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Incidence, clinical features, management and outcomes of ANCA-associated vasculitis in pregnancy- a systematic literature review

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Abstract. *Background and aim:* Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV) are rare multi-system conditions, usually presenting in older age groups. However, younger individuals are also affected. The average increase of childbearing age and lack of studies in pregnancy necessitates this comprehensive review of data to guide the management of AAV in pregnancy. This systematic review (SR) aimed to summarise the incidence, clinical features, management, and maternal and foetal outcomes in female patients with AAV. *Methods:* The protocol was registered on PROSPERO (CRD42023437482). Articles published in Medline, Embase, and Cochrane Databases from 1946 until June 2023 were included. Single case reports, reviews and conference abstracts were excluded. Articles meeting inclusion criteria were examined by two authors. Data on demographics, treatment, clinical features, flares during pregnancy, and maternal and foetal outcomes were extracted. *Results:* Eight studies were included, detailing 82 pregnancies in 64 women. The most common drugs used for remission induction pre-conception were cyclophosphamide, rituximab, prednisolone, and azathioprine. Serious maternal complications in pregnancy included progressive tracheal/subglottic stenosis (n=5), renal disease (n=2), preeclampsia (n=10), and miscarriages (n=5). Foetal anomalies were rare (n=5). The mean birth weight was 3.37kgs and mean gestation age was 38.26 weeks. No maternal deaths or vasculitis in newborns were reported. *Conclusions*: Patients can have positive maternal and foetal outcomes following strong induction therapy, vigorous monitoring and prompt treatment of flares during pregnancy. Serious complications and flares are not associated with worse outcomes for newborns.

Key words: vasculitis, pregnancy, ANCA, anti-neutrophil, AAV, biologics

Introduction

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a broad term used to describe small vessel inflammation and destruction, with symptoms ranging from epistaxis to multi-organ failure (1). The three main subsets include microscopic polyangiitis (MPA), eosinophilic granulomatosis with polyangiitis (EGPA), and granulomatosis with polyangiitis (GPA). These vasculitides tend to be more prevalent in women greater than the age of 50 (2), but have been observed to affect younger women as well. Along with the average increase of childbearing age, this has created a need to research immunologic therapy and the management of AAV in pregnancy. The relatively immunocompromised state during pregnancy can also lead to the rise of de novo autoimmune conditions, including AAV (3).

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Although a relatively rare disease, with a prevalence of 200-400 per million worldwide (4), the devastating consequences of AAV on morbidity and mortality warrants research in pregnant women, a high-risk population often excluded from clinical trials and research studies. The current treatment used in non-pregnancy associated AAV comprises a range of immunosuppressants and biologic agents including cyclophosphamide, rituximab, azathioprine, mycophenolate, and plasma exchange in combination with corticosteroids (5–7). Recent research has suggested teratogenic effects of the widely used cyclophosphamide, hindering its use pre-conception and in the first trimester (8). The ethics associated with conducting research during pregnancy has prevented randomised controlled trials from being conducted in this cohort due to the effects of cytotoxic agents - premature birth, limb abnormalities and haematological dysfunction in the foetus and risk of pre-eclampsia, spontaneous abortion and maternal death (2,8,9). Treatment decisions are often based on case reports to establish effective management along with its associated effects on the foetus and mother.

This systematic literature review (SLR) aimed to collate available data on incidence, clinical features, management options and outcomes of pregnant women with AAV, both diagnosed pre-conception and de novo during pregnancy.

Methods

The protocol for this SLR was developed by AA, MD and KK and registered in the Prospero Database of Systematic Reviews (CRD42023437482) in June 2023 (9). This study aimed to characterise the maternal and foetal outcomes for pregnant women diagnosed with AAV, along with summarising the treatment options offered and clinical outcomes reported.

The inclusion criteria were:

1. Pregnant women > 16 years of age with a clinician-confirmed diagnosis of AAV (MPA, GPA and EGPA) antepartum or within week 1-24 of gestation. A confirmed diagnosis of AAV was defined as per the Chapel Hill Criteria, including characteristics in clinical features and positive ANCA serology (1) ;
2. Neonates who were born to mothers with a confirmed diagnosis of AAV, who were under the age of 1;

Patients with unknown ANCA status or without confirmed histology consistent with AAV were excluded.

The main outcomes were maternal and foetal sequelae including morbidity, mortality, pregnancy-related diseases and complications (e.g. pre-eclampsia), intrapartum complications (e.g. major haemorrhage) and foetal anomalies (e.g. intrauterine growth retardation). Other outcomes included patients' demographics as well as treatment(s) administered.

Search strategy

The search strategy was formulated by the three authors AA, MD and KK with assistance from an expert librarian with extensive experience in carrying out SLRs (LR). The full search strategy can be found in the Figure 1. The following databases were searched: Medline, Embase, Cochrane and clinicaltrials.gov. All studies published between 1946 and 15th June 2023 were included. Only studies in English were considered. We included observational studies, case series as well as randomised and non-randomised trials. We excluded single case reports, opinion articles, conference abstracts and protocols.

The initial search for articles meeting the above criteria was performed in June 2023. Titles and abstracts were screened by AA for relevance to the review question, following which a second author, KK, reviewed abstracts and full papers to finalise the included articles. Any inconclusive results were resolved by a third author, MD, who also reviewed 10% of the articles to ensure an accurate screening.

Assessment of risk and data extraction

We assessed risk of bias through the Newcastle-Ottawa tool for cohort and case control studies (10) (Table 1). Data were extracted from included articles on study and patient demographics, and outcomes described above. AA extracted data from the articles, which was further corroborated by KK and MD to ensure accuracy of the data prior to analysis by KK and MD through descriptive statistics.

Results

The initial search, after deduplication and removal of conference abstracts, yielded 593 journal articles. After initial sifting by title and abstract,

Table 1. Risk of bias (Newcastle-Ottawa Scale) of cohort and case-control studies.

		Selection				Comparability	Outcome		
Author/Year	**Type of study**	**Representativeness of the exposed cohort**	**Selection of the non-exposed cohort/ control**	**Ascertainment of exposure**	**Demonstration that outcome of interest was not present at start of study**	**Comparability of cohorts on the basis of the design or analysis**	**Assessment of outcome**	**Was follow-up long enough for outcomes to occur**	**Adequacy of follow up of cohorts**
Nguyen et al 2019	Retrospective observational			*	*		*	*	
Pendergraft et al 2013	Retrospective observational			*	*		*		
Tuin et al 2012	Retrospective observational			*	*		*	*	*
Croft et al 2015	Retrospective observational			*	*		*	*	*
Author/Year	**Type of Study**	**Adequacy of case definition**	**Representativeness of cases**	**Selection of controls**	**Definition of controls**	**Comparability of cohorts on the basis of the design or analysis**	**Ascertainment of exposure**	**Same method of ascertainment for cases and controls**	**Non-response rate**
Ganhao et al 2021	Case control	*	*	*	*	**	*	*	
Sangle et al 2015	Case control	*	*	*	*	**	*	*	

40 articles reached the full-article screening stage, which was conducted by MD and KK. Eight articles ultimately met the requirements of our SLR which included two case-control studies (11,12), four retrospective cohort studies (13–16) and two case series (17,18). The study cohorts were from the United Kingdom (n=3), Canada (n=1), Italy (n=1), France (n=1), Netherlands (n=1) and the United States (n=1). Information about the authors, country of origin and patients' characteristics is summarised in Table 2.

Patient characteristics

From the eight studies analysed, there were a total of 64 women with 82 pregnancies, out of which 38 were diagnosed with GPA, 5 with EGPA, 4 with MPA and 17 with unspecified types of ANCA or renal vasculitis. In studies where the antibody subtype was reported, c-ANCA was present in 37 women, and p-ANCA in 10 women; 2 women had atypical antibodies. Pertinent outcomes for all studies are described in Table 2.

Regarding the comparability of patients across studies, the mean age of the women was 31.3 years (SD 4.2). Where mentioned, six women were para 0 or 1, and 28 women were para 2 or more. The studies reported a majority Caucasian population, ranging from 58-92%. Of note, patients were matched for ethnicity in the case-control study (12). The two case series did not report patients' ethnicities. The following comorbidities were reported: two pre-existing hypertension, one duplex kidney, one type 1 diabetes mellitus and one asthma with nasal polyp excision. However, overall, comorbidities were poorly recorded in the studies.

Organ involvement was reported in 38 patients; 27 patients had sinus, ear or nose involvement (71%), 15 patients had renal disease (39.5%), 16 patients had lung involvement (42.1%) and two patients had tracheal involvement (5.3%).

Induction and maintenance treatment

The studies in this SLR reported a variety of combinations for induction treatment prior to conception, including but not limited to Cyclophosphamide (CYC) only (n=24), Azathioprine (AZA) and Prednisone (PRED) (n=17), PRED/ hydrocortisone only (n=1), CYC and Rituximab (RTX) (n=1), Methotrexate (MTX) and PRED (n=3), Co-trimoxazole (n=4), Co-trimoxazole and PRED (n=1), CYC, Rituximab and Mycophenolate Mofetil (MMF) (n=1), RTX, MTX and PRED (n=1), PRED, AZA, MMF and MTX (n=1), PRED, plasma exchange and AZA (n=1), CYC, MMF, Ciclosporin and PRED (n=1), and other combinations (n=3). Other treatments administered included low molecular weight heparin and aspirin for patients at high risk of thrombotic disorder and pre-eclampsia respectively. Patients received induction therapy from a range of three months to four years prior to conception. One patient required dialysis and a renal transplantation after renal failure following CYC; she was then switched to PRED, ciclosporin, and MMF to maintain immunosuppression (15). Her MMF was changed to AZA prior to conception due to the former's teratogenic effects. One patient stopped co-trimoxazole therapy upon confirming her pregnancy; of note, she had a preterm birth at 33+3 weeks, without any other foetal complications. Intravenous CYC was used in patients with progressive renal disease till remission prior to conception (17,18). Patients used a combination of oral steroids and azathioprine for maintenance throughout pregnancy.

Flares of ANCA-associated vasculitis

Sixteen (16/64, 25%) patients had a flare of AAV during pregnancy, with five (5/16, 31%) flares postpartum. Most (9/16, 56%) were recorded as mild to moderate with symptoms such as congested nose, ear infections, nasal crusting and sinus pain and hence did not require any change in management during pregnancy (13). There were seven (7/16, 44%) severe presentations requiring surgery or an escalation of intervention. Two patients had severe tracheal stenosis during pregnancy, with one requiring CO2 laser therapy and an emergency tracheotomy and microlaryngoscopy, and another requiring an emergency C-section and tracheal debridement postpartum (15,16). One patient with GPA required surgery for progressive subglottic stenosis during pregnancy and another patient had the same flare postpartum (12). Another patient with GPA had a serious presentation of hemoptysis which resolved after red blood cell transfusions, plasma exchange, and pulses of methylprednisolone (13). One patient had progressive airway disease requiring an increase in their

Table 2. Patient characteristics, induction treatment, maternal and foetal outcomes for eight studies.

Study	Type of study	Number of patients; number of pregnancies	Mean age	Maternal comorbidities	Type of vasculitis	Matched group criteria	Induction regimen	Maternal outcome	Foetal outcome
Ganhao, S. et al 2021 (Italy)	case-control	3;3	35.35	Not available	3/3 EGPA	Matched for age and rheumatic disease ⏀	Not available for study population	Not available for study population	Twins - median gestation 35 weeks; mean birth weight 2.24 kg. Singletons - median gestation - 38.9 weeks; mean birthweight- 2.92 kg ⏀
Nguyen, V. et al 2019 (Canada)	retrospective cohort	16;20	33.4	6/20 - vasculitis related hypertension ⏀	Not available	Not applicable	13/20 - PRED and AZA ⏀	2/20- pre-eclampsia; 1/20 postpartum flare; 3/20 emergency C-section ⏀	2/20 - terminated pregnancy. Mean gestation - 37.8 weeks. Median birth weight - 2.9 kg. 5/18 preterm. ⏀
Sangle, S. R. et al 2015 (United Kingdom)	case-control	10;10	36	1/10 cases - duplex kidney	8/10- GPA, 1/10- EGPA, 1 /10 - AAV with renal involvement	Matched for BMI, parity, smoking, age, no of foetuses, ethnicity	6/10 -CYC, 4/10 CYC, MTX and AZA	1/10 - pre-eclampsia; 1/10 intrauterine death.	Median gestation 36.3 weeks; mean birth weight 4 kg.
Pendergraft, W. et al 2013 (United States)	retrospective cohort	5;7	27.8	Not available	6/7 -GPA, 1/7 - MPA	Not applicable	5/7 CYC and PRED, 1/7 CYC, PRED, RTX, 1/7 CYC, PRED, RTX, MMF	1/8 - progressive airway disease	1/7 miscarriage; 1/7 preterm; Median gestation - 40 weeks; median birth weight- 3.38 kgs.
Tuin, J. et al 2012 (Netherlands)	retrospective cohort	14;22	31	2/22 cases- hypertension; 3/22 cases - proteinuria at conception. ⏀	Unspecified no of GPA and MPA	Not applicable	9/14 CYC. 1/14 PRED, ciclosporin, MMF, 1/14 MTX and PRED, 4/14 co-trimoxazole ⏀	2/22 - pre-eclampsia; 1/22 -worsening tracheal stenosis with emergency tracheotomy; 1/22- episcleritis, arthralgia and renal disease; 2/22 - postpartum thyroiditis ; 1/22 - emergency C-sections. ⏀	Median gestation - 39.6 weeks; median birth weight 3.4 kgs; 2/22 preterm deliveries;; 1/22 - neonatal hypothyroidism; 1/22 congenital anomaly. ⏀

Table 2 (*continues*)

Table 2. Patient characteristics, induction treatment, maternal and foetal outcomes for eight studies. (*continued*)

Study	Type of study	Number of patients; number of pregnancies	Mean age	Maternal comorbidities	Type of vasculitis	Matched group criteria	Induction regimen	Maternal outcome	Foetal outcome
Croft et al 2015 (United Kingdom)	retrospective cohort	12;13	34	1/12 - hypertension	10/12- GPA, 2/12 - MPA,	Not applicable	11/12 - PRED and CYC; 1/12 - PRED, CYC and plasma exchange; 1/12 RTX	2/12 emergency C-section; 1/12 with twin pregnancy had preeclampsia; 1/12 had progressive tracheal stenosis requiring tracheal debridement post delivery; 1/12 worsening renal function	11/12 had gestation>37 weeks; 1/12 with twins delivered at 31 weeks for preeclampsia; median birth weight 3.12 kg
Auzary, C. et al 2000 (France)	case series	2;5	28.7	3/5 - Type 1 diabetes	GPA	Not applicable	1/5- CYC and PRED. 2/5 - PRED. 1/5 PRED, CYC, co-trimoxazole.	1/5 - termination of pregnancy. 1/5 - pre-eclampsia and HELLP syndrome. 1/5 - pre-eclampsia.	1/5 - congenital anomaly; Mean gestation 35.6 weeks; mean birth weight 3.93 kg
Lima, F. et al 1995 (United Kingdom)	case series	2;3	24	1/2- asthma and nasal polyp removal	GPA and eGPA	Not applicable	1/3- PRED and CYC; 1/3 - PRED, CYC, AZA.	1/3 flare; 1/3 postpartum flare	1/3 - stillbirth at 25 weeks. Mean gestation 39.5 weeks; mean birth weight 3.34 kg

Abbreviations: AAV: ANCA associated vasculitis; AZA: azathioprine; BMI: body mass index; CYC: cyclophosphamide; eGPA: eosinophilic granulomatosis with polyangiitis; GPA: granulomatosis with polyangiitis; HELLP: Hemolysis, Elevated Liver enzymes, Low Platelet syndrome; MMF: mycophenolate mofetil; MPA: microscopic polyangiitis; MTX: methotrexate; RTX: Rituximab. ⇳: heterogenous data across several vasculitides reported.

steroid regimen (14). One patient had arthralgias and glomerular erythrocyturia requiring daily high dose steroids (17). One patient had progressive renal disease with a biopsy showing tubular atrophy and segmental necrosis that resolved after plasma exchange, intravenous immunoglobulin, PRED, and AZA (16). There were five documented postpartum flares in patients with AAV, with one flare occurring as a result of stopping AZA postpartum (12,17). Of note, no patients had severe renal disease necessitating dialysis during pregnancy.

Maternal outcomes

The maternal outcomes are divided into antepartum and postpartum complications in this SLR, summarized in Table 3 where data are available. During the antepartum period, ten (10/64, 16%) patients had pre-eclampsia; three required an emergency C-section as a consequence of this (13,16). One patient progressed to haemolysis (H), elevated liver enzymes (EL), and low platelets (LP) (HELLP) syndrome, and was followed by delivery of a healthy newborn (18). There were additional rare outcomes reported across twin and singleton pregnancies including cholestasis of pregnancy (n=3), transaminitis (n=3), postpartum thyroiditis (n=2), progressive airway disease (n=1) and worsening tracheal stenosis (n=1) (13). Four elective C-sections were performed for obstetric reasons. In Sangle's and Nguyen's case control studies, the healthy control patients experienced antepartum haemorrhage (n=1), retained placenta (n=3), pre-eclampsia (n=4), cholestasis of pregnancy (n=1) and gestational diabetes (n=6) (12,13). Of note, there are no reports of maternal death in these studies.

Foetal outcomes

Where available, adverse foatal outcomes are summarized in Table 3. Among the 82 pregnancies evaluated in this paper, there were three terminations of pregnancies (one for encephalocele, one for premature rupture of membranes, and one for active AAV disease in the mother which had previously resulted in pulmonary haemorrhage) (13,18). In addition, there were four (4/82, 5%) first trimester miscarriages (15,16), including one for a congenital syndrome unrelated to AAV at 15 weeks (14) and an additional stillbirth of a macerated foetus at 25 weeks (17). The average gestational age across the 82 pregnancies was 38.26 weeks (SD = 1.6) and the average birth weight for live babies was 3.37 kg (SD= 0.42). Sangle et al's case-control study reported 13 spontaneous miscarriages across 51 pregnancies with systemic vasculitides (not limited to AAV). Compared to the 27 miscarriages in 156 pregnancies in the control group, this was not a statistically significant difference (12). This study also reported one intrauterine death in a patient with p-ANCA positive renal vasculitis (12). In Ganhao et al's study, twin pregnancies with vasculitis were more likely to have preterm births, lower birth weight, and shorter length (11). There were ten (10/82, 12%) preterm deliveries reported, either spontaneous (n=5), induced due to hypertension (n=4) or macrosomia (n=1) (13), all resulting in good outcomes for the newborn. Foetal malformations and diseases were observed in Ganhao's case control study and Tuin's cohort study with reports of congenital heart defects (n=2), congenital upper airway obstruction (n=1), orofacial deformities (n=2), and hypothyroidism (n=2); these outcomes were not specific to mothers with AAV.

Discussion

This SLR evaluated the maternal and foetal outcomes of pregnant women with AAV. Our analysis of eight studies shows that there were no maternal deaths and no ANCA-vasculitis symptoms in the newborns. Patients were administered a variety of combinations of CYC, PRED, MTX, AZA, ciclosporin, and MMF as induction treatment, and primarily used AZA and PRED for maintenance therapy during pregnancy. There were rare outcomes such as miscarriages and congenital anomalies, although this was comparable to control patients in case-control studies. The average birth weight was 3.37 kg and the average gestational age was 38.26 weeks. There were cases of preeclampsia and vasculitis flares during pregnancy and these were managed appropriately in each individual study.

Our initial search suggests that there is a lack of studies with high patient sample numbers correlating AAV in pregnancy. Due to the rare nature of AAV in young women, the available evidence is scarce. Our SLR shows that despite the devastating consequences of AAV such as tracheal stenosis, renal failure, and pulmonary haemorrhage, the majority of women have positive outcomes for themselves

Table 3. Summary of maternal and foetal outcomes.

Study	Number of patients; number of pregnancies	Pre-eclampsia (n)	Intrapartum flare (n); nature of flare where described	Post-partum flare (n)	Emergency Caesarean section (n)	Miscarriage/ spontaneous abortion (<20 weeks) (n)	Intrauterine death/ stillbirth (≥20 weeks) (n)	HELLP Syndrome (n)	Other maternal complication(s) (n)	Pre-term birth (n)	Congenital anomaly (n)	Other neonatal complications (n)
Ganhao, S. et al 2021 (Italy)	3;3											
Nguyen, V. et al 2019 (Canada)	16;20	2		1	3					5		
Sangle, S. R. et al 2015 (United Kingdom)	10;10	1					1					
Pendergraft, W. et al 2013 (United States)	5;7		1 (progressive airway disease)			1				1		
Tuin, J. et al 2012 (Netherlands)	14;22	2	2 (1 worsening tracheal stenosis needing tracheotomy; 1 episcleritis, arthralgia, renal disease)		1				2 postpartum thyroiditis	2	1	1 (neonatal hypothyroidism)
Croft et al 2015 (United Kingdom)	12;13	1	2 (1 progressive tracheal stenosis requiring tracheal debridement; 1 worsening renal function)		2							
Auzary, C. et al 2000 (France)	2;5	2						1			1	
Lima, F. et al 1995 (United Kingdom)	2;3		1	1			1					

Abbreviations: HELLP syndrome: Hemolysis, Elevated Liver enzymes, Low Platelet syndrome.

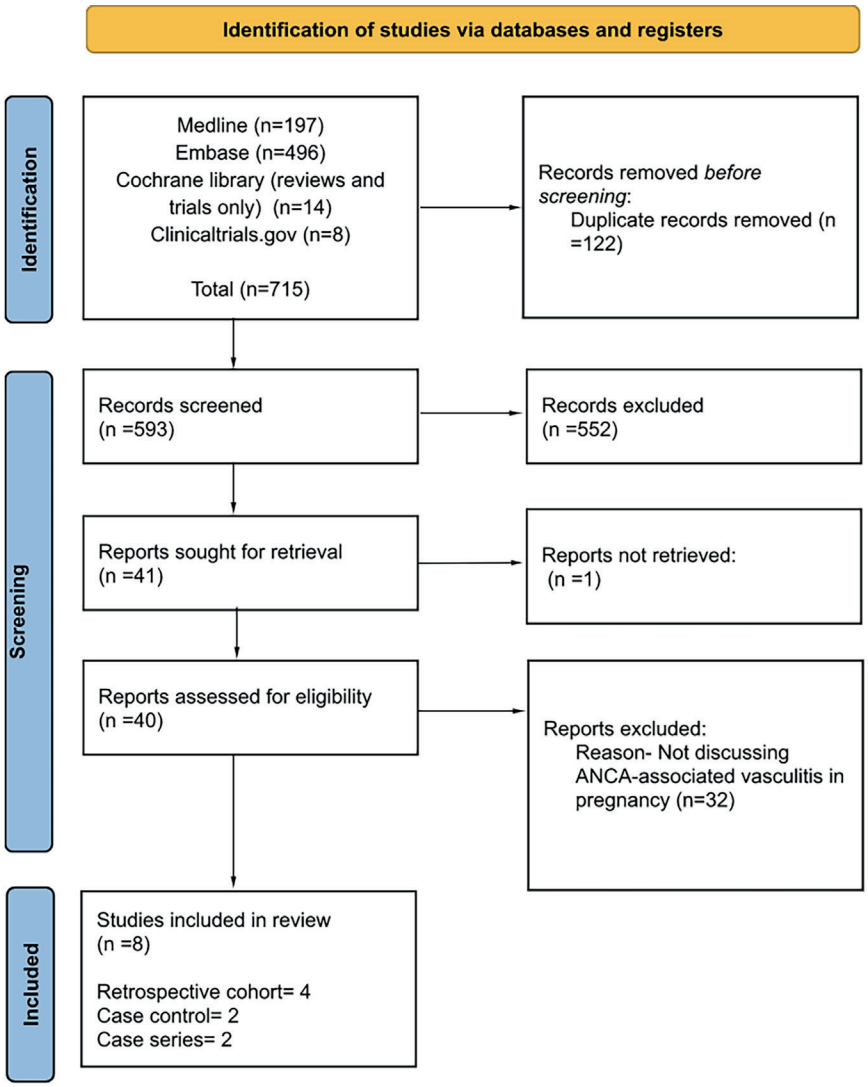

Figure 1. Flow diagram of stages of systematic literature review. Cochrane Library encompasses library of: systematic reviews; systematic review protocols; controlled clinical trials.

and their newborns. This can be due to several reasons. The first is that assessment and follow-up during pregnancy has advanced exponentially since the 1990s, especially in more developed countries where these studies took place (19,20). This also means patients in these countries have better access to preconception clinics to optimise disease management prior to a planned pregnancy regardless of comorbidities. There is no data reported in countries outside of North America or Western Europe. The results may have been different in resource-restricted countries where access to preconception clinics, specialist rheumatological cytotoxic agents or appropriate follow up care post-pregnancy is limited.

The second theory is articulated by Tuin et al in their cohort study (15); the authors note that despite most women in the study being ANCA positive and having placental immunoglobulin G (IgG), the antibodies should have transferred across the placenta. Surprisingly, none of the newborns from 82 pregnancies had any clinical signs of AAV. This may suggest that the simple transfer of ANCA may not be sufficient to cause disease. This is refuted by two individual case studies which describe a transfer of myeloperoxidase-ANCA (MPO-ANCA) between mothers with active disease and the foetus, resulting in pulmonary haemorrhage and renal failure in the newborns in both cases (21,22). These appear to be

the only reported cases of placental transfer of antibodies, and are seen exclusively in MPO (23). Hence it warrants further research into this phenomenon.

The third theory can be associated with the induction treatment for the patients and the time between induction and conception. Our results differed from Veltri et al's systematic review in 2020, which analysed maternal and foetal outcomes in de novo AAV diagnosed during pregnancy (24). They reported a higher rate of premature newborns (73% of births before 37 weeks, and 40% prior to 34 weeks) (25,26) and end-organ damage (56% of patients had alveolar haemorrhage, respiratory failure, limb ischemia, mesenteric ischemia and severe heart failure requiring transplantation). They also reported two maternal deaths secondary to intracranial haemorrhage in a patient with GPA and acute respiratory distress syndrome (ARDS) in a patient with MPA. In addition, C-sections were more likely to be performed in de novo vasculitis (41%) compared to vasculitis in remission (9-23%) (24). This could imply that patients with de novo cases of AAV may be at higher risk of complications compared to women who have induced remission at least one year prior to conception, possibly due to a delay in recognition of symptoms or delay in starting treatment. This is enforced by Croft et al's study in which 8/13 pregnancies reported a negative ANCA at conception with a further three patients having undetectable ANCA throughout the pregnancy (16). The good control of disease preconception and during pregnancy could explain the positive outcomes reported in this study. This may also provide evidence for termination of pregnancy if de novo vasculitis appears in the first trimester, in order to avoid the aforementioned maternal and foetal outcomes (24). Our results were in line with data from a 2018 systematic review by Singh et al, with favourable outcomes such as 91/137 (66.4%) term deliveries, 28/137 (20.4%) preterm deliveries and 3/137 stillbirths (2.2%) (27). This indicates that women with remission of their disease prior to conception may have better outcomes, as corroborated by this SLR. This again emphasises on the importance of optimal disease management prior to conception in women with AAV.

Through trials such as the CYCAZAREM, there is evidence to suggest that cyclophosphamide combined with glucocorticoids for 3-6 months can induce remission in 90% of patients (28,29). Furthermore, Rituximab (RTX) has proven to be more efficacious than CYC in treating relapsing vasculitis (30). However, CYC, MMF and methotrexate have widely known teratogenic effects and may affect ovarian function (31–34). In the studies evaluated in this SLR, CYC was widely used to induce remission successfully prior to conception and had little side effect on the patients; CYC may still have a role in induction treatment following appropriate counselling of women and the use of contraception during treatment.

With respect to Rituximab, a case report by Pefanis et al described positive results to treat de novo AAV at 12 weeks (32); however, another case report by Harris and colleagues reported poor outcomes including an emergency delivery at 29 weeks for worsening renal function secondary to Rituximab (35). In the latter case, the neonate was transiently lymphopenic, and the mother's CD 19+ was depleted. This is in keeping with several other studies which have found a temporary depletion of B cells in neonates which resolves within 6 months and has no infective complications (35,36). In Pendergraft et al's study, they also report undetectable CD 20+ cells in six out of eight mothers in their study, which further corroborates the immunosuppressive strength of Rituximab (14). Furthermore, a review by Leroy et al summarises several immunological therapies and their effects on gametogenesis and teratogenesis; ciclosporin appears to have no negative effect on ovarian function and inflicts limited harm on the foetus (37). Rituximab and ciclosporin in ANCA-vasculitis deserve more research as an alternative for patients in whom CYC is contraindicated, especially for patients with vasculitis diagnosed during pregnancy.

Lastly, the outcomes relating to twin pregnancies, such as early gestation, lower birth weight and smaller body length of the newborns seen in Ganhao and colleague's case control study appear to be comparable to twin pregnancies in the control group and in the literature (38). There was no statistically significant difference in pregnancy or neonatal complications between twins and singleton pregnancies with vasculitis and the control healthy group. There was a statistically significant increase in preterm births and rates of emergency C-sections in twin pregnancies with vasculitis compared to singleton pregnancies; however, it can be argued that this is not specific to patients with vasculitis and is a known obstetric risk of twin pregnancy regardless (39,40).

The results from our SLR suggest several key points for clinical practice. Optimization of vasculitis

control in mothers prior to conception, with a minimum of 1 year, through planned conception under the joint care of rheumatologists and obstetricians, appears to have the most favourable outcomes in this group of patients. This highlights the need for pre-conception counselling and joint clinics to ensure pre-conception planning can be as good as possible prior to pregnancy. This is consistent with international organizations such as EULAR who advocate for use of pre conceptions clinics and joint care between specialties for patients with complex autoimmune conditions including systemic lupus erythematosus and antiphospholipid syndrome. Our data demonstrate in frequent flares both during the pregnancy and post-partum period, as well as minimum complications in both mother and child. However, where optimization of disease during the pregnancy is required during pregnancy, AZA and PRED were the most frequently used whilst resulting in minimal side effects. This is consistent with current national and international guidelines, which recommend these drugs as safe options in pregnancy (42, 43). Orchestrating the care of the pregnant women through involvement of appropriate members of the wider multi-disciplinary team certainly helps to ensure that the points highlighted through our results, including planned pregnancies and managing intra- and post-partum flare, can be optimized.

Strengths and limitations

This SLR has several strengths including starting with a broad search and accepting several types of research studies, including case series, which has allowed for a comprehensive review of the literature. The case-control studies and two of the cohort studies also fare well with regard to a low risk of bias as seen in Table 1. This SLR will assist clinicians in making evidence-based decisions when treating pregnant patients with AAV, especially with regard to induction agents used pre-conception, the benefits of inducing remission early in the disease process and counselling patients on the risks of the disease and its management on themselves and their newborns.

A few studies combined data across several vasculitides and did not report data for AAV alone, leading to heterogeneity of the available data. The studies included are primarily from developed countries in North America and Western Europe, and hence are likely not generalizable to developing countries where lack of access to maternal health and resources are likely to contribute to worse outcomes. Lastly, there was a general lack of reporting of ethnicities, BMI and comorbidities which are likely to be confounding factors that improve or worsen patient outcomes, and this is worth exploring in future studies. It appears that there is limited reporting bias, as cases with both positive and negative outcomes have been published, which in turn helps to expand our knowledge of this disease.

Conclusion

In summary, this SLR included eight studies to assess the maternal and foetal outcomes of pregnancy associated with women who are diagnosed with AAV before or during the pregnancy. Our data are consistent with favourable outcomes in terms of no maternal death, no neonatal AAV, no rare congenital anomalies and appropriate gestational age and birth weight. Disease optimization via a prolonged remission period prior to conception with a minimum of 1 year appears to have the most favourable outcomes in this group of patients. The most common induction agents used include CYC, PRED and AZA, with further scope to research Rituximab and ciclosporin in pregnancy for treatment of this condition. Flares in pregnancy were treated with AZA and PRED, which appear to have a minimal side effect profile; in the face of complex flares such as tracheal stenosis and pulmonary haemorrhage, patients are still able to achieve positive outcomes and be treated in a timely manner. There is also evidence for the use of joint obstetric-rheumatology clinics as part of a multidisciplinary team to assist in decision making and counselling of the patient.

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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