Chapter two

Pregnancy in Women Diagnosed With Antineutrophil Cystoplasmic Antibody–Associated Vasculitis: Outcome for the Mother and the Child

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Abstract

Objective. Antineutrophil cytoplasmic antibody–associated vasculitis (AAV) is infrequently seen in women of childbearing age. Only a limited number of pregnancies in women with AAV have been reported, and often they were associated with complications.

Methods. This was a single-center retrospective observational study. All pregnancies in women with granulomatosis with polyangiitis (Wegener’s) (n = 13) and microscopic polyangiitis (n = 1) were included. Women of childbearing age were counseled to abstain from pregnancy during or shortly after disease activity or <1 year after cyclophosphamide treatment.

Results. We described 22 pregnancies in 14 women with AAV (median age at diagnosis was 25 years [range 19–36 years]) diagnosed between 1982–2008. The ear, nose, and throat region (71%) and kidneys (50%) were predominantly involved. All women were in remission at conception and cyclophosphamide had been administered to 9 women (15 pregnancies). The median gestational age was 39+4 weeks, including 2 preterm deliveries. The median birth weight was 3,400 gm (1,860–3,890 gm). Hypothyroidism occurred in 1 newborn and a cleft palate in 1 newborn of a twin pregnancy. Otherwise, the fetal outcome was excellent. Preeclampsia was diagnosed in 2 pregnancies. A caesarean section was performed in 2 patients. The median followup after the last conception was 98 months (range 11–307 months). Eight women experienced a relapse 21 months (range 7–62 months) after conception, 1 during pregnancy, and 7 after delivery.

Conclusion. In this study, the pregnancy outcome in patients with AAV in remission was excellent. Pregnancy in women with AAV in remission does not seem to be associated with increased risk of relapse. Counseling, careful management, and close followup are essential in pregnant women with AAV.

Significance & innovations

• Only a limited number of pregnancies in women with antineutrophil cytoplasmic antibody–associated vasculitis (AAV) have been reported, predominantly case reports and small series, often with a complicated outcome.
• A small cohort of consecutive pregnancies in women with AAV with good outcome is added to the existing literature.
• Using strict criteria when considering pregnancy (or planning a pregnancy) in women of childbearing age with AAV may be associated with good fetal and maternal outcome.
Introduction

Antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis (AAV) is a systemic autoimmune disease causing small vessel vasculitis and inflammatory damage with predilection for the kidneys, lungs, and the upper airways (1). ANCA against proteinase 3 (PR3) and myeloperoxidase are present in most patients with active disease and are thought to play a role in its disease pathogenesis (2). Treatment consists of immunosuppressive drugs, primarily cyclophosphamide in combination with high-dose corticosteroids, and is able to induce remission in most patients. During followup, AAV has a clear tendency to relapse necessitating renewed treatment. With increased survival rates, long-term treatment side effects are now of increasing importance. Among the various serious side effects of immunosuppressive drugs such as cyclophosphamide are gonadal toxicity and teratogenicity. Since AAV is predominately diagnosed in the fifth to seventh decade of life (3), the disease is not frequently observed in women of early childbearing age. Until now, only 58 pregnancies in women with granulomatosis with polyangiitis (Wegener’s) (GPA) and microscopic polyangiitis (MPA) have been reported, of whom at least 35 conceived while in remission (4-16). Pregnancies occurring in active disease or pregnancies complicated by new-onset disease or recurrent disease have a documented unfavourable outcome for both the mother and the child (4). However, pregnancies occurring during remission also seem to be associated with increased risk of complications. When a pregnancy is complicated by recurrent disease activity, therapy may threaten fetal and maternal health.

The main goal at our center was to minimize risk for renewed disease activity during pregnancy and optimize pregnancy outcome for the mother and the child. Therefore, women of childbearing age were counseled, and if an active pregnancy wish was present, they were managed with close followup. This study outlines the outcome of 22 pregnancies in 14 women with GPA or MPA following this policy.

Patients and methods

Patients

Between 1982–2008, 39 women younger than 36 years of age were diagnosed with GPA or MPA and treated at our center. None of these women were pregnant or had given birth within the 3 months prior to diagnosis. Fourteen of these women had at least 1 pregnancy reaching the third trimester after the diagnosis and treatment of AAV and were included in this single-center retrospective study. Data on patient characteristics, type of AAV, organ involvement, ANCA status, treatment before (induction, maintenance, and relapse) and during pregnancy, cumulative cyclophosphamide dose before pregnancy, hypertension (before and during pregnancy), renal function, occurrence of preeclampsia and other maternal complications, gestational age at delivery, type of delivery (i.e., vaginal, caesarean), induction of labor, birth weight, fetal health status, and the occurrence of a relapse during or after the pregnancy were collected.

Patients were classified as either GPA or MPA according to the criteria adapted from the Chapel Hill Consensus Conference Nomenclature/Criteria for Vasculitis (1). All patients were followed until July 1, 2011. A positive ANCA in indirect immunofluorescence was confirmed by antigen-specific enzyme-linked immunosorbent assay. Creatinine clearance was obtained from 24-hour urine collection; if not
available, the Cockcroft-Gault formula was used to estimate the creatinine clearance (17). Disease activity at diagnosis was scored using the Birmingham Vasculitis Activity Score (BVAS) (18). Damage due to vasculitis presence at the time of conception was scored by the Vasculitis Damage Index (VDI) (19). Birth weight was expressed as median birth weight in grams and percentiles for singleton Dutch newborns with adjustment for sex and parity (20), and for twin newborns with adjustment for race (21).

**Definitions**

Remission was defined as no clinical signs of active disease (BVAS = 0) and no biochemical evidence of active inflammation (C-reactive protein [CRP] level <10). A relapse was defined as clinical signs or biopsy-proven histologic evidence of vasculitis activity that resulted in renewed or intensified immunosuppressive therapy. Preexistent hypertension was defined as systolic blood pressure >140 mm Hg, diastolic blood pressure >90 mm Hg, or receiving antihypertensive drugs. Preeclampsia was defined as the appearance of hypertension with systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg accompanied by proteinuria of >300 mg/24 hours after 20 weeks of gestational age in a previously normotensive woman (22). Preeclampsia superimposed on chronic hypertension was defined as an increase in blood pressure in combination with the appearance of or increase in proteinuria after gestational week 20 (23). Preterm delivery was defined as delivery before 37 completed weeks of gestational age. A caesarean section could be planned (planned before delivery), primary (first caesarean section), or repeat (after a previous caesarean section).

**Statistical analysis**

Disease-free survival after conception was calculated using Kaplan-Meier estimates. For data analysis and graphs, GraphPad Prism software (version 4.03) was used.

**Results**

**Patient and treatment characteristics before pregnancy**

Fourteen women (13 with GPA and 1 with MPA) in remission became pregnant once or twice after diagnosis at our center. A total of 22 pregnancies were identified, including 1 bichorial biamniotic twin pregnancy. Four of the 39 women failed to conceive and remained involuntarily childless. Two of the 14 women included for study reported 1 spontaneous abortion each. Due to the short time of gestation, 7 and 10 weeks, there was no clinical documentation of these pregnancies. An overview of patient, treatment, and pregnancy characteristics is shown in Table 1. The median age of the women at diagnosis was 25 years (range 19–36 years). Organ involvement was variable, but there was a high rate of ear, nose, and throat (ENT; 71%) and renal (50%) involvement. The clinical picture of recurrent ENT symptoms (crusting, epistaxis) together with a positive PR3 ANCA and characteristic histology resulted in the diagnosis of limited AAV in 4 patients. The median BVAS at diagnosis was 14 (interquartile range 6–19).

Immunosuppressive induction treatment after diagnosis consisted of a combination of cyclophosphamide and prednisolone in 9 women. In addition, 1 patient in whom dialysis-dependent renal failure persisted after induction therapy received prednisolone, cyclosporine, and mycophenolate mofetil as immunosuppressive therapy after kidney transplantation. The median cumulative cyclophosphamide dose before conception in these 9 women was 13.5 gm (range
### Table 1. Patient characteristics and pregnancy outcome of 22 pregnancies in 14 women*

<table>
<thead>
<tr>
<th>Patient no./age at conception</th>
<th>Diagnosis/type of ANCA/BVAS</th>
<th>Treatment before conception</th>
<th>Treatment during pregnancy</th>
<th>Delivery/gestational age</th>
<th>Birth weight/health status of the child</th>
<th>Complications</th>
<th>Relapse after conception, months</th>
<th>Followup, months</th>
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<tr>
<td>1/36</td>
<td>GPA/PR 3/6</td>
<td>ENT</td>
<td>Co Trim</td>
<td>SVD/39+3</td>
<td>3,420 gm/GH</td>
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<td>None</td>
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<td>Co Trim</td>
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<td>Co Trim</td>
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<td>PCS/37+5</td>
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<td>Co Trim</td>
<td>SVD/40+2</td>
<td>3,400 gm/Hypoglycemia, hypothyroidism</td>
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<td>Co Trim</td>
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<td>Co Trim</td>
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<td>3,500 gm/GH</td>
<td>None</td>
<td>None</td>
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<td>GPA/PR 3/30</td>
<td>ENT, N, A</td>
<td>Co Trim</td>
<td>SVD/39+3</td>
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<td>13/28</td>
<td>GPA/PR 3/30</td>
<td>ENT, S, A</td>
<td>Co Trim</td>
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<td>14/29</td>
<td>GPA/PR 3/30</td>
<td>ENT, S, P, A</td>
<td>Co Trim</td>
<td>SVD/39+3</td>
<td>3,645 gm/GH</td>
<td>None</td>
<td>None</td>
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</tbody>
</table>

* ANCA = antineutrophil cytoplasmic antibody; BVAS = Birmingham Vasculitis Activity Score, at diagnosis; VDI = Vasculitis Damage Index, at conception; GPA = granulomatosis with polyangiitis (Wegener’s); PR3 = proteinase 3; ENT = ear, nose, and throat; SVD = spontaneous vaginal delivery; GH = good health; K = kidney; S = skin; N = neurologic; A = arthralgia; E = eye; CS = corticosteroids; CYC = cyclophosphamide (cumulative dose); Aza = azathioprine; MPA = microscopic polyangiitis; MPO = myeloperoxidase; CoTrim = cotrimoxazole; CGPS = cheilognathopalatoschisis; VSDs = ventricular septum defects; P = pulmonary; GI = gastrointestinal; IVD = induction and vaginal delivery; T = trachea; PF = plasmapheresis; PSC = planned caesarean section; CsA = cyclosporine; MMF = mycophenolate mofetil; PLCS = planned caesarean section; MTX = methotrexate.
4.9–28.4 gm). The median cyclophosphamide-free period before the first conception was 47 months (range 10–67 months). All women observed a cyclophosphamide-free period of >1 year before conception, with the exception of 1 woman who conceived 10 months after discontinuing cyclophosphamide. One woman received cyclophosphamide therapy after her first pregnancy and before her second conception, resulting in a cumulative dose at the second conception of 27 gm. A cyclophosphamide-free period of >1 year was observed in this case as well. Methotrexate and prednisolone were taken by 1 woman to induce remission. Four women with limited GPA (ENT involvement and in 1 case additional episcleritis) were successfully treated with cotrimoxazole (trimethoprim/sulfamethoxazole) monotherapy, which was stopped in all 4 patients (in 3 before conception and in 1 after confirming pregnancy). The episcleritis was treated successfully with dexamethasone eye drops.

The median time between diagnosis and conception of the first pregnancy was 47 months (range 14–82 months). The median disease-free period between the last disease episode (new-onset disease or relapse) and the following pregnancy was 35 months (range 6–69 months). All women had >1 year of stable remission before conception, with the exception of 1 woman who conceived 6 months after attaining remission.

**Conception and pregnancy**

The median age of the women at conception of the first pregnancy was 29 years (range 23–38 years) and at the second pregnancy was 33 years (range 28–39 years; n = 8). One patient became pregnant with assisted reproduction (intrauterine insemination/in vitro fertilization); all others conceived naturally, although 2 women reported fertility problems before becoming pregnant. The first woman developed an irregular menstrual cycle after diagnosis and induction treatment of GPA. The second woman was relatively old at the time of conception of the 2 pregnancies (37 and 39 years). In both women it took relatively longer to become pregnant, median time to conception was 2.5 years (range 1–3 years). At evaluation, no fertility disorders were found in both patients and their partners, and both women subsequently conceived naturally.

The median VDI score at the time of conception was 2 (range 0–3) and in 20 pregnancies a VDI score of ≥1 was present at the time of conception. An overview of damage as scored in the VDI and laboratory results at the time of conception are shown in Table 2.

Fourteen pregnancies were conceived when the patient was not receiving treatment, and the patients remained off treatment during the pregnancy. One pregnancy was conceived when the patient was not receiving treatment, but due to a relapse, treatment with prednisolone was required at 28 weeks of gestation. One woman received cotrimoxazole in the first month of her pregnancy, but when her pregnancy was confirmed, the medication was stopped. In 4 pregnancies, immunosuppressive medication with corticosteroids (n = 4) and azathioprine (n = 2) was taken for maintenance therapy after attaining remission. In 2 pregnancies in 1 woman immunosuppressive therapy after kidney transplantation with cyclosporine and corticosteroids was continued, but mycophenolate mofetil was switched to azathioprine before conception, since mycophenolate mofetil might be teratogenic (24).
Table 2. Patient and laboratory characteristics at time of conception*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ANCA titer at conception, median (range) (n = 20)</td>
<td>80 (0-640)</td>
</tr>
<tr>
<td>CRP at conception, median (range) mg/liter (n = 19)</td>
<td>4 (1-9)</td>
</tr>
<tr>
<td>Serum creatinine at conception, median (range) μmol/liter (n = 22)</td>
<td>78 (54-181)</td>
</tr>
<tr>
<td>Proteinuria at conception, median (range) gm/24 hours (n = 22)</td>
<td>0.1 (0.0-0.8)</td>
</tr>
<tr>
<td>VDI, pregnancies (total VDI score)+</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>0</td>
</tr>
<tr>
<td>Skin/mucous membranes</td>
<td>0</td>
</tr>
<tr>
<td>Ocular</td>
<td>0</td>
</tr>
<tr>
<td>ENT</td>
<td>17 (24)</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>0</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>0</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>0</td>
</tr>
<tr>
<td>Renal</td>
<td>6 (11)</td>
</tr>
<tr>
<td>Neuropsychiatric</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Other damage/drug reaction</td>
<td>3 (3)</td>
</tr>
</tbody>
</table>

* ANCA = antineutrophil cytoplasmic antibody; CRP = C-reactive protein; VDI = Vasculitis Damage Index; ENT = ear, nose, and throat.  
† Number of pregnancies with ≥1 positive VDI item(s).

Hypertension and hypertensive disorders

In 20 of 22 pregnancies no gestational hypertension or (superimposed) preeclampsia was observed. In 2 of these 20 pregnancies preexistent hypertension was present, well controlled (<140/90 mm Hg), and treated around the time of conception with labetalol in 1 patient and metoprolol in the other. Proteinuria was present at conception in 3 of these 20 pregnancies, while a creatinine clearance <60 ml/minute (stage 3 chronic kidney disease) was present in one of the patients with preexisting hypertension. In 2 of 22 pregnancies, preeclampsia developed (week 35 and week 40), which included the twin pregnancy. In both cases hypertension had been present before conception and was treated with labetalol with an acceptable blood pressure (<140/90 mm Hg) at conception. Both women were managed by raising the dose of labetalol and both had spontaneous vaginal labor. A healthy singleton newborn was born at week 41 and the twin newborns were born at week 36+0 (see “Outcome in child and mother” below). In addition, the mother of the twin newborns had reduced renal function with a creatinine clearance <60 ml/minute and proteinuria. None of the pregnancies were associated with acute or persistent loss of renal function in the mother.

ANCA

In 20 of 22 pregnancies ANCA s were measured around the time of conception and during followup. In 5 pregnancies ANCA s were not detectable at the time of conception. ANCA s remained stable during pregnancy in all with an ANCA-negative titer and an ANCA-positive titer at the time of conception, with the exception of 1 patient who experienced fluctuating ANCA titers during 2 pregnancies, of which the second pregnancy was complicated by a relapse at week 28. None of the newborns showed signs or symptoms of neonatal systemic vasculitis.
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Complications during pregnancy

No major life-threatening complications occurred except for worsening of a preexisting tracheal stenosis in 1 woman. A biopsy sample showed tracheitis with non-specific inflammation without signs of vasculitis activity or granulomatous inflammation, and was therefore probably of infectious origin. At 8 weeks of gestation high-dose intravenous prednisolone and antibiotic therapy were administered. At 10 weeks of gestation CO2 laser surgery of the stenosis was successfully performed and prednisolone was tapered. At 16 weeks of gestation an emergency tracheotomy for dyspnea was performed, which was followed by a microlaryngoscopy and dilation of the trachea. At 37+2 weeks of gestation a healthy newborn was delivered.

In 1 woman, local disease activity with episcleritis developed in the fifth week of gestation. This was controlled with dexamethasone eye drops. At 28 weeks of gestation the disease was exacerbated with symptoms of arthralgia and development of glomerular erythrocyturia with stable and normal renal function. During pregnancy, this was treated with increasing dosages of prednisolone up to 25 mg daily, with a cumulative dose of 922.5 mg. Directly following the delivery azathioprine (2 mg/kg/day) was added to the therapy. One month after the delivery the patient achieved complete remission. ANCA titers during pregnancy varied between 1:320 and >1:640. CRP level rose from 5 mg to 15 mg maximum and the BVAS score was 10. Shortly after the delivery the mother was diagnosed with postpartum thyroiditis and later with Graves’ disease.

Labor induction was required in 5 pregnancies, twice at the patient’s request, once due to the need for a tracheostomy insertion, once for an unknown reason, and once due to maternal fever. Despite labor induction in this last pregnancy, a primary caesarean section was performed, since fetal distress arose combined with an intrauterine infection. A planned caesarean section due to a breech presentation was performed in 1 woman.

Figure 1. Disease-free survival after 22 conceptions in 14 women with antineutrophil cytoplasmic antibody–associated vasculitis. Women were censored when no relapse occurred before July 1, 2011 or when a second conception occurred.
Outcome of Pregnancy in ANCA-Associated Vasculitis

**Outcome in the child and the mother**

All 22 pregnancies resulted in liveborn infants (n = 23). The median gestational age was 39+4 weeks (range 33+3–41+2 weeks). Two pregnancies ended with preterm (<37 weeks) delivery. One was a twin pregnancy with delivery at 36+0 weeks and the other preterm delivery at 33+3 weeks was a singleton pregnancy in which the mother had received cotrimoxazole in the first gestational month. Two of the 3 premature newborns were clinically healthy. One of the twin newborns was diagnosed with a bilateral orofacial cleft (cheilognathopalatoschisis) and multiple minor ventricular septum defects. These ventricular septum defects did not have hemodynamic consequences and gradually closed without interference.

The 20 term deliveries resulted in 18 healthy newborns. One newborn was clinically suspected to have an intrauterine infection, despite a negative blood culture. After antibiotic therapy the newborn recovered completely. The second pregnancy in the same mother was complicated by a relapse at 28 weeks of gestation and the mother had undiagnosed Graves’ disease during pregnancy. The gestational age was 38 + 3 weeks and the newborn weighed 3,400 gm. This newborn experienced a short episode of hypoglycemia directly after the delivery and was later diagnosed with a hypopituitary hypothyroidism, due to an isolated thyroid-stimulating hormone deficiency. The thyroid axis gradually regained function at the age of 4.5 years and as a result, medication was able to be tapered and was eventually stopped.

The median weight of all the newborns was 3,400 gm (range 1,860–3,890 gm). All singleton newborns (n = 21) had a birth weight between the 10th and 90th percentile for birth weight in Dutch newborns, adjusted for sex and parity. Both of the twin newborns had low birth weight (<2,500 gm), 1,860 gm (<5th percentile) and 2,290 gm (25th–50th percentile). All children were in good health until the end of followup, at a median age of 8 years (range 0–24 years).

All women were referred to a gynecologist in second line at the start of their pregnancy. Complications in the mother were rarely seen. Two women developed postpartum thyroiditis, which was transient in 1, but the other woman was later diagnosed with Graves’ disease. A relapse following conception occurred after 8 conceptions after a median period of 21 months (range 7–62 months), with only 1 relapse occurring during pregnancy (28 weeks), while all other relapses occurred some period after delivery (range 1–53 months). All remaining pregnancies were not followed by a relapse. The occurrence of a relapse following conception is shown in a Kaplan-Meier survival graph in Figure 1. The median followup after the last conception was 98 months (range 11–307 months).

**Discussion**

Due to the age distribution at the onset of AAV, experience with pregnancies at the time of diagnosis and during followup in women with this disease is very limited. The sparse data that are available do suggest that both with respect to maternal and fetal outcome, problems during and following pregnancy can occur. Given the paucity of data it is difficult to counsel women who present with AAV at a childbearing age and have or develop a wish to conceive. Using a very cautious policy, which starts with the avoidance of cyclophosphamide and, if treatment with cyclophosphamide is inevitable, reduction in cyclophosphamide exposure, our retrospective single-center data on 22 pregnancies in 14 women show that pregnancies occurring in women with AAV in remission may have a favourable outcome for both the mother and the child.
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The 22 pregnancies resulted in 23 liveborn infants and 20 were in excellent health. Prematurity occurred in 2 pregnancies (9%), which is less than previously reported in comparable study populations (29% [4] and 53% [5]). One of these preterm births was a twin pregnancy, which itself is associated with a shorter term of gestation (25). The other pregnancy was a singleton pregnancy in which the mother had inadvertently taken cotrimoxazole, a folic acid antagonist, in the first gestational month. A recent study showed that exposure to cotrimoxazole during pregnancy was associated with prematurity and low birth weight, although the gestational month of exposure or dose were not further specified in relation to the occurrence of prematurity or low birth weight (26). A congenital malformation occurred in one of the twin newborns, while no congenital malformations were observed in the other children directly after birth or during followup. One pregnancy was complicated by an intrauterine infection, which was successfully treated with antibiotics. The second pregnancy in the same mother was complicated by a relapse of AAV and the mother was diagnosed with Graves’ disease shortly after the delivery. Transient hypoglycaemia and isolated hypopituitary hypothyroidism occurred in this newborn. To our knowledge, there are no similar descriptions of the occurrence of ventricular septum defects, orofacial clefts, or hypopituitary hypothyroidisms in infants of women with AAV or in infants of pregnancies in autoimmune diseases with similar therapy, although, a higher incidence of ventricular septum defects has been reported in preterm newborns (27).

AAV remained in remission during 21 pregnancies, 1 relapse during pregnancy occurred (5%). This was despite the fact that in 15 pregnancies ANCAs were present at the time of conception and during pregnancy. In 2 study populations of young women with AAV relapse rates of 0% (5) and 38% (4) have been reported. Although transplacental transfer of ANCA from the mother to the fetus has been reported in the literature (6,11,12), and has resulted in a neonatal pulmonary-renal syndrome in 1 case (12), none of our newborns showed signs or symptoms of AAV. Although we did not test for the presence or absence of ANCA in the newborn, a substantial number of women were ANCA positive during pregnancy and placental IgG and thereby ANCA transfer must have occurred. Whether this lack of clinical sequelae despite transfer of ANCA is related to the fact that the ANCA-positive women that were pregnant with only 1 exception did not show any disease activity is unclear. The pathogenicity of ANCA could therefore be questioned.

In contrast to some reports in the literature, our study showed a more positive outcome for both the mother and the child when pregnancy occurred. Publication bias may have occurred, which resulted in underreporting of successful outcome of pregnancy in women with AAV. Conversely, the outcome could have been more favorable since our patients were young and had relatively limited disease- and treatment-related damage as reflected by a relatively low VDI at the time of conception. Additionally, in 4 patients, vasculitis was limited to the ENT and the eyes. Furthermore, our cohort consisted mainly of patients diagnosed with GPA (93%) and may therefore not be representative for patients diagnosed with MPA.

It is tempting to speculate that the outcome and lack of pregnancy- or vasculitis-associated complications may be related to our rather cautious and conservative approach. First, cyclophosphamide was not taken by all women and when treatment with cyclophosphamide was unavoidable, a cyclophosphamide-free period of at least 1 year had to be observed before conception in order to minimize any potential teratogenic effect. In addition, in this way the patient
had to prove to be in stable remission for at least that period without intensive immunosuppression. This may have induced a selection bias with women with more relapse-prone disease not reaching the possibility to become pregnant. Furthermore, all other therapies were evaluated before conception and when possible, all potentially harmful medication was stopped or tapered. Likewise, blood pressure was strictly regulated before conception and during pregnancy.

Future therapies of AAV with complete avoidance of cyclophosphamide, for example with rituximab, may further improve pregnancy chances and possibilities for women presenting with AAV at a childbearing age. Adequate short-term disease control has been reported, and gonadal toxicity has not been reported and is also not expected with this therapy (28). Rituximab could therefore be the first-choice treatment in young women of childbearing age to prevent gonadal toxicity and fertility-related problems.

Our study showed that pregnancy in women with AAV in remission can have a favorable outcome for both the mother and the child. It is possible that the strict selection criteria used in our center contributed to this positive outcome. Based on our results, we suggest the following selection criteria when considering a pregnancy: ideally, women should be in stable remission for >1 year. In addition, a cyclophosphamide-free period of 1 year is recommended. Also, other teratogenic medication should be avoided during pregnancy.

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. Ms Tuin 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.

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**Analysis and interpretation of data.** Tuin, Sanders, de Joode, Stegeman.
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