



A comprehensive guide for managing the reproductive health of patients with vasculitis

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Abstract | Vasculitides and their therapies affect all areas of the reproductive life cycle. The ACR, EULAR and the Drugs and Lactation database offer guidance on the management of the reproductive health of patients with rheumatic diseases; however, these guidelines do not address patients with vasculitis specifically. This Review discusses the guidance from multiple expert panels and how these recommendations might apply to men and women with vasculitis, including the safety of contraception, use of assisted reproductive technology, preservation of fertility during cyclophosphamide therapy, disease management in pregnancy and the use of medications compatible with pregnancy and lactation. These discussions are augmented by the existing literature on vasculitis in pregnancy to enable physicians to provide comprehensive, precise and high quality care to patients with vasculitis. The contents of this Review, in conjunction with educational tools, serve to empower patients and physicians to participate in shared decision-making regarding pregnancy prevention, planning and management.

Vasculitides encompass a group of diseases defined by inflammation of the blood vessels that can clinically manifest as damage to single or multiple organ systems. The incidence of these diseases is 40 to 60 cases per 1 million persons¹. Given the rarity of vasculitis, limited information is available to guide reproductive health care for women with these diseases. Despite the dearth of available data, women living with vasculitis still need to make decisions about contraception, pregnancy and lactation to live the full life they desire.

Specific forms of vasculitis cause distinct challenges in reproductive health care. Some types of vasculitis, including giant cell arteritis (GCA) and Kawasaki disease, do not typically occur in women of reproductive age, whereas others, such as the Takayasu arteritis and Behçet disease, are more common during this time period. IgA vasculitis is most commonly diagnosed during childhood but can affect women of reproductive age. Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is often diagnosed after the reproductive years, but can occur in younger women, and now that treatment has moved away from ovary-toxic cyclophosphamide, more women with vasculitis are able to conceive. Because each of these forms of vasculitis affects different blood vessels, their effects on pregnancy are very different (TABLE 1). The safety of contraceptives and medications, however, is relatively universal between these diseases.

The ACR², the American College of Obstetricians and Gynecologists (ACOG)³, the European Board & College of Obstetrics and Gynaecology (EBCOG)⁴ and EULAR⁵ provide guidelines for managing the reproductive health care of patients with rheumatic diseases. However, none of the pre-existing recommendations specifically mentions vasculitis, and the most recent ACR vasculitis treatment guidelines do not mention reproductive health^{6–8}. In this Review, we discuss how these guidelines apply to the specific medical needs of women with vasculitis and their providers as they make these challenging and life-changing decisions. Although various case series, observational studies and literature reviews of pregnancies in women with Takayasu arteritis, Behçet disease, IgA vasculitis and AAV are available, to fill in the gaps we have also extrapolated other available data and guidelines to these unique, rare populations. Men and women with vasculitis require reproductive management similar to patients with systemic lupus erythematosus (SLE) and anti-phospholipid (aPL) syndrome (APS) but additional considerations are needed for disease activity and pregnancy complications including structural vascular lesions (stenosis and aneurysms), renopulmonary syndrome, fetal loss and spontaneous abortion. Proactive pregnancy prevention and planning for women with vasculitis is important, and various resources to guide provider–patient discussions are available, including

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Key points

- Rheumatologists have the opportunity to initiate discussions with patients with vasculitis regarding family planning to make proactive decisions leading to improved pregnancy planning, management and outcomes.
- Birth control options and infertility interventions for women with vasculitis depend on their risk of thrombosis, serological profile and comorbid conditions.
- The majority of pregnancies in patients with vasculitis can be successful with the use of advanced family planning, medications compatible with pregnancy and lactation, and multidisciplinary collaboration among specialists.
- Vasculitis exacerbations and pregnancy complications can present with similar and overlapping clinical manifestations.
- Multiple expert panels provide guidelines and risk stratification regarding medication use in pregnancy and breastfeeding that can be applied to patients with vasculitis.

those from the Vasculitis Foundation (Supplementary Fig. 1). To improve our understanding of pregnancy in patients with vasculitis and to help inform and create data-driven approaches to clinical guidance and management, women with vasculitis can sign up to the [Vasculitis Pregnancy Registry \(VPREG\)](#).

Classification and epidemiology

Vasculitides are classified by the size of the inflamed blood vessels (small, medium and large). According to the 2012 revised Chapel Hill Consensus Conference⁹, large vessel vasculitis (LVV) encompasses those vasculitides that affect the aorta and its major branches. The main types of LVV are Takayasu arteritis and GCA. Medium vessel vasculitides, such as polyarteritis nodosa (PAN) and Kawasaki disease, affect visceral arteries, veins and initial branches. The small vessel vasculitides, affecting the arterioles, capillaries, venules and veins, are further delineated into AAV (granulomatosis with polyangiitis (GPA), eosinophilic granulomatosis with polyangiitis (EGPA) and microscopic polyangiitis (MPA)) and immune complex vasculitides (that include IgA vasculitis, cryoglobulinaemic vasculitis and hypocomplementaemic urticaria vasculitis).

In 2022, the ACR and EULAR updated the classification criteria for AAV with weights assigned to specific clinical and serological characteristics to improve diagnostic sensitivity and specificity^{2,5}. For GPA, sinonasal congestion and positivity for cytoplasmic ANCA (c-ANCA) and/or anti-proteinase 3 (PR3) antibodies are the highest weighted criteria¹⁰. For MPA, perinuclear ANCA (p-ANCA) and/or anti-myeloperoxidase (MPO) positivity are the highest weighted criteria, followed by pauci-immune glomerulonephritis and interstitial lung disease¹¹. By contrast, the criteria for EGPA focus on eosinophilia, nasal polyps and obstructive airway disease, with ANCA positivity functioning as a negative item for classifying EGPA¹⁰. IgA vasculitis is an immune complex vasculitis that affects the small blood vessels and is characterized by palpable purpura, arthralgias, glomerulonephritis and enteritis¹². Some vasculitides, such as Behçet disease, have variable vessel involvement and do not fit into a single category (labelled as variable vessel vasculitis). Recognizing the size and location of the inflamed vessels within each disease is essential for monitoring and predicting organ involvement and for predicting the effect of the vasculitis on pregnancy.

A patient's age and ancestry contribute to the likelihood of developing specific forms of vasculitis. The vasculitides that are most likely to affect young women include Takayasu arteritis, Behçet disease and PAN^{13–15}. Takayasu arteritis is considered most common in patients of Asian ancestry with a typical age at onset ranging from ~20 to ~32 years¹³. Various HLA class I and II molecules are implicated in the susceptibility or development of Takayasu arteritis¹⁶. The age at onset of Behçet disease peaks between 20 and 30 years¹⁴, and this disease is thought to be more prevalent in men than in women, with a male to female ratio that varies from 1.5:1 to 5:1 (REF¹⁷). However, a Brazilian study revealed a female predominance¹⁷. The prevalence of Behçet disease is highest in areas that span the ancient Silk Road (including eastern Mediterranean regions and China)¹⁸. PAN, affecting those of European descent, is typically seen in the fifth to sixth decade of life and has a male to female ratio of 1.5:1 (REF¹⁵). AAV most commonly occurs in white populations and the peak age of onset ranges between 60 and 70 years¹⁹; however, a notable number of young patients also develop this form of small vessel vasculitis. Other forms of vasculitis are less likely to affect young women, and hence to affect pregnancy. IgA vasculitis most commonly affects children between the ages of 4 and 7 years²⁰. It remains rare in the adult population, with an annual incidence of 0.1–1.8 per 100,000 individuals²¹. Disease is more frequent in males, with a male to female ratio of 1.5:1 (REFS^{21,22}). GCA mainly affects patients who are aged 50 years or older, with the highest incidence occurring in Northern Europe, especially Scandinavian countries; hence, this disease is unlikely to affect pregnancy.

Reproductive health of female patients**Family planning**

Taking a proactive approach to reproductive health can have a lasting, positive affect because the timing of pregnancy is a crucial variable in terms of optimizing pregnancy outcomes for mother and infant. The EULAR, EBCOG and ACR reproductive health guidelines strongly recommend considering pregnancy in the context of quiescent or low activity of the woman's rheumatic disease^{2,4,5}. If a woman with vasculitis conceives when her vasculitis is active, she is at increased risk of miscarriage, intrauterine growth restriction, prematurity and pre-eclampsia²³. When these risks are present, patients and providers might need to make difficult decisions about initiating therapy that would control disease but could potentially harm the fetus. According to the 2020 ACR reproductive health guidelines, some disease manifestations, such as pulmonary arterial hypertension, renal dysfunction and heart failure, could serve as contraindications to pregnancy². Although these conditions are not listed as contraindications in the EULAR guidelines⁵, they are recognized as notable threats to the health of the patient and pregnancy. EBCOG recommends counselling against pregnancy if the patient has had active lupus nephritis, severe renal impairment, severe pulmonary arterial hypertension, advanced heart failure or stroke within the prior 6 months⁴. If women with vasculitis have any of the listed

Table 1 | Stratification of potential pregnancy and vasculitis complications by disease type

Type of vasculitis	Potential pregnancy complications	Signs of active vasculitis	Characteristics of high risk patients	Evaluation for pregnancy risks	Intervention
Small vessel (GPA, MPA and EGPA)	Preterm delivery, pre-eclampsia, bleeding diathesis, spontaneous abortion, low birthweight, intrauterine growth restriction, respiration complications and decreased renal function	Renal insufficiency or failure, pulmonary haemorrhage, rash, joint swelling and fever	Active renal disease (proteinuria (>1 g per day) or active glomerulonephritis) and severe lung disease (recent pulmonary haemorrhage or severe decrease in lung function)	Urinalysis (microscopy and urine protein to creatinine ratio), serum creatinine, pulmonary function tests and chest imaging	Control active disease prior to conception and during pregnancy with pregnancy-compatible medications Daily low-dose aspirin to decrease the likelihood of pre-eclampsia
Medium vessel (PAN)	Hypertension, proteinuria, preterm birth and intrauterine growth restriction	Proteinuria, hypertension and abdominal pain	Uncontrolled hypertension and renal failure	Blood pressure monitoring and angiography to check the status of blood vessels	Control of hypertension with pregnancy-compatible medications Control active disease prior to conception and during pregnancy with pregnancy-compatible medications Daily low-dose aspirin to decrease the likelihood of pre-eclampsia
Large vessel (Takayasu arteritis)	Pre-eclampsia and low birthweight	Central occult hypertension, heart failure and renal insufficiency or failure	Renal artery and/or abdominal aorta involvement, aortic regurgitation and heart failure	Blood pressure monitoring and angiography to check status of the blood vessels	Control hypertension and active disease prior to conception and during pregnancy with pregnancy-compatible medications Daily low-dose aspirin to decrease the likelihood of pre-eclampsia
Behçet disease	Preterm delivery and spontaneous abortion	Worsening of oral ulceration, eye inflammation and arthralgias	Prior arterial or venous thrombosis	Evaluate for prior thrombosis	Anticoagulation therapy if the patient has a history of prior thrombosis Daily low-dose aspirin to decrease the likelihood of pre-eclampsia
IgA vasculitis	Preterm delivery, spontaneous abortion and gestational hypertension	Palpable purpura, abdominal pain, arthralgias and haematuria	Uncontrolled hypertension and renal failure	Blood pressure monitoring and urinalysis (microscopy and urine protein to creatinine ratio) and serum creatinine measurements	Control hypertension Active disease usually self resolves, but recalcitrant disease might require control with pregnancy-compatible medications

EGPA, eosinophilic granulomatosis with polyangiitis; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; PAN, polyarteritis nodosa.

clinical features or manifestations, discussions with their rheumatologist and obstetrician regarding maternal morbidity and mortality if pregnancy were pursued is warranted.

The ACR, EULAR, EBCOG and ACOG guidelines strongly suggest that medical professionals engage women in conversations about family planning on a regular basis²⁻⁵. Exploring the woman’s desire, or lack thereof, to have children can help guide recommendations regarding contraception, infertility and medication regimens. Early initiation of these conversations also allows collaboration with specialists including specialists in maternal fetal medicine, obstetrics–gynaecology and reproductive endocrinology. A possible strategy to start these conversations is via the **One Key Question** online tool, beginning with the question “Would you like to become pregnant in the next year?”. This data-driven tool gives patients the opportunity to discuss if, when and under what circumstances they want to get pregnant. Resources offered by this tool enable providers to undergo interactive training to understand the root

causes of mistimed pregnancies, poor birth outcomes and disparities in maternal and infant health. The ACR reproductive health guidelines note that patients are appreciative of this discussion with their rheumatologist, who are viewed by the patients as “the doctors who know them and their medications best”².

Contraception

To make informed and personal decisions, patients should be made aware of the safe and effective contraception options available. Selection of contraception depends on both the safety of contraception and its efficacy (Supplementary Fig. 1). For an individual woman, the use of contraception depends heavily on her motivation to avoid pregnancy and her comfort with the form of contraception; these factors can be influenced by the provider but are often dependent on the lived experience of the woman outside the context of her vasculitis. Respecting the woman’s desire, motivations and opinions about contraception is essential to effective and collaborative pregnancy planning. Comprehensive guidance

to contraception that can facilitate provider–patient discussions is available from the Vasculitis Foundation (Supplementary Fig. 1).

EULAR stresses the importance of considering disease-related risk factors (such as disease activity level and risk of thrombosis) and non-disease-related risk factors (such as hypertension, obesity, tobacco use and family history of hormone-related cancers) when counselling about contraception⁴. Effective birth control is particularly important for women taking teratogenic medications. Several medications used to treat vasculitis increase the risk of major birth defects, including methotrexate, mycophenolate mofetil and cyclophosphamide². In women taking these medications, avoiding pregnancy will decrease the likelihood of suffering the emotionally challenging situations of deciding to continue or terminate a pregnancy, pregnancy loss or delivering an infant with a permanent birth defect.

The ACR strongly recommends the use of effective contraception (hormonal contraceptives or intrauterine devices) over less effective options or no contraception in fertile women with a rheumatic disease (that is, women of reproductive age without documented menopause), with special considerations for those patients who have SLE or those who are positive for aPL antibodies owing to the risk of thrombosis². Although the ACR reproductive health guidelines and EULAR recommendations define women at high risk of thrombosis as those who are positive for aPL antibodies and/or have moderate to highly active SLE^{2,5}, this guideline might also be applied to women with vasculitis who are considered at high risk of thrombosis. The risk of thrombosis is highest during early and active vasculitic disease, but a procoagulant state might also be present in some patients with non-active AAV²⁴. In the WeCLOT study, an observational cohort study that included 167 patients with GPA, the risk of venous thrombosis in patients with GPA was seven times higher than in patients with SLE²⁵. Despite this increased risk of thrombosis in patients with vasculitis, no formal studies have assessed the risk

associated with oestrogen-containing birth control in this population.

Emergency contraception (that is, progesterone-only contraceptives such as levonorgestrel) should also be discussed for patients with vasculitis because the risks associated with this contraceptive are lower than those associated with unplanned pregnancy. Levonorgestrel is widely available and has no medical contraindications²⁶, including for women with any form of vasculitis. Emergency contraception will not cause an abortion, which is a common misconception among patients that might limit its use²⁷. Instead, this contraceptive prevents the sperm and egg from meeting and hence prevents fertilization²⁷. Levonorgestrel is widely available in North America and Europe. The need for prescription to obtain this contraceptive is dependent on country-specific legislation.

Fertility preservation

High doses of cyclophosphamide can cause ovarian insufficiency, leading to infertility and/or premature menopause^{28,29}. To avoid this adverse effect, EULAR recommends and ACR conditionally recommends monthly gonadotropin-releasing hormone agonist therapy (such as leuprolide) in women receiving monthly cyclophosphamide infusions^{2,5}. Leuprolide is typically given as a 3.75 mg monthly dose, with the first dose being administered at least 10 days prior to the cyclophosphamide infusion to avoid cyclophosphamide exposure during the initial surge of oestrogen caused by leuprolide. This recommendation originates from studies in women undergoing treatment for breast cancer whose ovarian function remained stable with this intervention³⁰. Fewer data are available regarding patients with rheumatic diseases, but the outcomes of the existing studies were positive^{31–34}. Higher cumulative doses of cyclophosphamide and older age at the time of cyclophosphamide treatment both increase the risk of ovarian failure^{28,29}. Although women who receive high dose oral or intravenous cyclophosphamide have a high risk of ovarian damage, women who receive a lower dose, such as the Euro-Lupus regimen of 500 mg intravenous cyclophosphamide every 2 weeks for six doses, have little ovarian damage³⁵.

Infertility and assisted reproductive technology

For women with infertility or women who wish to freeze eggs prior to cyclophosphamide therapy for later use, the ACR guidelines recommend avoiding assisted reproductive therapy (ART) when vasculitis is active². Women considering ART should discuss options appropriate for their clinical situation with a reproductive endocrinologist. BOX 1 summarizes the various types of ART. For women with inactive vasculitis who have a limited risk of thrombosis, ART can proceed according to the standard of care. EULAR recommends low-dose aspirin or low molecular weight heparin (LMWH) during ART according to the patient's individual risk profile⁵. The ACR recommends LMWH during ART for women with aPL antibodies³. These recommendations can be extrapolated to women with vasculitis at high risk of thrombosis.

Box 1 | Types of assisted reproductive technology

- Egg retrieval for egg and/or embryo freezing: this procedure enables the possibility of a future pregnancy, which can then be delayed by months to years. Patients can continue their immunosuppressive and biologic therapies (including methotrexate and mycophenolate mofetil) during ovarian stimulation and cryopreservation without concern for teratogenesis. If a patient decides to freeze an embryo, the egg is fertilized prior to the freezing process. Low-dose aspirin should be stopped 3 days before egg retrieval and resumed the following day.
- Surrogate: if a woman (donor) chooses to have another woman (surrogate) carry her pregnancy, the donor can continue to take vasculitis medications while the eggs are being retrieved, then continue therapy while the pregnancy is carried safely without possible teratogen exposure.
- Embryo transfer: when an embryo is transferred into the uterus of a woman with vasculitis, her vasculitis should be under control via the use of a pregnancy-compatible medication regimen before pursuing the transfer. Patients taking low molecular weight heparin (LMWH) to decrease the risk of thrombosis should stop this therapy at least 12 h prior to the procedure and resume LMWH the very same day as long as no bleeding occurs. All patients who are not taking low dose aspirin during the ovarian stimulation period should start low dose aspirin on the day of the embryo transfer as pre-eclampsia prophylaxis for the expectant pregnancy, usually in combination with LMWH (which should be continued during pregnancy).

Pregnancy and breastfeeding

Planning pregnancy is a crucial aspect of reproductive health care for women with rheumatic disease. Timing pregnancy to coincide with both disease quiescence and pregnancy-compatible medications increases the likelihood of pregnancy success. As such, rheumatologists have the opportunity at every clinic visit to address family planning goals to ensure an effective pregnancy planning process. Prior to and during pregnancy, rheumatologists should collaborate with other specialists to provide comprehensive care and close monitoring dictated by the patient's type of vasculitis and disease manifestations.

Pregnancy and vasculitis

The physiological changes that occur during pregnancy, such as an increase in blood volume, hormonal changes and fluid shifts, can affect the functionality of organs previously or currently affected by vasculitis³⁶. For example, a woman with valvular disease or cardiac dysfunction from Takayasu arteritis might have difficulty adjusting to the increased blood volume that occurs during pregnancy. Quiescent and well-controlled vasculitis with thorough evaluation of all sequelae will aid physicians in anticipating complications and the need for close monitoring. Active vasculitic disease can complicate the ability to assess and stratify pregnancy risks, which further emphasizes the importance of planned pregnancies. Active vasculitis can worsen hypertension, especially in the setting of renal disease, and compromise critical blood flow to the placenta for fetal development, resulting in increased risk of maternal and fetal complications²³.

Most women with vasculitis can have a successful pregnancy, although they are all at higher risk of pregnancy complications owing to their disease than patients without vasculitis^{34,37–44} (TABLE 1). Vasculitis complications during pregnancy are dependent on the type of vasculitis, but generally include preterm delivery, fetal loss, intrauterine growth restriction, severe hypertension and pre-eclampsia³⁷ (TABLE 2), and some diseases of pregnancy can mimic vasculitis activity (TABLE 3). The best approach to mitigating these risks is to ensure that a woman's vasculitis is under good control with pregnancy-compatible medications prior to and throughout pregnancy (TABLE 4).

Pregnancy planning and monitoring

Importance of a multidisciplinary approach. The pregnancy interests of a patient should be discussed often to ensure that pregnancy planning can begin several months to years prior to conception. This approach allows the patient to understand her risks in pregnancy and provides time to build a multidisciplinary team, make medication changes and ensure vasculitis activity is controlled prior to conception.

Given the complexities of pregnancy in women with vasculitis, all pregnant women with vasculitis should ideally consult with a maternal–fetal medicine physician (also known as a high-risk obstetrician or perinatologist). Although some patients can be followed by their local, low-risk obstetrician, the maternal–fetal medicine

provider will give important guidance regarding medication use and pregnancy monitoring. Additionally, a patient's other organ-specific specialists should be involved in pregnancy planning and management.

Differentiating active vasculitis from pregnancy complications. An important concern regarding vasculitis during pregnancy is differentiating active vasculitis from pregnancy complications. For example, glomerulonephritis from AAV can present similarly to pre-eclampsia with proteinuria, oedema and hypertension; furthermore, microangiopathic haemolytic anaemia can mimic haemolysis, elevated liver and low platelets (HELLP) syndrome^{45–47} (TABLE 3). Physiological changes of pregnancy include an increase in intravascular volume and an increase in glomerular filtration rate, which can exacerbate pre-existing cardiac and renal abnormalities³⁶.

Women with vasculitis are at increased risk of hypercoagulability and thrombosis^{24,25}, as previously discussed. Pregnancy itself induces a state of hypercoagulability that results in a compounded risk of thrombosis for pregnant women with vasculitis⁴⁸. The treating rheumatologists should be aware of presentation overlap between active vasculitis and pregnancy complications as anchoring on a diagnosis can increase the risk of morbidity and mortality for the mother and baby. Rheumatologists and maternal–fetal medicine physicians should collaborate to determine the aetiology of a presentation.

Monitoring rheumatic disease during pregnancy. The ACR reproductive health guidelines recommend that rheumatologists evaluate pregnant patients at least once per trimester and the frequency of rheumatological follow-up should be individualized according to the needs of the patient². The primary role of the rheumatologist is to assess the level of vasculitis activity and adjust the anti-rheumatic medications accordingly; these tasks are typically outside the scope of practice for obstetricians or maternal–fetal medicine providers. EULAR recommends completing an evaluation of the patient by umbilical and uterine artery doppler ultrasonography at 20–24 weeks to assess the risk of placenta-associated pregnancy disorders (for example, pre-eclampsia and intrauterine growth restriction), which can affect the mode and timing of delivery⁵. Rheumatologists can stratify patients according to their risk of pregnancy complications by assessing for the presence of anti-Ro and aPL antibodies, which include IgM, IgA and IgG anti-cardiolipin antibodies, anti- β_2 glycoprotein antibodies and lupus anticoagulant. Although these autoantibodies are more commonly observed in patients with SLE than in patients with vasculitis, treating providers can screen to assess for additional risks if they have concerns regarding overlap syndrome^{49,50}. If the patient is positive for anti-Ro antibodies, fetal echocardiograms are recommended by the ACR, EBCOG and EULAR between 18 and 24 weeks to assess for fetal atrioventricular block^{2,4,5,51}. Hydroxychloroquine decreases the risks of neonatal lupus including atrioventricular block and is recommended by the ACR, EBCOG and EULAR for all women who are pregnant and are positive for

anti-Ro antibodies^{2,4,5,52}. For aPL antibody-positive women, whether anticoagulation therapy is advisable will depend on whether the disease is classified as obstetric APS or thrombotic APS and whether the patient has a history of thrombosis, and can be discussed with a haematologist.

Medication management during pregnancy

Fortunately, multiple medications used to manage vasculitis are considered compatible with pregnancy (TABLE 4). These include azathioprine, colchicine, TNF inhibitors, cyclosporin, tacrolimus and NSAIDs. Glucocorticoids are considered safe during pregnancy, but their use

Table 2 | Pregnancy outcomes in women with vasculitis

Study	Number of pregnancies	Pregnancy losses, n (%) ^a	Preterm deliveries, n (%) ^b	IUGR or low birthweight, n (%)	Caesarean delivery, n (%)	Pre-eclampsia or gestational hypertension, n (%)	Other
ANCA-associated vasculitis							
Pagnoux et al. (2011) ³⁴	16	3 (18.8)	6 (37.5)	4 (25)	6 (37.5)	7 (43.8)	Acute maternal heart failure: 1 (6.25%) PROM: 2 (12.5%)
Gatto et al. (2012) ³⁸	79	10 (12.7)	25 (31.6)	14 (17.7)	22 (27.8)	8 (10.1)	Maternal death: 5 (6.3%)
Fredi et al. (2015) ³⁹	16	1 (6.3)	4 (25)	2 (12.5)	9 (56.3)	0 (0)	–
Nguyen et al. (2021) ³⁷	20	0	5 (25)	6 (30)	7 (35)	2 (10)	–
Behçet disease							
Gatto et al. (2012) ³⁸	229	21 (9.2)	3 (1.3)	2 (0.87)	12 (5.2)	3 (1.3)	–
Iskender et al. (2014) ⁴⁰	49	8 (16.3)	6 (14.6)	3 (7.3) with only low birthweight	17 (41.4)	8 (19.5) with gestational hypertension and IUGR	NICU admission: 5 (12.2%)
Fredi et al. (2015) ³⁹	31	3 (9.7)	6 (21.4)	3 (9.68)	10 (32.3)	8 (28.5)	1 pregnancy loss past 10 weeks
Clowse et al. (2013) ⁴¹	6	3 (60)	0	NR	NR	NR	–
Orgul et al. (2018) ⁴²	66	18 (27.3)	12 (24)	12 (24)	NR	2 (4)	Higher rate of preterm labour and low birthweight in patients treated with colchicine
Barros et al. (2021) ⁴³	49	12 (24.5)	3 (9.1)	9 (18.4)	16 (43.2)	0 (0)	–
Takayasu arteritis							
Gatto et al. (2012) ³⁸	214	30 (14)	35 (16)	42 (20)	78 (36)	92 (43)	Maternal death: 2 (0.9%)
Tanaka et al. (2014) ⁴⁴	27	0	3 (11)	4 (15)	9 (33)	4 (15)	80% of pregnant women with chronic hypertension had a stricture of the renal artery
Alpay-Kanitez et al. (2015) ¹⁰⁴	84	5 (6)	3 (4)	4 (5)	15 (18)	7 (8.3)	No neonatal abnormalities observed
Assad et al. (2015) ¹⁰⁵	38	0	16 (45.7)	12 (34.2)	24 (68.5)	12 (31.5)	More pregnancy complications in women with hypertension
Comarmond et al. (2015) ⁶⁸	98	9 (9)	8 (8)	5 (5) reported in combination with fetal death	16 (16)	21 (21)	Neonatal deaths: 3 (3%) Maternal new onset or worsening hypertension: 26 (26%)
Fredi et al. (2015) ³⁹	8	2 (25)	3 (50)	0 (0)	5 (83)	2 (33.3)	–
Gupta et al. (2020) ¹⁰⁶	38	10 (26.3)	2 (5.2)	6 (15.8)	NR	15 (39.4)	Gestational diabetes: 2 (5.2%)
Nguyen et al. (2021) ³⁷	12	1 (8.3)	3 (37.5)	0 (0)	1 (14.3)	2 (25)	Gestational diabetes: 1 (12.5%)
Polyarteritis nodosa							
Pagnoux et al. (2011) ³⁴	4	1 (25)	2 (50)	0 (0)	1 (25)	3 (75)	PROM: 3 (75%)
Fredi et al. (2015) ³⁹	4	0 (0)	2 (50)	2 (50)	1 (25)	1 (25)	–
IgA vasculitis							
Nossent et al. (2019) ¹⁰⁷	247	25 (10.1)	17 (8.3)	NR	57 (26.9)	27 (5.6)	Gestational diabetes: 19 (6.4%)

ANCA, anti-neutrophil cytoplasmic antibody; IUGR, intrauterine growth restriction; NICU, neonatal intensive care unit; NR, not reported; PROM, premature rupture of membranes. ^aExcluding therapeutic abortions. ^bPrior to 37 weeks gestation.

Table 3 | Distinguishing between active vasculitis and mimics during pregnancy

	Active vasculitis ^{108,109}	Pre-eclampsia ¹¹⁰⁻¹¹³	Chronic hypertension ¹¹⁰	Gestational hypertension ¹¹⁰	HELLP syndrome ^{45-47,114}
Traditional clinical features	Dependent on type of vasculitis	Headache, elevated blood pressure, vision changes and abdominal pain	Systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg	Systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg	Nausea, abdominal pain and elevated blood pressure
Timing	Any time	After 20 weeks gestation and postpartum	Onset before pregnancy or before 20 weeks gestation	Onset after 20 weeks gestation	Third trimester and postpartum
Proteinuria	Yes, if the vasculitis has renal involvement	Yes; ≥ 0.3 mg/mg (urine protein to creatinine ratio) or ≥ 300 mg/24 h (24-h urine protein test) or $\geq 1+$ (dipstick)	Stable if present	No	Can be present, but not necessary for diagnosis
Platelets	High	$< 100,000/\mu\text{l}$ in severe cases	Normal	Normal	Low
AST to ALT ratio	Normal	High	Normal	Normal	High
LDH	Normal	High	Normal	Normal	High
CRP	High	High	Normal	Normal	High
Uric acid	Normal	High	Normal	Normal	Can be elevated
Intervention	Increased immunosuppression and glucocorticoids	Blood pressure control, magnesium, betamethasone < 36 weeks and timely delivery	Blood pressure control	Blood pressure control	Blood pressure control, glucocorticoids and timely delivery

ALT, alanine aminotransferase; AST, aspartate transaminase; CRP, C-reactive protein; HELLP, haemolysis, elevated liver enzymes and low platelets; LDH, lactate dehydrogenase.

should be minimized to mitigate adverse effects. A vasculitis flare, particularly of internal organ disease, in pregnancy is probably riskier to the pregnancy than these medications. Nevertheless, some medications should be avoided, such as those medications known to cause major birth defects (teratogenic medications), particularly during the early stages of pregnancy. In this section, we discuss the best approach for managing patients with vasculitis during pregnancy and the safety of relevant drugs and medical interventions.

Discontinuation of teratogenic medications. Women should ideally discontinue medications known to cause major birth defects, including methotrexate, cyclophosphamide and mycophenolate mofetil, prior to conception² (TABLE 4). Despite this recommendation, some women will conceive on one of these medications; guidance for this situation is outlined in BOX 2.

The ACR guidelines recommend switching women from teratogenic to pregnancy-compatible immunosuppressant medications prior to conception². This switch should be followed by a waiting period during which the stability of vasculitis on the new medication can be assessed. The duration of this waiting period depends on the patient's personal risk of a vasculitis flare following the change in medication. The benefit of quiescent disease prior to conception is exemplified in SLE, for which disease activity 6–12 months prior to conception increases the likelihood of disease activity and possible complications during pregnancy⁵³. A 2013 study in 54 patients with SLE who were planning for pregnancy found that replacing mycophenolate mofetil with azathioprine in those with quiescent lupus nephritis rarely

led to disease flare and was associated with favourable pregnancy outcomes⁵⁴. Similar data are not available for women with vasculitis at this time; however, maintaining quiescent vasculitis by using pregnancy-compatible medications is the current best-practice approach².

Management of inactive vasculitis during pregnancy.

Initiation or escalation of the dose of pregnancy-compatible immunosuppressants should be considered prior to pregnancy to obtain or maintain vasculitis remission. These medications can include azathioprine, tacrolimus, cyclosporin, colchicine or TNF inhibitors². Given the periodic dosing of rituximab, which enables this drug to be effective for a prolonged period after a single dose, administering a dose of rituximab prior to conception can be an effective approach for controlling AAV disease activity.

The ACR recommends tapering glucocorticoids to an equivalent of less than 10 mg of prednisone daily, if possible, depending on the level of disease activity, to decrease the risk of adverse effects such as hypertension, intrauterine growth restriction and preterm birth^{2,55}. The maintenance dose of prednisone (≥ 10 –20 mg per day) is associated with an increased risk of preterm birth in women, with an odds ratio of 3.5 (REF.⁵). Additional pregnancy-compatible DMARD therapy is preferable to chronic high-dose glucocorticoid therapy and can improve disease control over the length of the pregnancy and postpartum period. Dexamethasone and betamethasone are fluorinated, synthetic glucocorticoids that readily cross the placenta². Fetal uptake of prednisone, on the other hand, is limited due to its conversion to inactive metabolites by placental 11- β -dehydrogenase

Table 4 | Medication recommendations during pre-conception, pregnancy and breastfeeding

	ACR ²	ACOG ³	EULAR ^a (REF. ⁵)	EBCOG ^b (REF. ⁴)	LactMed ^c	Notes
Azathioprine						
Pregnancy	++	+	+ (3C)	+	NA	Check thiopurine S-methyltransferase levels in mothers before initiating azathioprine; increased risk of preterm birth and fetal growth restriction in pregnant patients taking azathioprine, although how this affect relates to medication use versus maternal disease is unclear ^{82–85}
Breastfeeding	+/-	+	NA	+	+	Compatible; consider monitoring complete blood count in infants as cases of mild, asymptomatic neutropenia have been reported ⁸⁶
Colchicine						
Pregnancy	++	NA	NA	NA	NA	–
Breastfeeding	++	NA	NA	NA	+	Compatible; avoid breastfeeding within 4 h of dose to minimize infant exposure
TNF inhibitors						
Pregnancy	+/-	+	NA	+/-	NA	The ACR recommends continuing TNF therapy in first and second trimesters but consider discontinuing in the third trimester (except for certolizumab) if disease is under control to decrease transplacental transfer; by contrast, the Society for Maternal-Fetal Medicine recommends continuing TNF inhibitors in the third trimester ³
Breastfeeding	++	+	NA	+	+	Compatible; large protein molecules and IgG antibodies do not cross into breastmilk in high concentrations ⁸⁷
Cyclosporine and tacrolimus						
Pregnancy	+/-	+	+ (3C)	+	NA	Monitoring of blood pressure is recommended; these drugs are associated with an increased risk of preterm birth and growth restriction ⁸⁸
Breastfeeding	+/-	+	NA	NA	+/-	Compatible; consider monitoring infant drug levels if the infant shows signs of potential adverse effects
NSAIDs						
Pregnancy	+/-	NA	NA	+; contra- indicated beyond 32 weeks	NA	A FDA black box warning has been issued against NSAID use after 20 weeks due to oligohydramnios and closure of ductus arteriosus ⁸⁹ ; the ACR recommends NSAIDs over COX2-specific inhibitors
Breastfeeding	+/-	NA	NA	+	+/-	Compatible; ibuprofen is preferred over aspirin and naproxen owing to its extremely low levels in breastmilk, short half-life and safe use in infants at doses much higher than those transferred to breastmilk ⁹⁰
Rituximab						
Pregnancy	+	+	NA	–	NA	Discontinue when pregnancy is confirmed; can be used if organ-threatening or life-threatening disease occurs during pregnancy
Breastfeeding	++	+/-	NA	–	+/-	Compatible; large protein molecules and IgG antibodies do not cross into breastmilk in high concentrations ⁹¹
Cyclophosphamide						
Pregnancy	+/-	+/-	–	–	NA	Discontinue cyclophosphamide 3 months prior to conception owing to the high risk of birth defects with first trimester exposure ² ; can be considered for life-threatening and organ-threatening disease during the second and third trimesters
Breastfeeding	--	+	NA	–	+/-	This drug enters breastmilk in potentially toxic amounts and has highly toxic active metabolites that add risk to the infant ⁹² ; most sources consider breastfeeding to be contraindicated during cyclophosphamide treatment; the Academy of Breastfeeding Medicine recommends withholding breastfeeding for 72 h after a dose ⁹³
Methotrexate						
Pregnancy	--	–	--	–	NA	Stop 1–3 months prior to pregnancy; if a patient becomes pregnant while taking methotrexate, stop the methotrexate and start 5 mg folate daily
Breastfeeding	+/-	–	NA	–	+/-	Some evidence that breastmilk contains <1% of the maternal weight-adjusted methotrexate dose, which decreases within 24 h of weekly dosing ^{94,95} ; this level of transfer is unlikely to harm an infant and monitoring the infant's complete blood count and differential can be considered

Table 4 (cont.) | Medication recommendations during pre-conception, pregnancy and breastfeeding

	ACR ²	ACOG ³	EULAR ^a (REF. ⁵)	EBCOG ^b (REF. ⁴)	LactMed ^c	Notes
Mycophenolate mofetil						
Pregnancy	--	-	--	-	NA	Associated with cleft lip and palate, micrognathia, microtia and auditory canal abnormalities ^{96,97} ; expert opinion suggests that pregnancy should be delayed 6 weeks after discontinuing mycophenolate ⁹⁸
Breastfeeding	--	NA	NA	-	+/-	-
Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers						
Pregnancy	+/-	NA	NA	-	NA	Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers increase birth defects and should be avoided throughout pregnancy and especially in the second and third trimesters as they can cause severe, irreversible fetal renal injury ²
Breastfeeding	NA	NA	NA	+	+/-	Compatible; captopril is transferred to the breastmilk at low levels and so the amount ingested by the infant would be small ⁹⁹ ; adverse effects are not expected
Glucocorticoids						
Pregnancy	+	+	+(3C)	+	+	ACR conditionally recommends continuing low-dose (≤10 mg/day) prednisone during pregnancy if clinically indicated and tapering higher doses to <20 mg/day by adding pregnancy-compatible glucocorticoid-sparing agents if needed
Breastfeeding	+	+	NA	+	+	Only low levels of prednisone are transferred into breastmilk and no adverse effects have been reported

ACOG, American College of Obstetricians and Gynecologists; EBCOG, European Board & College of Obstetrics and Gynaecology; LactMed, Drugs and Lactation database; NA, not addressed. ^aFor the EULAR recommendations: the information in parentheses refers to the level of evidence (1–5) and grade of recommendation (A–D); -- indicates that this medication should be avoided. ^bFor the EBCOG recommendations: +, relatively safe, when absolutely necessary; -, to be avoided; +/-, not enough evidence. ^cFor all other guidelines: ++, strongly recommend continuing; +, recommend continuing; +/-, conditionally recommend; -, recommend discontinuing; --, strongly against continuing.

isoenzyme 2. Therefore, when using low to moderate doses of prednisone for vasculitis during pregnancy the majority of the drug will be metabolized prior to reaching the fetus².

Management of active vasculitis during pregnancy.

If active vasculitis is suspected, especially pulmonary and/or renal vasculitis, initiation or increased doses of glucocorticoids might be warranted including pulse-dose glucocorticoid therapy in organ-threatening or life-threatening situations. A glucocorticoid-sparing agent should also be considered with plans to taper glucocorticoids if medically safe². The ACR guidelines conditionally recommend the use of rituximab or cyclophosphamide if the woman has life-threatening or organ-threatening disease, such as glomerulonephritis or diffuse alveolar haemorrhage².

Although limited data are available on the safety of rituximab in pregnancy, this drug is being increasingly used prior to and early in pregnancy for diseases including vasculitis. However, rituximab dosing after 16 weeks gestation, when the medication is more likely to cross the placenta, puts the infant at risk of being born without B cells, a situation with unclear risks⁵⁶. The ACOG notes that although limited data are available regarding rituximab in pregnancy, the existing data are encouraging from a safety aspect^{57,58}.

Although cyclophosphamide has known teratogenic effects during the first trimester, some data suggest that this drug can be safely used in the second and third trimesters once organ formation is complete⁵⁹. In a 2005 case series of four pregnancies, fetal loss was 100% after

the use of cyclophosphamide during the first or second trimester for the treatment of SLE, although discerning the role of cyclophosphamide from the role of severe disease in causing pregnancy loss is difficult⁶⁰. Data on pregnant women with malignancies treated with chemotherapy, including cyclophosphamide, suggest that this drug can be used safely^{61,62}. The risks and benefits of these medications should be discussed with the patient in conjunction with appropriate specialists on the treatment team.

New therapies with limited pregnancy data.

Given the rapid development of treatment options for vasculitis, data regarding the safety of several medications during pregnancy and/or lactation are unavailable, including data on avacopan, abatacept, apremilast, belimumab, mepolizumab, tocilizumab and tofacitinib. A major concern is the potential effect of small molecules, including avacopan and tofacitinib, on the fetus and on the newborn, owing to likely transfer across the placenta and/or into breastmilk. Large protein molecules, including abatacept and mepolizumab, are unlikely to cross the placenta in the first half of pregnancy and only small amounts are expected in breastmilk^{63,64}. A panel of experts from Europe, Australia and New Zealand concluded that mepolizumab is possibly acceptable during breastfeeding⁶⁵. According to the ACR reproductive guidelines², all biologic drugs are expected to have minimal transfer owing to their large molecular size; therefore, continuation of these medications during breastfeeding is conditionally recommended.

Box 2 | Conception on a teratogenic medication

If conception occurs while the patient is taking a potentially teratogenic medication:

- Stop all teratogenic medications
- Start a prenatal vitamin
- If taking methotrexate during pregnancy: start folic acid 5 mg daily
- If taking leflunomide during pregnancy: start cholestyramine washout of 8 g three times daily for 11 days
- Estimate time of exposure: calculate based on timing of conception (estimated as 2 weeks after the first day of the patient's last menstrual period) and timing of teratogenic medication administration
- Assess vasculitis activity and transition to a pregnancy-compatible regimen (TABLE 4)
- Obstetrics: discuss the exposure with the patient and evaluate using ultrasonography
- Contact *Mother To Baby* or other country/region-specific teratogen resources for guidance

Risks relating to drug exposure during the first trimester:

- Mycophenolate mofetil: ~40% pregnancy loss; ~25% birth defects¹¹⁵
- Cyclophosphamide: ~50% pregnancy loss¹¹⁶; ~25% birth defects¹¹⁷
- Methotrexate: 40% pregnancy loss; ~7% birth defects¹¹⁸
- Leflunomide: no increase in pregnancy loss or birth defects with cholestyramine washout¹¹⁹

Management of hypertension in pregnancy. Hypertension during pregnancy increases the risk of poor placental development, which can lead to pregnancy loss, preterm birth, pre-eclampsia and fetal growth restriction⁶⁶. According to the 2020 ACOG clinical management guidelines, labetalol, hydralazine and nifedipine can be used for blood pressure control during pregnancy⁶⁷.

The prevalence of hypertension might be underestimated in women with Takayasu arteritis as a small number of these patients present with stenoses of all four extremity vessels or the abdominal aorta, leading to a misleadingly low blood pressure recording in one to four extremities⁶⁸. Blood pressure monitoring on all limbs, or limbs without stenosis, might help provide a more accurate assessment. At delivery, in the absence of a reliable approach to peripheral blood pressure monitoring, continuous arterial blood pressure assessments are required to avoid severe hypertension that could increase maternal morbidity.

Use of aspirin to prevent pre-eclampsia. The ACOG, ACR, EULAR and EBCOG recommend that women with one or more high-risk factors for pre-eclampsia (that is, a history of pre-eclampsia, multifetal gestation, renal disease, autoimmune disease, type 1 or type 2 diabetes mellitus and/or chronic hypertension) and women with more than one moderate-risk factor (that is, first pregnancy, age 35 years or older, a BMI of more than 30 kg/m² and/or a family history of pre-eclampsia) should receive low-dose aspirin (typically 81–162 mg) for pre-eclampsia prophylaxis^{2–5}. This therapy should be initiated before 16 weeks gestation and continued until delivery; such an approach can reduce the risk of preterm pre-eclampsia by 62% in women at high risk⁶⁹. The utilization of prophylactic aspirin to prevent pre-eclampsia has been extrapolated within the ACR guidelines to include women with SLE and APS². Given that women with all forms of vasculitis are at increased risk

of pre-eclampsia owing to placental dysfunction^{70,71}, this recommendation should also apply to them.

Use of regional anaesthesia. Anaesthesia during delivery is managed by an anaesthesiologist. For pain relief during delivery, regional anaesthesia prior to delivery in patients with vascular stenoses might control arterial pressure while also allowing neurological assessment in awake patients⁷². Neurological assessment during delivery is critical as a change in neurological status, such as altered mental status, could indicate a medical emergency. General anaesthesia can trigger a hypertensive response owing to inadequate anaesthetic depth prior to rapid sequence intubation⁷³, which might exacerbate pregnancy or vasculitic complications. In patients with difficult airways, such as patients with subglottic stenosis caused by GPA, regional anaesthesia permits the avoidance of airway manipulation.

Vaccination considerations

Chronic immunosuppression in patients with autoimmune conditions increases the risk of cervical dysplasia, vaginal cancers and vulvar cancers, all of which are associated with human papilloma virus (HPV) infection^{74–76}. According to EULAR, the HPV vaccine should be offered to young patients with stable and/or inactive SLE and/or APS³; given that the level of immunosuppression is similar in patients with vasculitis, the HPV vaccine might also be advisable for these patients. Although very rare, venous thromboembolic events have occurred following administration of the quadrivalent HPV vaccine; of 31 patients with such a venous thromboembolic event, 90% had a known risk factor for thrombosis, including APS in two⁷⁷. As vasculitis increases the risk of thrombosis, patients with vasculitis should be offered the vaccine following a discussion of their disease activity and risk of thrombosis with their rheumatologist. HPV vaccination during pregnancy is not recommended by the ACOG but can be administered in the pre-pregnancy or postpartum periods⁷⁸. Women with SLE exposed to immunosuppression are at particularly high risk of these malignancies; however, limited data are available for women with vasculitis⁷⁶. Papanicolaou (PAP) smear examination should be performed annually in heavily immunosuppressed patients (for example, patients taking cyclophosphamide) or in accordance with local screening guidelines for low-risk individuals⁷⁹.

According to the ACOG, all pregnant women should receive a tetanus toxoid, reduced diphtheria toxoid and acellular pertussis (Tdap) vaccine during each pregnancy between 27 and 36 weeks of gestation, and an inactivated influenza vaccination during the influenza season⁷⁸. Additional vaccinations can be considered in special populations. In women with lung disease or immunocompromising conditions including vasculitis, 23-valent pneumococcal polysaccharide vaccine (PPSV23) and 13-valent pneumococcal vaccine (PCV13) can be considered⁷⁸. However, whether to administer these vaccines should be jointly discussed by the patient and the patient's obstetrician. The measles–mumps–rubella (MMR) vaccination is a live attenuated vaccine and is

contraindicated in pregnancy⁷⁸; it should be administered in the pre-pregnancy or postpartum periods. In patients with vasculitis taking immunosuppressive medication, an MMR booster can be considered outside pregnancy after discussions with their rheumatologist⁸⁰. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccinations are recommended in all pregnant and lactating individuals⁸¹.

Breastfeeding

Breastfeeding should be discussed prior to delivery. The ACOG recommends exclusive breastfeeding for the first 6 months after delivery to optimize immunity and nutrition of the newborn, and recommends that, ideally, breastfeeding is continued until the child's first birthday². The ACR reproductive health guidelines also encourage all women with rheumatic disease to breastfeed if they choose to do so². Whether a woman breastfeeds is a personal choice, with some women not wishing to breastfeed or struggling to breastfeed owing to having a low milk supply, fatigue or illness. Regardless of how a woman feeds her infant, showing understanding and empathy will help the patient through this challenging period of her life.

Almost all medications used for vasculitis are considered compatible with breastfeeding^{2-5,82-99} (TABLE 4). All medications that are pregnancy-compatible are also lactation-compatible, including azathioprine, colchicine, low-dose glucocorticoids (<20 mg prednisone equivalent), TNF inhibitors, NSAIDs, cyclosporine and tacrolimus². For woman taking more than 20 mg prednisone equivalent daily, breastfeeding should be delayed for 4 hours after each dose. Biologic therapies, including anakinra, belimumab, abatacept, tocilizumab, secukinumab and ustekinumab, are also considered safe with breastfeeding as their very large molecular weight makes notable passage into breastmilk unlikely². If breastfeeding patients require NSAIDs for pain control, ibuprofen is the drug of choice owing to the low amount of the drug transferred to the breastmilk². Lactation information is not currently available for newly developed small-molecule medications (such as tofacitinib, baricitinib, upadacitinib and avacopan). Because of their small size, these drugs might transfer into breastmilk, so their use during breastfeeding is not currently advised. The [Drugs and Lactation database \(LactMed\)](#) is a free, online pharmaceutical database managed by the National Center for Biotechnology Information, that contains up-to-date information pertaining specifically to the safety and adverse effect profiles of medications during breastfeeding, and is a useful resource for patients and physicians.

Reproductive health of male patients

Family planning discussions involving men with vasculitis can be much simpler than for women. All anti-rheumatic medications are compatible with fathering a child except for cyclophosphamide and thalidomide, which should be stopped prior to conception². The ACR strongly recommends sperm cryopreservation prior to cyclophosphamide therapy to protect a man's ability to conceive a child². Cyclophosphamide

is toxic to developing sperm and can lead to permanent azoospermia due to damage of the spermatogonial stem cells in the testes¹⁰⁰. Sperm should be collected before treatment and even one frozen sperm sample can lead to a future pregnancy. Urologists can assist with acquiring sperm quickly in an acutely ill patient. Unfortunately, sperm that develop during cyclophosphamide therapy have a high degree of genetic damage¹⁰¹, making sperm collected in the days and weeks following cyclophosphamide treatment the most likely to be abnormal. For this reason, urologists recommend waiting at least 3 months after completion of therapy with chemotherapeutic agents such as cyclophosphamide before sperm collection or attempts at conception¹⁰². However, male patients might develop infertility after treatment with cyclophosphamide². The ACR strongly recommends against testosterone co-therapy for men receiving cyclophosphamide as evidence suggests that this approach does not help with preservation of fertility^{2,103}.

Conclusion

Although managing women and men with vasculitis throughout the reproductive cycle is complicated, most patients will have successful outcomes with the assistance of a multidisciplinary team and careful planning. Avoiding conception while taking teratogenic medications and/or during periods of active vasculitis can decrease the risks of suffering the emotional and medical tragedies associated with pregnancy loss, birth defects and preterm birth. Rheumatologists can help by having a proactive approach and addressing pregnancy prevention and/or planning at each visit. Guidance on birth control options is available from the Vasculitis Foundation (Supplementary Fig. 1), which can aid in such discussions.

Overall, for women with vasculitis who may want to become pregnant, performing disease-specific laboratory and imaging diagnostic tests prior to conception should enable anticipation of any potential complications, identification of additional interventions and monitoring requirements and the need for subspecialist collaboration throughout the pregnancy. Providers need to enquire about specific patient characteristics including history of thrombosis and the presence of anti-Ro autoantibodies as their presence might change the appropriate management approach during pregnancy. In patients with unexpected pregnancies, medications should be reviewed for teratogenicity, possible antidotal options should be sought, and medication-compatible and lactation-compatible alternatives should be discussed. Patients should be informed of the risk of miscarriage and fetal development abnormalities than can occur with exposure to the teratogenic medication. During pregnancy, rheumatologists should evaluate women with vasculitis at least once per trimester to assess for disease activity and the need for escalation of therapy. A reproductive endocrinologist should evaluate those men and women who are experiencing infertility issues and discuss the various fertility treatment options, which can be affected by vasculitis disease activity and treatment regimens.

To address the limited amount of data that are currently available on pregnancy management and outcomes among women with vasculitis, we encourage participation in the VPREG, which is an online, international, patient-driven registry in which pregnant women

with all types of vasculitis can enrol and provide information about their vasculitis activity, medications and pregnancy outcomes.

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Author contributions

Both authors contributed equally to all aspects of the article.

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M.E.B.C. and C.S. have collaborated closely with the Vasculitis Foundation to create a patient-oriented handout educating men and women with vasculitis on safe birth control options and pregnancy planning. This project was funded by an educational grant from UCB. UCB provided no guidance or comment on the content of the handout. These educational materials are referenced in this article to offer clinical tools to be used by rheumatologists. M.E.B.C. serves as a primary investigator for the Vasculitis Pregnancy Registry (VPREG). M.E.B.C. is a consultant to UCB and GSK and has received grants from GSK. C.S. has received an educational grant from UCB.

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