recent cesarean section excluded thrombolysis).

Complications in Pregnancy and Post Partum

In pregnancy, complications can result from both the course of GPA and pregnancy itself. In the literature, various complications have been described from placenta previa, subglottic stenosis or renal deterioration to maternal and fetus death due to cranial bleeding[11,14,18,19].

Renal involvement in the course of GPA may be difficult to differentiate from a pre-eclampsia state. However, a flare-up of GPA is usually characterized by positive ANCA titer, the presence of extra-renal symptoms and a lack of hypertension (which is more characteristic for the pre-eclampsia condition).

Kayatas et al[18] presented a case of pregnancy with GPA complicated by severe pre-eclampsia and placental abruption. The patient had elevated blood pressure and liver enzymes, proteinuria, hemoconcentration, thrombocytopenia, negative c-ANCA and positive p-ANCA (however, the disease was localized during the first two years and remitted before conception). In an analysis of cases, Pagnoux et al[11] reported such complica-

tions as hypertension, renal deterioration and placenta previa; however, no patient had placental abruption or pre-eclampsia. Moreover, none of the children experienced vasculitis manifestations or other systemic diseases.

In the course of the disease, upper and lower airways are involved and the granulomatous inflammation may cause scar tissue formation leading to permanent subglottic stenosis (SGS), which complicates GPA in 6-23% of cases. This results from inflammation, edema and fibrosis at the level of the cricoid cartilage, up to 4 cm below the vocal cords[19]. If subglottic stenosis is present, possible anesthetic options for caesarean section in such patients are either neuraxial anesthesia or general anesthesia with a small tube or laryngeal mask and possible tracheotomy. However, intubation in cases of SGS may be difficult, especially in emergent cesarean section, and general anesthesia should be avoided if there is a permanent upper airway stenosis. The subglottic stenosis may be successfully treated by laser ablation of the excessive tissue[20].

Not only mothers but also neonates may reveal complications, because the antibodies can pass though the placenta and the neonate may be PR3-ANCA positive[21]. Neonates can be asymptomatic[21] or can present some signs characteristic for GPA – e.g. pulmonary renal syndrome[22].

Treatment in Pregnancy

The standard treatment of the localized form is based mainly on glucocorticosteroids (prednisone, prednisolone, and hydrocortisone)[23]. In many cases, the immunosuppressive therapy of multisystem involvement is effective and a combination of glucocorticosteroids and cyclophosphamide (CYC) or azathioprine has been used in pregnancy. Cyclophosphamide is a cytotoxic and teratogenic medication; however, the standard treatment with this drug (in combination with corticosteroids) induces remission and improves survival, also in pregnancy (it seems to be safe in the third trimester). Methotrexate is highly teratogenic and is contraindicated[8,10]. Prophylactic treatment with trimethoprim/sulfamethoxazole (TMP-SMX) reduces infections and the risk of relapses during remission, but such treatment is not effective in the induction of remission and is contraindicated in pregnancy[23].

The immunosuppressants, which can be used during pregnancy include glucocorticosteroids (GCS) and azathioprine[12,24]. However, after successful treatment with azathioprine at the beginning, remission is not always stable and durable[21]. In some cases, women have conceived under glucocorticosteroids and cyclophosphamide and therapeutic abortion has been implemented at the eighth week. However, there is also a report of an unexpected pregnancy in a 39-year-old woman in remission after six CYC pulses and receiving GCS and rituximab (500 mg, every 6 months) for maintenance, as part of an ongoing trial. In this case, the pregnancy was continued because no fetal abnormality was observed (normal ultrasonography examination and fetal karyotype)[11]. Indeed, these studies[11,25] underscore the fact that CYC exposure does not necessarily induce sterility, especially in the youngest women and when the cumulative CYC dose remains lower than 8 g/m^2. Even though the infertility rate during treatment with cyclophosphamide can be as high as 50% in women of childbearing age, many pregnancies are still reported during such therapy[26]. In the literature, cases of conceptions are described in women receiving CYC and continuous oral progestative drugs or a gonadotropin-releasing hormone agonist, like triptorelin, to try to preserve ovarian function (with good global outcome, since no mother has died and all liveborn infants have been healthy). However, one mother developed life-threatening complications during pregnancy, i.e. thrombotic microangiopathy, which caused severe renal insufficiency with persistent vasculitis-related renal impairment[11].

If the women entered remission on AZA or GCS around conception, it seems better to continue the treatment throughout the pregnancy to prevent a flare-up of GPA, which may be life threatening for both mother and fetus. Biological agents should be stopped before conception or avoided in women of child-bearing age without effective contraception, because several uneventful pregnancies have been reported in women on biological therapy (rituximab-exposed women using this medication for other diseases)[27].

Intravenous immunoglobulins (IVIG) are also used in pregnancy as a potential therapy for GPA. IVIG enable binding of ANCA to their antigens through idiotypic mechanisms, inhibit ANCA-induced neutrophilic activation and are used in many cases of systemic vasculitis. IVIG are usually implemented in refractory GPA, if treatment with glucocorticosteroids and cyclophosphamide is not sufficient and can induce remission[23]. Such treatment is reported to be effective in *de novo*

GPA in the first trimester (in combination with glucocorticosteroids) causing remission of the disease[16,28]. Thus, IVIG therapy can be used as a safe alternative to cytotoxic therapy for a patient with GPA during pregnancy. In summary, individual treatment as well as the prophylactic activities typical for pregnancy should be implemented in this time, which influences the course of pregnancy and neonate wellbeing[29].

Conclusions

Women of child-bearing age with GPA can envisage pregnancy, but a few conditions should be adhered to for the safety of mother and fetus. The best time to plan conception is a minimum of six months after entering remission. It is beneficial to stop potentially toxic immunosuppressants (if it possible) and the woman and child should be closely monitored by obstetricians and rheumatologists. Remission may be entered after cyclophosphamide induction and thereafter azathioprine can be taken with good results before conceiving.

The activity of GPA and complications at unexpected conception appears to be a major parameter to take into account when evaluating the risk of pregnancy. A multidisciplinary treatment of pregnant women should be the approach during pregnancy and after delivery. In our opinion, multicentre registry may also be a good basis for clinical outcomes, which may indicate new possibilities for future treatment.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

References

1) Schilder AM. Wegener's granulomatosis vasculitis and granuloma. Autoimmun Rev 2010; 9: 483-487.
2) Reinhold-Keller E, Beuge N, Latza U, de Groot K, Rudert H, Nölle B, Heller M, Gross WL. An interdisciplinary approach to the care of patients with Wegener's granulomatosis: long-term outcome in 155 patients. Arthritis Rheum 2000; 43: 1021-1032.
3) Jennette JC, Falk RJ, Bacon PA, Basu N, Cid MC, Ferrario F, Flores-Suarez LF, Gross WL, Guillevin L, Hagen EC, Hoffman GS, Jayne DR, Kallenberg CG, Lamprecht P, Langford CA, Luqmani RA, Mahr AD, Matteson EL, Merkel PA, Ozen S, Pusey CD, Rasmussen N, Rees AJ, Scott DG, Specks U, Stone JH, Takahashi K, Watts RA. 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. Arthritis Rheum 2013: 65: 1-11.
4) Leavitt RY, Fauci AS, Bloch DA, Michel BA, Hunder GG, Arend WP, Calabrese LH, Fries JF, Lie JT, Lightfoot RW Jr, et al. The American College of Rheumatology 1990 criteria for the classification of Wegener's granulomatosis. Arthritis Rheum 1990; 33: 1101-1107.
5) Ferguson BJ. Fungal rhinisinosits. In: Flint WP, Haughey BH, Lund VJ, Niparko JK, Richardson MA, Robbins KT, Thomas JR, Editors. Cummings Otolaryngology – Head and Neck Surgery. 5th Edition. China, Mosby Elsevier 2010; 1: 708-716.
6) Radice A, Bianchi L, Sinico RA. Anti-neutrophil cytoplasmic autoantibodies: methodological aspects and clinical significance in systemic vasculitis. Autoimmun Rev 2013: 12: 487-495.
7) Stone JH, Hoffman GS, Merkel PA, Min YI, Uhlfelder ML, Hellmann DB, Specks U, Allen NB, Davis JC, Spiera RF, Calabrese LH, Wigley FM, Maiden N, Valente RM, Niles JL, Fye KH, McCune JW, St Clair EW, Luqmani RA; International Network for the Study of the Systemic Vasculitides (INSSYS). A disease-specific activity index for Wegener's granulomatosis: modification of the Birmingham Vasculitis Activity Score. International Network for the Study of the Systemic Vasculitides (INSSYS). Arthritis Rheum 2001; 44: 912-920.
8) Lamprecht P, Gross WL. Wegener's granulomatosis. Herz 2004; 29: 47-56.
9) Koukoura O, Mantas N, Linardakis H, Hajiioannou J, Sifakis S. Successful term pregnancy in a patient with Wegener's granulomatosis: case report and literature review. Fertil Steril 2008: 89: 457.e1-5.
10) Auzary C, Huong DT, Wechsler B, Vauthier-Brouzes D, Piette JC. Pregnancy in patients with Wegener's granulomatosis: report of five cases in three women. Ann Rheum Dis 2000: 59: 800-804.
11) Pagnoux C, Le Guern V, Goffinet F, Diot E, Limal N, Pannier E, Warzocha U, Tsatsaris V, Dhote R, Karras A, Cohen P, Damade R, Mouthon L, Guillevin L. Pregnancies in systemic necrotizing vasculitides: report on 12 women and their 20 pregnancies. Rheumatology (Oxford) 2011; 50: 953-961.
12) Seo P. Pregnancy and vasculitis. Rheum Dis Clin North Am 2007; 33: 299-317.
13) Palit J, Clague RB. Wegener's granulomatosis presenting during first trimester of pregnancy. Br J Rheumatol 1990; 29: 389-390.
14) Milford CA, Bellini M. Wegener's granulomatosis arising in pregnancy. J Laryngol Otol 1986; 100: 475-476.
15) Sahni V, Agarwal SK, Singh NP, Sikdar S, Yadav A, Wadhwa A, Aggarwal G. Successful pregnancy in untreated limited Wegener's granulomatosis. Med J Malaysia 2005; 60: 492-494.
16) Masterson R, Pellicano R, Bleasel K, McMahon LP. Wegener's granulomatosis in pregnancy: a novel approach to management. Am J Kidney Dis 2004; 44: e68-72.

17) Bessias N, Moulakakis KG, Lioupis C, Bakogiannis K, Sfyroeras G, Kakaletri K, Andrikopoulos V. Wegener's granulomatosis presenting during pregnancy with acute limb ischemia. J Vasc Surg 2005; 42: 800-804.

18) Kayatas S, Asoglu MR, Selcuk S, Sargin MA. Pregnancy in a patient with Wegener's granulomatosis: a case report. Bull NYU Hosp Jt Dis 2012; 70: 127-129.

19) Blaivas AJ, Strauss W, Yudd M. Subglottic stenosis as a complication of Wegener's granulomatosis. Prim Care Respir J 2008; 17: 114-116.

20) Scholz A, Srinivas K, Stacey MR, Clyburn P. Subglottic stenosis in pregnancy. Br J Anaesth 2008; 100: 385-388.

21) Alfhaily F, Watts R, Leather A. Wegener's granulomatosis occurring de novo during pregnancy. Clin Exp Rheumatol 2009; 27: S86-68.

22) Bansal PJ, Tobin MC. Neonatal microscopic polyangiitis secondary to transfer of maternal myeloperoxidase-antineutrophil cytoplasmic antibody resulting in neonatal pulmonary hemorrhage and renal involvement. Ann Allergy Asthma Immunol 2004; 93: 398-401.

23) Bellisai F, Morozzi G, Marcolongo R, Galeazzi M. Pregnancy in Wegener's granulomatosis: successful treatment with intravenous immunoglobulin. Clin Rheumatol 2004; 23: 533-535.

24) Langford CA, Kerr GS. Pregnancy in vasculitis. Curr Opin Rheumatol 2002; 14: 36-41.

25) Ioannidis JP, Katsifis GE, Tzioufas AG, Moutsopoulos HM. Predictors of sustained amenorrhea from pulsed intravenous cyclophosphamide in premenopausal women with systemic lupus erythematosus. J Rheumatol 2002; 29: 2129-2135.

26) Pauzner R, Mayan H, Hershko E, Alcalay M, Farfel Z. Exacerbation of Wegener's granulomatosis during pregnancy: report of a case with tracheal stenosis and literature review. J Rheumatol 1994; 21: 1153-1156.

27) Kimby E, Sverrisdottir A, Elinder G. Safety of rituximab therapy during the first trimester of pregnancy: a case history. Eur J Haematol 2004; 72: 292-295.

28) Kim SY, Linton JM, Kolasinski SL. Successful treatment of new onset Wegener's granulomatosis with IVIG (intravenous immunoglobulin) during pregnancy: a case report. Mod Rheumatol 2008; 18: 177-780.

29) Karowicz-Bili ska A, Nowak-Markwitz E, Kedzia W, Spaczy ski M. Response paper to the article, "the need of activity in the field of prenatal public health in Poland". Ginekol Pol 2012; 83: 953-955.