HHS Public Access

Author manuscript

Arthritis Care Res (Hoboken). Author manuscript; available in PMC 2015 March 19.

Published in final edited form as:

Arthritis Care Res (Hoboken). 2013 August ; 65(8): 1370–1374. doi:10.1002/acr.21983.

Pregnancy Outcomes Among Patients With Vasculitis

Megan E. B. Clowse, MD, MPH[1], **Rachel L. Richeson, PhD, MPH**[2], **Carl Pieper, DrPH**[1], **Peter A. Merkel, MD, MPH**[3], and **for the VASCULITIS CLINICAL RESEARCH CONSORTIUM**

[1]Duke University Medical Center, Durham, North Carolina

[2]Duke University School of Nursing, Durham, North Carolina

[3]University of Pennsylvania School of Medicine, Philadelphia

Abstract

Objective—Pregnancy outcomes of patients with vasculitis are unknown, but are of great concern to patients and physicians. Through an online survey, this study assessed pregnancy outcomes among patients with vasculitis.

Methods—Participants in the Vasculitis Clinical Research Consortium Patient Contact Registry were invited to respond to an anonymous, internet-based survey that included questions about pregnancy outcomes, the timing of pregnancy relative to a diagnosis of vasculitis, and medication use.

Results—A total of 350 women and 113 men completed the survey. After a diagnosis of vasculitis, 74 pregnancies were reported by women and 18 conceptions were reported by men. The rate of pregnancy loss was higher among women who conceived after a diagnosis of vasculitis compared to those who conceived prior to diagnosis (33.8% versus 22.4%; $P = 0.04$). Among women, the rate of preterm births increased significantly for pregnancies conceived after a diagnosis of vasculitis relative to those conceived before diagnosis (23.3% versus 11.4%; $P = 0.03$). Only 18% of women reported worsening of vasculitis during pregnancy, but those who experienced increased vasculitis activity were more likely to deliver preterm. Exposure to cyclophosphamide or prednisone did not appear to impact pregnancy outcomes; however, the number of pregnancies among women taking these medications was small. Among the pregnancies conceived by men with vasculitis, the timing of diagnosis had no significant effect on the rate of pregnancy loss.

Conclusion—Women who conceived after a diagnosis of vasculitis had a higher rate of pregnancy loss than those who conceived prior to diagnosis. Vasculitis did not worsen during the majority of pregnancies conceived after diagnosis.

Address correspondence to Megan E. B. Clowse, MD, MPH, Box 3535, Trent Drive, Durham, NC 27710. megan.clowse@duke.edu.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Clowse had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Clowse, Richeson, Pieper, Merkel.

Acquisition of data. Clowse, Richeson, Merkel.

Analysis and interpretation of data. Clowse, Pieper, Merkel.

Introduction

Although vasculitis can cause significant morbidity and mortality, improved therapies now help many patients to survive and live full lives following diagnosis. For some, this will include building a family despite the presence of vasculitis. Because of the relative rarity of pregnancies among patients with vasculitis, little is known about associated risks, success rates, or treatments associated with such pregnancies. Many questions remain unanswered for women and men who develop vasculitis prior to conception, including whether their disease or medications will harm the fetus, how pregnancy will impact their own health, and what the consequences of prior therapies, especially cyclophosphamide, may have on pregnancy outcomes.

Our goal was to identify pregnancies that occurred within a large cohort of women and men with vasculitis and assess whether such pregnancies were at greater risk for adverse outcomes and whether vasculitis activity increased during pregnancy.

Patients and methods

Study design

All registrants of the Vasculitis Clinical Research Consortium (VCRC) Patient Contact Registry (online at www.RareDiseasesNetwork.org/VCRC/Registry) were invited via e-mail to participate in a reproductive health questionnaire. The VCRC Patient Contact Registry, an internet-based resource open to individuals based upon a self-report of a vasculitis condition, notifies all registered participants about research projects for which they may be eligible. Although registry documents are currently only in English, participants from all parts of the world are invited to join.

This study was approved by the Institutional Review Boards of both the University of South Florida and Duke University. Invitations were sent by e-mail to registry participants at 3 separate times: February, March, and April 2011. The patients provided consent electronically. The study questionnaire had different versions provided for women and men. Skip logic was employed to guide participants to specific sets of questions based on responses. Participants were given the option either to simply report the number of pregnancies and their outcomes, or to provide more detailed information for each pregnancy.

Due to the anonymity of this study, we could not confirm the diagnosis of vasculitis through medical record review. To help identify participants with a diagnosis of vasculitis, we asked all participants to state the type of vasculitis they had, the type of doctor who established their diagnosis, and the medications they had taken to treat vasculitis. We excluded participants who reported not being diagnosed by a specialist and never having taken an immunosuppressant other than glucocorticoids for their vasculitis, since the likelihood that such patients had systemic vasculitis was low.

Participants who reported a diagnosis of granulomatosis with polyangiitis (Wegener’s) (GPA), microscopic polyangiitis (MPA), eosinophilic granulomatosis with polyangiitis

(Churg Strauss) (EGPA), polyarteritis nodosa (PAN), Behçet's disease (BD), or Takayasu arteritis (TAK) were included in this analysis.

Participants were asked to report the total number of pregnancies they had carried (women) or fathered (men), as well as the outcomes of live birth, pregnancy loss, or preterm birth. For pregnancies that occurred following diagnosis with vasculitis, participants were asked to report all medications for vasculitis that they took within 3 months prior to conception (men) and/or during pregnancy (women). Women were asked whether their vasculitis disease activity improved, worsened, or was unchanged during pregnancy.

Statistical analysis

We performed separate analyses for women and men. In most analyses, all forms of vasculitis were grouped.

Outcomes for pregnancies conceived before the onset of vasculitis were compared with those for pregnancies conceived after a diagnosis of vasculitis, with the lack of independence between multiple pregnancies in the same person taken into account. Cochran-Mantel-Haenszel statistics were calculated to assess the differences between pregnancies conceived prior to and following the diagnosis of vasculitis. For participants who reported more than one pregnancy, a generalized estimating equation was used to adjust for the lack of independence among these pregnancies.

Results

At the time of this survey, the VCRC Patient Contact Registry included 2,764 participants. A total of 463 participants (17%) completed the questionnaire. VCRC participants who responded to this survey were, on average, younger and more likely to be women than nonrespondents. For reference, 31% of VCRC registrants are men, whereas only 25% of respondents were men ($P < 0.01$); the mean age for the entire VCRC cohort is 51.0 years, compared to age 47.0 years for female respondents and age 54.6 years for male respondents.

Women

A total of 350 women responded to the questionnaire, 328 of whom were included in this analysis. Nine women were removed from the analysis because they had been neither diagnosed by a specialist nor treated with immunosuppressant medications beyond prednisone; another 13 women were excluded because they reported having a form of vasculitis not encompassed by this study. None of the women excluded from the study had a pregnancy following a diagnosis of vasculitis. The vasculitides reported included GPA in 140 women, MPA in 22, EGPA in 59, PAN in 18, BD in 43, and TAK in 46. The mean ± SD age at diagnosis was 39.7 ± 14.1 years (range 10–78 years) and varied between diagnoses: GPA (age 39.6 years), MPA (age 41.6 years), EGPA (age 43.7 years), PAN (age 42.1 years), BD (age 36.0 years), and TAK (age 35.9 years). The mean ± SD age at entry into the study was 47.0 ± 13.4 years (range 18.0–84.0 years).

The women reported 496 pregnancies before and 74 pregnancies after the diagnosis of vasculitis. Of these, 58 prevasculitis pregnancies (11.7%) and 9 postvasculitis pregnancies

(12.2%) were electively terminated, and 4 pregnancies were ongoing at the time the questionnaire was completed (Table 1).

Excluding elective terminations, the rate of pregnancy loss was significantly higher for women who delivered after a diagnosis of vasculitis (33.8% following diagnosis compared to 22.4% prior to diagnosis; relative risk 1.77 [95% confidence interval (95% CI) 1.02–3.09], $P = 0.04$). Among live births, the rate of preterm birth, defined as delivery prior to 37 weeks of gestation, increased significantly for pregnancies conceived after a diagnosis of vasculitis (23.3% following diagnosis compared to 11.4% prior to diagnosis; relative risk 2.35 [95% CI 1.07–5.16], $P = 0.03$). Pregnancy outcomes following a diagnosis of vasculitis are shown in Table 2. The maternal age at first conception was, on average, ~5 years older for women with pregnancy following vasculitis diagnosis, which may have some impact of pregnancy morbidity. The small size of the cohort precludes multivariate analysis.

Approximately half of the women who reported pregnancies after a diagnosis of vasculitis took medications for vasculitis during gestation, most commonly prednisone, followed in frequency by azathioprine, methotrexate, and cyclophosphamide. Of the 36 pregnancies exposed to prednisone, 3 were currently ongoing, 7 were electively terminated, 1 (4%) ended in a miscarriage, and 5 (20%) were delivered preterm. Azathioprine was taken during 7 pregnancies, including 3 for GPA, 2 for EGPA, and 2 for BD. These 7 pregnancies resulted in 1 elective abortion, 2 live term births, and 2 miscarriages (50% pregnancy loss rate), with 2 pregnancies ongoing. Of the 2 pregnancies exposed to methotrexate, one was electively aborted and the other ended in a miscarriage. Cyclophosphamide was administered during 1 pregnancy, which resulted in a live term birth.

Of the 19 pregnancies conceived by women who had previously received cyclophosphamide, 4 (26.7%) resulted in spontaneous pregnancy loss, 4 were electively terminated, and 2 (18.2%) of the 11 live births were born preterm. These rates were statistically similar to those for pregnancies conceived without preceding cyclophosphamide.

With regard to vasculitis disease activity during pregnancy, 18% of women reported increased symptoms, 59% reported no change, and 23% reported an improvement. The type of vasculitis did not impact this report. The rate of pregnancy loss among women with increased disease activity (18.2%) was comparable to that among women whose disease activity decreased or did not change (37.7%; relative risk 2.72 [95% CI 0.57–13.1], $P = 0.21$), but there was a non–statistically significant trend toward a higher rate of preterm delivery in pregnancies with increased vasculitis activity (44.4% with increased activity versus 18.2% with stable or decreased activity; relative risk 3.60 [95% CI 0.78–16.3], $P = 0.09$).

Men

A total of 113 men responded to the questionnaire, and 107 were included in the analysis. Of the 6 men who were excluded, 3 reported a vasculitis not included in this study and 3 had been neither diagnosed by a specialist nor treated with immunosuppressant medications. The vasculitis diagnosis reported was GPA in 61 men, MPA in 8, EGPA in 24, PAN in 9, TAK

in 1, and BD in 4. The mean ± SD age at diagnosis was 54.6 ± 13.1 years (range 23–86 years). Overall, 6 men reported conceiving 18 pregnancies after being diagnosed with vasculitis, 1 of which was electively terminated for fetal anomalies. Forty-eight men reported conceiving 139 pregnancies prior to the diagnosis of vasculitis, of which 11 were electively terminated. For men, the pregnancy loss rate was not significantly higher among pregnancies conceived following a diagnosis of vasculitis (41.2% following diagnosis compared to 23.0% prior to diagnosis; relative risk 2.34 [95% CI 0.71–7.70], $P = 0.16$). A neonatal death due to cardiac abnormalities prior to vasculitis diagnosis in the father is included as a "pregnancy loss." No postdiagnosis pregnancies were delivered preterm, compared to 14.6% of prediagnosis pregnancies.

Three men with prior cyclophosphamide treatment reported subsequent pregnancies. One man received cyclophosphamide 1 year prior to his first conception and reported 2 subsequent pregnancies that resulted in live births without complications. Two men, both of whom received cyclophosphamide at least 10 years prior to conceiving their children, reported significant pregnancy complications: one of them reported 2 pregnancy losses and 3 live births; the other reported 5 pregnancy losses, 2 with anencephaly, followed by 1 live birth.

Discussion

The results of this study indicate that, compared to pregnancies conceived before a diagnosis of vasculitis, those conceived after diagnosis have a higher rate of adverse outcomes, including pregnancy loss and preterm delivery. The expected rate of miscarriage in the general US population is approximately 15–20% and the rate of preterm birth is approximately 13%, suggesting that the pregnancies that occurred prior to a diagnosis of vasculitis had rates close to the general population and pregnancies following a diagnosis of vasculitis had higher rates than the general population. Although vasculitis disease activity either remained the same or improved during pregnancy for the majority of women, those pregnancies complicated by worsening vasculitis were more likely to result in preterm birth. For women, prior treatment with cyclophosphamide did not appear to compromise pregnancy outcomes, but 2 men with remote cyclophosphamide therapy experienced a disproportionate number of pregnancy losses. However, it should be noted that the number of pregnancies that occurred following cyclophosphamide was small.

Several prior cohorts of pregnancies in women with vasculitis have been published in the past 10 years. A review of 214 pregnancies in 168 women with TAK, which were collected from 8 case series plus multiple case reports, found that hypertension and/or preeclampsia occurred in 43% of pregnancies and 20% of infants had low birth weight. Only 7 of 214 pregnancies were accompanied by a flare of the TAK (1–6). Although most of these women fared well during pregnancy without significant disease progression, instances of aneurysm rupture, renal insufficiency, pulmonary embolism, and myocardial infarction were reported.

The limited data available on pregnancy outcomes for small vessel vasculitis (GPA, MPA, and EGPA) indicate a high rate of pregnancy complication. Two reports have somewhat disparate results: one reported a pregnancy loss rate of 45.7% among 35 pregnancies and the

other reported a pregnancy loss rate of 22% among 22 pregnancies. Preterm birth was a frequent occurrence in both cohorts, with half of the live births being delivered before 37 weeks of gestation and both studies reporting a high level of vasculitis activity (7,8). Other publications have presented only isolated cases.

Prior case series of pregnancies in women with BD show generally good outcomes (6). In this cohort, 4 women with BD reported 6 pregnancies following diagnosis (pregnancy loss rate of 60%). All 4 women had received azathioprine and 2 others had received at least 4 different immunosuppressant medications, suggesting that these women had more severe disease than is typically seen.

For other systemic rheumatic diseases, in particular systemic lupus erythematosus (SLE), increased disease activity is the main predictor of pregnancy loss or preterm birth (9). The current study indicates that increased vasculitis disease activity may be associated with preterm delivery. In SLE, experience suggests that maintaining medications in order to control disease activity is likely beneficial to the success of pregnancy. The data in this study are too limited to confidently offer a similar recommendation for treatment of vasculitis during pregnancy; however, it is notable that half of the women with vasculitis chose to continue medications during pregnancy.

Although this is the largest cohort of pregnancies among patients with vasculitis collected to date, the study design introduces several possible areas of bias. While there are multiple causes of poor pregnancy outcomes, this study was not powered to determine the role of factors such as increased maternal age in women with vasculitis at the time of pregnancy, prior pregnancy complications, or tobacco use. Larger trials will be required for this analysis. The diagnosis of vasculitis was based on self-report and diagnostic misclassification was possible. To limit the possibility of including data from patients without true vasculitis, we excluded those participants who reported neither immunosuppression beyond glucocorticoids nor a diagnosis by a specialist. Because the data were self-reported and retrospective, we do not have detailed information about disease activity or organ involvement during pregnancy. In addition, although prior studies have shown a good correlation between self-report and medical records regarding pregnancy loss and gestational age, we limited the types of pregnancy outcomes in this study in order to improve the reliability of patient reporting (10). There may also be bias in reporting, since patients with more reproductive health difficulties may be more inclined to complete a long survey on the topic, a bias likely furthered by the low response rate of the study. This bias may be evident, for example, in the reported pregnancies conceived by women with BD and men with vasculitis. The number of men in this cohort is small, with a high proportion reporting multiple pregnancy losses. It is unclear from this study whether this ratio truly indicates an increased rate of pregnancy loss among men with vasculitis or simply reflects the greater interest that these particular men might have in responding to such a survey.

The current study demonstrates that pregnancies conceived following vasculitis have a higher rate of pregnancy loss and preterm birth than do pregnancies conceived prior to vasculitis. Although more than 80% of pregnancies did not result in a flare of vasculitis activity, those with increased activity had a higher rate of preterm birth. Therefore,

comprehensive management of vasculitis disease activity during pregnancy may improve pregnancy success in this population. These data should be useful to patients and clinicians facing the challenge of managing pregnancy in this set of rare diseases. How to best manage vasculitis during pregnancy requires further study.

ACKNOWLEDGMENTS

The authors wish to thank the following individuals for their assistance on developing and implementing the VCRC Patient Contact Registry and this project: Rajesh Adusumalli, Heather Guillette, Jennifer Harris, Renee Leduc, Jennifer Lloyd, Carol McAlear, Thuy Nguyen, Kathleen Paulus, Denise Shereff, and Kenneth Young. We also thank members of the VCRC Steering Committee for support of the project and assistance in reviewing the questionnaires, and Patricia Mickleberry for assistance in preparation of the manuscript.

Supported by a research grant from the Vasculitis Foundation and the Vasculitis Clinical Research Consortium, which has received support from the National Institute of Arthritis and Musculoskeletal and Skin Diseases (grants U54-AR057319 and U01-AR51874-04), the National Center for Research Resources (grant U54-RR019497), and the Office of Rare Diseases Research. The Vasculitis Clinical Research Consortium Contact Registry is hosted by the Data Coordinating Center at the University of South Florida for the Rare Diseases Clinical Research Network, which is supported by the Office of Rare Diseases Research, the National Institute of Neurological Disorders and Stroke (grant U54- RR019259), and the National Library of Medicine (grant RC1-LM010455).

REFERENCES

1. Matsumura A, Moriwaki R, Numano F. Pregnancy in Takayasu arteritis from the view of internal medicine. Heart Vessels Suppl. 1992; 7:120–124. [PubMed: 1360957]
2. Aso T, Abe S, Yaguchi T. Clinical gynecologic features of pregnancy in Takayasu arteritis. Heart Vessels Suppl. 1992; 7:125–132. [PubMed: 1360958]
3. Ishikawa K, Matsuura S. Occlusive thromboaortopathy (Takayasu's disease) and pregnancy: clinical course and management of 33 pregnancies and deliveries. Am J Cardiol. 1982; 50:1293–1300. [PubMed: 6128919]
4. Sharma BK, Jain S, Vasishta K. Outcome of pregnancy in Takayasu arteritis. Int J Cardiol. 2000; 75(Suppl):S159–S162. [PubMed: 10980356]
5. Wong VC, Wang RY, Tse TF. Pregnancy and Takayasu's arteritis. Am J Med. 1983; 75:597–601. [PubMed: 6137952]
6. Gatto M, Iaccarino L, Canova M, Zen M, Nalotto L, Ramonda R, et al. Pregnancy and vasculitis: a systematic review of the literature. Autoimmun Rev. 2012; 11:A447–A459. [PubMed: 22155197]
7. Sangle SR, Vounotrypidis P, Chaib A, Salas-Manzanedo V, Briley AI, Angel S, et al. Pregnancy related morbidity and mortality in patients with systemic vasculitis: a single centre controlled study [abstract]. Arthritis Rheum. 2010; 62(Suppl):S851.
8. Pagnoux C, Le Guern V, Goffinet F, Diot E, Limal N, Pannier E, et al. Pregnancies in systemic necrotizing vasculitides: report on 12 women and their 20 pregnancies. Rheumatology (Oxford). 2011; 50:953–961. [PubMed: 21183452]
9. Clowse ME, Magder LS, Witter F, Petri M. The impact of increased lupus activity on obstetric outcomes. Arthritis Rheum. 2005; 52:514–521. [PubMed: 15692988]
10. Herrmann D, Suling M, Reisch L, Siani A, De Bourdeaudhuij I, Maes L, et al. Repeatability of maternal report on prenatal, perinatal and early postnatal factors: findings from the IDEFICS parental questionnaire. Int J Obes (Lond). 2011; 35(Suppl):S52–S60. [PubMed: 21483423]

Significance & Innovations

- Pregnancies conceived following a diagnosis of vasculitis have a higher rate of pregnancy loss and preterm birth than pregnancies conceived prior to vasculitis diagnosis.
- Fewer than 20% of pregnancies in women with vasculitis are accompanied by an increase in vasculitis activity.

Table 1

Pregnancy outcomes among women and men with vasculitis

	Women		Men	
	Pregnancies delivered prior to diagnosis of vasculitis	**Pregnancies delivered after diagnosis of vasculitis**	**Pregnancies delivered prior to diagnosis of vasculitis**	**Pregnancies delivered after diagnosis of vasculitis**
No. of pregnancies	496	74	139	18
Elective terminations, no.	58	9	11	1
Pregnancy loss, no. (%)	98 (22.4)	22 (33.8)*	29 (23.0)	7 (41.1)
Miscarriages, no. (%)	93 (94.9)	21 (95.5)	27 (93.1)	7 (100)
Stillbirths, no. (%)	5 (5.1)	1 (4.5)	2 (6.9)	0
Preterm births, no. (%)†	36 (11.1)	10 (23.3)*	13 (14.6)	0

*$P < 0.05$ comparing pregnancies before and after vasculitis diagnosis.

†Preterm birth rate based on the total number of live births with a report of either term or preterm delivery.

Table 2

Pregnancy outcomes for women who conceived after the diagnosis of vasculitis*

	GPA	MPA	EGPA	PAN	BD	TAK
No. of women	16	2	10	1	4	8
Age at diagnosis, mean ± SD years	25.5 ± 4.6	21.5 ± 4.9	25.1 ± 7.0	22.0 ± 0.0	28.8 ± 3.8	22.3 ± 5.6
Age at study entry, mean ± SD years	36.4 ± 7.8	39.0 ± 8.5	40.7 ± 9.1	34.0 ± 0.0	41.8 ± 7.9	36.3 ± 5.6
Pregnancy outcomes after a diagnosis of vasculitis†						
No. of pregnancies	26	6	11	2	6	23
Current pregnancies, no.	2	0	2	0	0	0
Elective terminations, no.	2	3	1	0	1	2
Pregnancy loss, no. (%)	9 (40.9)	0	2 (25.0)	0	3 (60.0)	8 (38.1)
Preterm birth, no. (%)‡	3 (23.1)	1 (33.3)	1 (16.7)	2 (100)	0	3 (23.1)

*Due to the limited number of pregnancies in each category, statistical comparisons were not calculated.

GPA = granulomatosis with polyangiitis (Wegener's); MPA = microscopic polyangiitis; EGPA = eosinophilic granulomatosis with polyangiitis (Churg Strauss); PAN = polyarteritis nodosa; BD = Behçet's disease; TAK = Takayasu arteritis.

†Data include only pregnancies with known outcomes.

‡Only live births are included in calculating the rate of preterm births.

Arthritis Care Res (Hoboken). Author manuscript; available in PMC 2015 March 19.