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Pre-pregnancy counselling of patients with vasculitis

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The knowledge about the risk of pregnancy in vasculitides mostly derives from single case reports or at best from retrospective studies with all the caveats that these observations include. Primary systemic vasculitides are uncommon, encompassing a broad spectrum of severity, from mild to life-threatening manifestations and with different natural histories, from self-limiting to relapsing or chronic active disease. The treatments require a cautious use of immunosuppressants tailored to each specific condition. Furthermore, most of the cytotoxic drugs necessary to treat vasculitis act by modifying the cell cycle and cell differentiation, biological effects that are particularly hazardous for the foetus. In order to have an uncomplicated pregnancy, conception should be planned when the disease is inactive. Moreover, organ failure or damage, due to previous disease activity, must also be taken into account since it can lead to adverse obstetrical and fetal outcomes.

Key words: Risk, Pregnancy, Systemic vasculitis, Cytotoxic drugs.

Introduction

The increasing awareness of primary systemic vasculitides along with the improvement of diagnostic skills have led to an earlier detection and treatment of such diseases with the consequent amelioration of survival rate as well as quality of life. For these reasons patients with systemic vasculitides are affected in their childbearing age more frequently than in the past.

Thus, procreation is becoming an important issue in patients with vasculitides and the use of cytotoxic therapies raises critical concerns regarding fertility, both in male and female and potential fetal toxicity when these drugs are administered to the mothers during gestation.

Pregnancy is a condition in which profound immune and endocrine changes occur. The physiological increase of cortisol, progesterone, oestradiol and testosterone during the third trimester of pregnancy seems to lead to Th-2 cytokine polarization both at the systemic level and at the feto–maternal interface [1–3]. Whether this could affect maternal and fetal pregnancy outcomes in each specific vasculitis is still uncertain.

Theoretically, the immunological changes induced by pregnancy could improve the maternal disease in primarily Th-1-mediated vasculitides, such as Takayasu's arteritis (TA) and Behçet's disease (BD), and worsen ANCA-associated vasculitides that are mainly Th2 mediated.

To date no studies have evaluated the disease activity variations of the different vasculitides and their relationship with immunoendocrine changes during pregnancy. The majority of the studies have been focused on the effect of disease complications including organ failure or irreversible vascular lesions, in maternal and fetal pregnancy outcomes.

This article is focused on the relationship between pregnancy and systemic primary vasculitis (Tables 1 and 2). Guidelines for the management of these conditions during pregnancy are also provided.

Takayasu arteritis

TA is a granulomatosus vasculitis that affects large vessels such as aorta, its major branches and the pulmonary arteries. TA typically occurs in women during their childbearing age; therefore, it is more common to observe pregnancy in patients with TA than in those with other vasculitis [4]. We have been able to identify in the literature 136 pregnancies in 99 patients affected with TA. In seven cases (5%), the patient was advised to have a termination of pregnancy.

In the remaining 129 pregnancies, maternal complications, particularly hypertension and/or pre-eclampsia, were reported in 57 (44%) cases. Although less frequently, congestive heart failure (three cases), progression of renal insufficiency and cerebral haemorrhage (one case each) have been reported [5, 6]. No cases of maternal death have been reported.

The outcome of pregnancy was favourable in 85% of cases. Spontaneous abortion was reported in 8–16% of cases [5–7] and intrauterine fetal death in 20% of cases studied by Sharma *et al.* [5], but this complication was not observed in other studies [6, 7]. IUGR and premature delivery were found in ~40% of the cases [5–7] and occurred more frequently in infants born to patients with more severe disease.

The risk of TA associated with pregnancy seems to be mainly due to arterial hypertension and/or pre-eclampsia and it has been mentioned that this risk is greater in more severe and extensive cases [6].

Severe aortic valvular disease and aortic aneurysm are risk factors for maternal morbidity and fatality; therefore, patients with these complications should be discouraged from pregnancy and, if pregnancy unexpectedly occurs, therapeutic abortion should be considered.

In the case of disease relapse during pregnancy, treatment consists of prednisone 1 mg/kg/day until the disease control is obtained, thereafter prednisone can be tapered to the lowest effective dose. In refractory cases, the use of AZA is recommended. Hypertension has to be managed very aggressively with α-methyldopa, channel blockers or hydralazine. Angiotensin-converting enzyme inhibitors are contra-indicated because of their fetal toxicity.

Wegener's granulomatosis

WG is an uncommon, small-vessel, necrotizing vasculitis, which usually affects the upper respiratory tract, the lungs and the kidney. The disease peaks after the age of 40; thus, pregnancies in women with WG are uncommonly observed [4].

Reports of pregnancy in patients with WG are rare: 23 pregnancies in 19 patients [8–11].

From the revision of these case reports, we can summarize that patients with active disease at conception or those with disease onset during pregnancy are at high risk of poor outcome because of fetal and maternal death. In patients who conceived when the disease was in remission, relapse occurred in 25% of the cases. However, it is not known if this figure is higher than that expected in non-pregnant WG patients. The relapse or worsening of renal

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TABLE 1. Effect of pregnancy on the course of systemic vasculitis

	Status of disease at conception	
	Active	Inactive
WG	Frequent flares Risk of maternal death	Rare flares (25%)
PAN	Frequent flares	Rare flares
MPA	Risk of maternal death	
CSS	Frequent flares (~50%) (asthma, mononeuritis multiplex, skin rash)	
TA	Rare flares. High risk of maternal morbidity and fatality in patients with severe aortic valvular disease or aortic aneurysm	
BD	Rare flares (25%) Frequent improvement (50%)	

The frequencies of maternal morbidity and fatality are higher in patients with disease onset during pregnancy. MPA: Microscopic polyangiitis; CSS: Churg–Strauss syndrome.

TABLE 2. Effects of systemic vasculitis on pregnancy: frequency of fetal complications

	Spontaneous abortion	Stillbirth	Pre-term birth
General obstetric USA population (%)	15	≤3.5	10
WG	High	High	Very high
CSS	Low	Low	Very high
PAN	High	High	Very high
MPA	High	High	Very high
TA	Low	Low	Very high
BD	Low	Low	Low

All these figures worsen in patients with active disease at conception or in those with disease onset during pregnancy. MPA: Microscopic polyangiitis; CSS: Churg–Strauss syndrome.

disease in the late pregnancy can be difficult to differentiate from pre-eclampsia. Very few parameters are useful in this regard; among them, active urine sediment that is indicative of WG nephritis and hypertension that is more commonly observed in pre-eclampsia seem to be the most reliable. Moreover, as in SLE patients, the possibility that both features coexist at the same time cannot be ruled out.

Premature delivery is a common complication of pregnancy in patients with WG, particularly in those with active disease during gestation or if WG onsets during pregnancy [4].

The treatment of disease relapse during pregnancy largely depends on the type and extension of the disease manifestations. For features limited to the upper airways we recommend local treatment, antibiotics and, if necessary, low-dose oral prednisone. Systemic manifestations require more aggressive treatment with high-dose oral prednisone (1 mg/kg/day), or i.v. pulse methylprednisolone 0.5–1 g daily for three consecutive days. In case of insufficient response to corticosteroids, AZA should be started. In presence of life-threatening manifestation occurring during the second or third trimester of pregnancy, cyclophosphamide was also considered [4–11].

Churg–Strauss syndrome

Churg–Strauss syndrome (CSS) is a disorder characterized by pulmonary and systemic small vessel vasculitis, extravascular granulomas and hypereosinophilia, occurring in patients with asthma and allergic rhinitis [4]. Fifteen pregnancies have been described in the literature, 14 of them concluding with a delivery of a healthy baby.

CSS relapse was reported in 50% of women who conceived while disease was in remission [10, 12], which in one case was lethal [13]. During relapse, the prevalent manifestations were worsening with asthma, mononeuritis multiplex and skin rash. Although prematurity is commonly observed, the majority of these patients delivered normal but low birth weight infants.

Patients with disease onset during pregnancy had a very poor prognosis [13, 14]. In these cases pregnancy complications were very common, including fetal and maternal death.

Treatment of CSS relapses during pregnancy consists of prednisone, whose dosage has to be adjusted according to the severity of manifestations. In CSS patients, special care should be taken in monitoring bronchospasm during pregnancy and postpartum [4].

Polyarteritis nodosa

Paylarteritis nodosa (PAN) is a disorder characterized by necrotizing inflammation of medium size or small arteries. In patients with PAN, prevalent features are general symptoms, musculoskeletal, skin and gastrointestinal manifestations, and peripheral neuropathy, especially mononeuritis multiplex [4].

Few case reports on pregnancy in PAN patients are available and in the last 10 yrs only two cases were reported in the world literature [15, 16]. Patients who conceive during disease remission seem to have a favourable outcome with no maternal death, rare disease relapse and, in the majority of cases, delivery of healthy—although premature and low birth weight—babies. Conversely, pregnancy outcome was poor when PAN was diagnosed during pregnancy [4].

These patients are at high risk of death, therefore, therapeutic abortion should be considered in early phase of pregnancy, whereas high-dose corticosteroid and cyclophosphamide are indicated in late pregnancy [4].

Microscopic polyangiitis

Microscopic polyangiitis (MPA) is a systemic, pauci-immune, necrotizing, small-vessel vasculitis. MPA is initially recognized as a subset of PAN from which it may be difficult to distinguish. It is also possible that in many series reported in literature MPA patients had been grouped with PAN. However, unlike PAN, most patients with MPA developed severe renal disease and pulmonary haemorrhage [4].

Only two case reports on pregnancy in patients with MPA are available in the literature.

Cetinkaya *et al.* [17] described a patient who developed MPA at 16th week of gestation. Treatment with high-dose methylprednisolone (1 g/day for 3 days) and one pulse cyclophosphamide (0.5 g) was given, but unfortunately the patient died due to pulmonary infections.

Milne *et al.* [18] reported another case in whom MPA occurred at 24th week of gestation and was successfully treated with plasma exchange, 1 g i.v. cyclophosphamide and 1 g daily i.v. methylprednisolone, changed to 60 mg oral prednisone after 3 days. To reduce the risk of infections, prophylactic treatment with co-trimoxazolo and oral anti-fungal agents was introduced.

It is possible that, as for PAN or other vasculitis, patients with MPA diagnosed prior to pregnancy have a more favourable outcome with no need of aggressive treatment, which may increase the risk of maternal and fetal mortality.

Behçet's disease

Behçet's disease (BD) is a chronic, relapsing, multisystemic, inflammatory process characterized by recurrent oral and genital ulcers, ocular, gastrointestinal, neurological manifestations and thrombosis. It predominantly affects young women during childbearing age, therefore it is not rare to observe pregnancy in patients with BD [4]. Data regarding the reciprocal influence of BD and pregnancy derive from the analysis of 220 pregnancies in 128 patients diagnosed with BD concerning anecdotal case

reports, five small series and one large retrospective series on the disease during pregnancy, which have been published in the world literature [19–25].

The disease tends to improve during pregnancy in ~63% of cases, whereas disease relapse was reported in 28% of cases. During relapses, disease manifestations consisted of oral or genital ulcers, arthritis and eye inflammation. Vascular involvement, such as deep vein thrombosis and pulmonary embolism, although rare, has been very recently described [25].

A recent, large case–control study, in which 77 pregnancies in BD patients and 288 pregnancies in healthy controls were enrolled, showed that in BD patients the pregnancy complication rate was 26%, significantly higher than that observed in the control group (2%). Moreover, the frequency of spontaneous abortion in BD patients was significantly higher as compared with controls (20.8% *vs* 5.2%) [24]. Other pregnancy complications in BD patients mainly consisted of hypertension and gestational diabetes mellitus [24].

Although the lack of prospective studies makes it difficult to draw a firm conclusion, these data suggest that pregnancy does not have a deleterious effect on the maternal disease and may even ameliorate its course. However, it seems that BD may adversely affect pregnancy outcome. Therefore, the patients should be strictly monitored during pregnancy and post-partum, since relapses could occasionally occur and early diagnosis and prompt treatment can guarantee the most favourable pregnancy outcome.

Conclusions

The physiological adaptation of the immune system to pregnancy can potentially act as disease-modifying agent on the state of the vasculitis; conversely the immunological abnormalities characteristic of these conditions may jeopardize the fetal outcome [4].

Unfortunately, data on pregnancy of patients with systemic vasculitis are particularly poor due to their low incidence, low female to male ratio or their disease onset after the childbearing age. Prospective studies are lacking and most of the information we have derives from case reports and retrospective studies. Nevertheless, some general principles were elaborated, which could be summarized as follows: (i) patients should receive contraception advice at least while receiving high dose of cytotoxic medications (ii) pregnancies should be planned when the disease is in remission since it reduces maternal complications (e.g. pre-eclampsia) improving the chances of a successful pregnancy; (iii) patients should be strictly monitored during gestation and post-partum by a multidisciplinary team including rheumatologist, obstetrician and neonatologist; (iv) in the case of disease relapse an adequate treatment, even aggressive if necessary, should be recommended since active disease can be detrimental for fetus more than drugs; (v) pregnancies complicated by the onset of vasculitis have a particularly severe prognosis; in these cases, prompt treatment and very close clinical surveillance is indicated; (vi) in patients with systemic vasculitis, the risk of thromboembolic events is increased as pregnancy *per se* is associated with a thrombophilic milieu; therefore, a treatment with aspirin or heparin should be considered.

Rheumatology key messages

- Limited data are available on pregnancy outcome in vasculitic patients.
- It is strongly advised to plan the pregnancy and to closely monitor and adequately treat patients during pregnancy.

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