Review Article

Pregnancy and Systemic Vasculitis

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Abstract

The systemic vasculitides are rare diseases of vessel wall inflammation. They are classified according to the vessel wall size. Systemic vasculitis is usually diagnosed after the fifth decade of life, except Takayasu arteritis and Bechet's disease which can manifest earlier. The increase in understanding of etiopathogenesis and effective treatment strategies have significantly improved outcomes associated with vasculitis, and more patients are living longer than ever. Primary systemic vasculitis in women of reproductive age group poses a special challenge. The diseases as well as the drugs used in their treatment affect fertility. Vasculitis increases maternal and fetal complications during pregnancy. However, there is some immunological rationale to suggest that normal hormonal and immunological changes in the maternal body may improve the tolerance to certain Th1-modulated syndromes. The successful outcome of pregnancy depends on vasculitis activity status, type of immunosuppressive medications, and maternal comorbidities. The inherent risks and ethical dilemmas of conducting clinical trials in this group of patients remain an obstacle in collecting high-quality evidence. The pregnancy should be monitored closely by a specialist team comprising a rheumatologist, an obstetrician, and other specialties as per organ involvement to ensure a successful outcome.

Key Words: *Pregnancy, systemic vasculitis*

Introduction

The primary systemic vasculitides are a group of rare diseases characterized by vessel wall inflammation, which may result in stenosis, aneurysm, infarction, and/or hemorrhage. They are classified according to the vessel wall size and renamed recently at the 2012 Chapel Hill Consensus Conference.[1] The annual incidence of systemic vasculitis in the adult population is about 50/million in Northern Europe.[2] We do not have such detailed information from the Indian subcontinent. The focus of this paper is the interplay between vasculitis and pregnancy. The primary systemic vasculitis most likely to present at that age and affect pregnancy is Takayasu arteritis, but antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis and adult-onset IgA vasculitis are not uncommon.[3,4]

The interest in pregnancy outcomes in patients with primary systemic vasculitis is increasing and a result of increasingly improving results – increasing survival, sustained remission, safer drugs, etc., Vasculitis may be affected by the immunological changes in pregnancy, and the activity and damage of vasculitis may affect outcomes in pregnancy and related to fertility even before that. We discuss some of the problems pertaining to fertility and pregnancy in patients with vasculitis in this paper.

Changes in Immune System in Pregnancy

Pregnancy is a condition where the female body learns to tolerate a 50% foreign tissue. In a cohort of 33 patients with rheumatoid arthritis who had 45 pregnancies between them, improved outcomes were seen in cases with greater Class II incompatibilities between fetus and mother.[5] This suggests that maternal immunology bends to meet the requirements of tolerance. The resultant downregulation of "nonself" recognition may be responsible for amelioration of certain rheumatic diseases. There is some evidence to suggest that the hormonal changes in pregnancy lead to a Th2 shift in the prevalent cytokine profile.[6] At the same time, there may be an active downregulation of Th1 cytokines.[7] There is a reduction in the ability of neutrophils to produce respiratory burst[8] and perhaps

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other as yet not understood mechanisms. This may mean that diseases with predominant Th1 pathogenetic mechanisms ameliorate and those with Th2 cytokine overproduction are accentuated.

Effects of Systemic Vasculitis on Fertility

Infertility is defined as failure to conceive after 1 year of regular sexual intercourse. It is present in about 10% of normal couples. Loss of 2–3 consecutive pregnancies is defined as recurrent pregnancy loss and occurs in 1% of normal couples. Autoimmune diseases are rare cause of infertility and recurrent pregnancy loss.

Systemic vasculitis can directly affect organs of reproduction of both genders, leading to infertility.[9] Prior treatment of vasculitis with cyclophosphamide in women results in a diminished ovarian reserve as demonstrated by a fall in anti-Mullerian hormone.[10] There is some evidence that the effect of cyclophosphamide on fertility may be related to the number of viable oocytes at the time of receiving the chemotherapy. Therefore, it may take a smaller cumulative dose of cyclophosphamide to render older women infertile.[11] While this is of academic interest – the exact dose of cyclophosphamide required to adversely affect fertility in a woman is impossible to accurately determine. The authors now prefer rituximab in preference to cyclophosphamide (where clinically indicated) for remission induction in men and women in reproductive ages.[12] Other commonly used immunosuppressive agents in vasculitis seem to be relatively safer in this regard.[13] A nondrug-dependent reduction of anti-Mullerian hormone has been demonstrated in women with Takayasu arteritis[14] and Behcet's disease.[15]

Systemic vasculitis can be a life-threatening condition, and it is not unusual that in trying to treat the immediate problems, longer-term issues such as fertility and family planning are not considered. These issues significantly affect the quality of life and need to be addressed early on at the time of treatment and once again when discussing conception. Potentially, these patients may be offered cryopreservation of sperm or ovarian tissue. However, this is not common place in our practice. A Cochrane review of the use of gonadotropin-releasing hormone agonists during or before the use of chemotherapy concluded that its intramuscular or subcutaneous use resulted in a greater return to menstruation and ovulation. The authors concluded that its use should be recommended in women of reproductive age receiving chemotherapy.[16] While these discussions are important, in the Indian scenario, they should not be allowed to overtake the welfare of the patient to meet the family's concerns about future reproductive potential.[17]

Preconception Counseling

Pregnancy should be planned during a phase of sustained remission. However, patients in remission may have enough damage to adversely affect the fetus and the mother. Pregnancy should be avoided in patients with cardiac failure, pulmonary hypertension, uncontrolled hypertension, end-stage kidney disease, and tracheal stenosis. The antenatal planning must be led by a multidisciplinary team involving a vasculitis physician and an obstetrician. These pregnancies need specialist centers having established management protocols and requisite experience. Women on teratogenic drugs such as cyclophosphamide, mycophenolate, methotrexate, and leflunomide need effective contraception. Paternal exposure to rituximab, methotrexate, leflunomide, mycophenolate mofetil, and azathioprine does not need deferral for conception planning.[13] Intrauterine devices and implantable progesterone are effective options. Preconception assessment should include assessment of general health, infections, cardiovascular risk factors, assessment of end-organ damage, review of medications, previous pregnancy outcomes, smoking, and alcohol intake status. The vasculitis disease activity should be accurately assessed and patients with high activity should be treated aggressively and advised to delay the pregnancy till sustained remission is achieved. The patient should be assessed for hypertension, diabetes, renal function, liver function, and cardiac status. While planning pregnancy, teratogenic medication should be stopped with adequate washout and changed to pregnancy safe medications. In our practice, we use azathioprine and corticosteroids during this phase. There are very little data about rituximab, but the current British recommendations suggest conception after 6 months from the last infusion.[13]

Effects of Systemic Vasculitis on Pregnancy

In a British cohort, 51 pregnancies in 29 women with systemic vasculitis were compared to 156 pregnancies in 62 age-, body mass index-, and ethnicity-matched healthy pregnant controls.[3] Babies of mothers with vasculitis were born at a median gestational age of 36 weeks versus 40 weeks for controls ($P < 0.03$). The median birth weight for the babies with affected mothers was 3.0 kg versus 3.5 kg for the control babies ($P = 0.004$). Affected mothers suffered 13 miscarriages, three had preeclampsia, and two had an intrauterine death. In the control group, twenty patients had 27 miscarriages, one had preeclamptic toxemia, and one had an antepartum hemorrhage. This simple study of mothers with disparate vasculitis syndromes demonstrates the adverse outcomes of a chronic inflammatory condition needing immunomodulatory treatment on the babies and the mothers.[3] In a prospective Italian cohort[18] of 65 pregnancies in fifty women with systemic vasculitis, there was a higher incidence of preterm, particularly early preterm (<34 weeks) deliveries and cesarean sections (11% vs. 5% in general population, $P = 0.049$ and

48% vs. 31%, $P = 0.009$). Vasculitis-related complications occurred in 23 pregnancies (35%), with five severe events (8%) including three cases of transient ischemic attack.

Takayasu arteritis is perhaps the most relevant disease to discuss in this section. It specifically affects young women of childbearing age and is relatively more common in the Indian subcontinent and results in poor fetal outcomes.[19] In a retrospective Indian study,[20] 16 patients with Takayasu arteritis who had 29 pregnancies were compared to sixty matched controls. Twenty pregnancies were delivered by cesarean sections (71%). Significant maternal complications included pregnancy induced hypertension (100% vs. 2%; $P < 0.001$), preeclampsia (93% vs. 0%; $P < 0.001$), postpartum hemorrhage (17% vs. 2%; $P < 0.001$), and preterm labor (17% vs. 3%; $P < 0.001$). One mother died from a cerebrovascular accident. The affected mothers had 26 live births with an increased incidence of intrauterine growth restriction (IUGR) (52% vs. 2%; $P < 0.001$) and neonates requiring intensive support (59% vs. 5%; $P < 0.001$). In a much larger retrospective French study of 240 pregnancies in 96 patients with Takayasu arteritis, obstetric and maternal outcomes were analyzed stratifying for diagnosis before and/or at the same time as or after diagnosis.[21] Fifty-two women had 142 pregnancies before a diagnosis of Takayasu arteritis was made and compared to 98 pregnancies in 52 women with a concomitant diagnosis of Takayasu arteritis. There was a 13-fold higher rate of obstetric complications in women with a concomitant diagnosis and a 40% frequency of obstetric complications, including preeclampsia/eclampsia premature delivery and intrauterine fetal growth restriction or death.

Women with Behcet's disease seem to have relatively unaffected pregnancies. A systemic review of literature published in 2014 which included 11 case series and 21 case reports concluded that the disease was unchanged or ameliorated in most cases.[22] In a French series of 76 pregnancies in women with Behcet's disease,[23] the mean (standard deviation) annual relapse rate was 0.49 (0.72) during pregnancy and 1.46 (2.42) during the nonobstetric period. Colchicine seems to protect against relapses and venous thromboembolism is associated with increased obstetric complications (odds ratio 7.25, 95% confidence interval 1.21–43.46, $P = 0.029$).[23] For obvious reasons, the use of a combined oral contraceptive in patients with Behcet's disease is not recommended for contraception.

Data about the direct effect of other primary systemic vasculitides are case report material[24-28] and cannot be used to make any authoritative statements. In the experience of the authors, there is no obvious direct effect of ANCA-associated vasculitis on pregnancy in the absence of life-altering damage.

Effects of Pregnancy on Systemic Vasculitis and Pharmacotherapy

Pregnancy is not generally known to affect the course of systemic vasculitis – certainly not adversely. There is some evidence that Behcet's disease improves during pregnancy.[23] This is counter-intuitive considering that there is almost always a reduction of immunosuppression that is used. This may suggest that there is actually a true amelioration in the pathogenetic mechanisms where lower levels of immunosuppression may produce continued remission maintenance. Identification of flare can be crucial for maternal and fetal outcome. The more relevant clinical problem is distinguishing relapse from pregnancy-related complications. Hypertension, renal dysfunction, proteinuria, and microscopic hematuria may all be pregnancy complications rather than relapsing disease. There is a great requirement, usually unmet even in the western world, of multidisciplinary care of such patients by a vasculitis physician and an obstetrician with experience of dealing with complex medical cases. Relapses of vasculitis in pregnancy pose unique problems because of our inability to use conventional immunosuppression. Corticosteroids form the bulk of the management plan in such situations. The current opinion suggests that even minor relapses of systemic vasculitis may need more than just increased doses of corticosteroids.[12] Cyclophosphamide is not currently recommended in any trimester of pregnancy unless the situation is life-threatening.[13] Rituximab in the second and third trimester can be used with the understanding that there will be B-cell depletion in the neonate with the resultant immunosuppressive consequences.[13] The specific cautions of other drugs that can or should not be used during pregnancy and breastfeeding have been discussed in detail in the new British Society guidelines[13] but are briefly discussed below.

- Corticosteroids are compatible with in all pregnancy trimesters and breastfeeding. Pregnancy with hypertension, kidney disease, and fluid retention should be monitored closely. There is an independent risk of IUGR and in women on large doses of continuous steroids during pregnancy and breastfeeding; the baby may need monitoring for adrenal suppression
- Methotrexate, mycophenolate mofetil, and leflunomide have to be avoided during pregnancy and breastfeeding
- Cyclophosphamide is undoubtedly toxic to the fetus and breastfeeding should be stopped if cyclophosphamide is used. However, if the mother has a severe relapse which becomes life or limb threatening, and if rituximab is either not available or not indicated, there may not be a choice but to use it. There is anecdotal case report evidence of the use of cyclophosphamide in pregnancy[29]
- Rituximab has anecdotal data for its use during pregnancy.[30] If used, B-cell depletion should be

expected in the neonate with appropriate precautions taken for vaccination planning
- TNF-α inhibitors do not seem to pose a major teratogenic risk for babies.[31] When necessary and clinically indicated, the safest agent is certolizumab pegol. The large molecular size means that there is no transplacental transport. The use of other agents may mean appropriate alterations in vaccination schedules for the baby
- Intravenous immunoglobulins are agents that have long been used for many autoimmune disorders with little or no justification primarily because it seems to be a relatively risk-free approach. In ANCA-associated vasculitis, it does have a role in inducing remission in grumbling disease[32] and could be used in place of cyclophosphamide or rituximab in situations where the disease is not life-threatening. It would be clinically inappropriate in situations such as pulmonary hemorrhage or rapidly progressive renal disease where the situation will demand stronger immunosuppression
- Azathioprine is the safest drug during pregnancy and breastfeeding. Where possible, it should be used. However, it may not be the most appropriate drug where quick effect is desired.

In vasculitides which are mediated by humoral immunity and where there are demonstrably high titers of circulating antibodies, plasma exchange may be a safe and effective way to buy time and improve prognosis.[33]

Conclusions

Pregnancy is a unique immunological event which remains incompletely understood. However, there seems to be some scientific rationale to suggest that the changes in the hormonal and immunological milieu to tolerate the fetal tissue may also improve the tolerance to the disease. The systemic vasculitides are challenging to manage at the best of times and offer special challenges during pregnancy. The damage that the vasculitis does before pregnancy is of greater relevance in predicting maternal and fetal outcomes. Thankfully, there does not seem to be a direct link between pregnancy and relapsing disease. Recent advances in pharmacotherapy have given us several tools for managing vasculitis, but most of these drugs are toxic to the fetus. Treating a full-fledged relapse of vasculitis in a pregnant woman is not just medically but also socially challenging.

Planning of conception, prepregnancy counseling, and risk assessment for existing comorbidities is a paramount first step to achieve good pregnancy outcomes. Indeed, it may be the difficult role of the physician to advise against conception in certain situations. Remission of vasculitis activity at the time of conception is an important determinant for a successful pregnancy. Immunosuppression should be changed to pregnancy compatible before conception if possible. Managing the preconception and antenatal phases should be undertaken in a multidisciplinary fashion. We are never going to be able to collect high quality of evidence for managing these situations because of the inherent risks and ethical dilemmas of conducting clinical trials in this group of patients. Hopefully, concerted efforts will lead to the formation of registries with detailed data collection of outcomes. We have a long way to go, and the journey is going to be challenging, but it also promises to be fulfilling.

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Conflicts of interest

There are no conflicts of interest.

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