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Review article

Cerebral venous sinus thrombosis in pregnancy and puerperium: A pooled, systematic review

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ABSTRACT

Pregnancy and puerperium are risk factors for cerebral venous sinus thrombosis (CVST); however studies describing diagnosis and management in this population are limited. The objective of this study was to amalgamate published case reports and series regarding diagnosis and management of CVST in pregnancy and puerperium. Searches of PubMed and the Cochrane library were performed using search terms "pregnancy"/"puerperium" and "sinus occlusion"/"sinus thrombosis". Studies were included in our pooled analysis if they included individual patient symptoms, management approach and follow-up condition. Multivariate regression was utilized to assess the effect of non-modifiable factors on excellent outcome (mRS 0). Sixty-six patients were included. Mean duration of symptom onset to diagnosis was 5.9 days (95% CI 4.2–7.6). Clot involvement of the superior sagittal sinus was seen in 67% of cases, the transverse/sigmoid in 64% and of the deep venous system in 15% of cases. Management approaches included anticoagulation (91% of patients), IA (intra-arterial) thrombolysis alone (26%), and IA thrombectomy with IA thrombolysis (8%). Fifty-nine percent of patients were mRS 0 at follow-up; 94% were mRS 0-2. Presentation with headache alone was associated with excellent outcome on multivariate analysis ($p = 0.04$); coma/obtundation predicted against excellent outcome ($p = 0.03$). As compared to IA thrombolysis alone, patients undergoing IA thrombolysis with IA thrombectomy demonstrated a trend toward better outcome ($p = 0.10$).

1. Introduction

Cerebral venous sinus thrombosis (CVST) is a rare disease with an estimated annual incidence of 5 per million, accounting for 0.5–1.0% of all stroke [1,2]. A conservative estimate of the prevalence of people who have suffered morbidity from CVST in the general US population alone with respect to cognitive impairments, dependency, or restrictions in lifestyle currently numbers over 20,000 [3–7]. Within the general population, women experience more than three times the incidence of CVST when compared to men, at approximately 10–12 in 1,000,000 people per annum [3,8–10]. Mortality from CVST has improved to a rate of <15%, with an in-hospital mortality of 6% and a 30-day mortality of 4% or less [8,9,11–23].

The incidence of CVST increases with sex-specific risk factors such as oral contraceptive use, hormone replacement therapy, pregnancy, and puerperium [24]. In a retrospective study of 113 patients with CVST, Cantú et al. reported that 59% of patients presented during pregnancy or puerperium [25]. Roughly 0.004–0.01% of pregnancies are complicated by CVST, which cause about 2% of pregnancy-associated strokes [26]. The frequency of pregnancy-associated CVST is highest during the third trimester and puerperium [27,28]. CVST is estimated to affect 0.012% of deliveries during the puerperal period, and this risk is further modulated by factors such as infection, instrumented delivery, cesarean section, increasing maternal age, increasing hospital size, excessive vomiting during pregnancy, and hyperhomocysteinemia [28–30].

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Although pregnancy and puerperium are known risk factors for CVST, studies describing this population are limited to case reports and small series. This study amalgamates results from published cases of CVST in pregnancy and puerperium, evaluating clinical presentation, diagnosis, and intervention strategies in order to delineate non-modifiable and modifiable prognosticators for poor outcomes.

2. Methods

2.1. Study selection

The authors queried the Pubmed and the Cochrane Library databases for relevant articles utilized in this study. We utilized the following search command to identify articles published through September 2016: "(((pregnant) OR pregnancy) OR puerperium) AND ((sinus thrombosis) OR sinus occlusion)". Articles were initially screened for relevance based on title and/or abstract content. Subsequently, we conducted a full-text review of the articles remaining to assess for patient eligibility for the study. We included English-written case reports and case series describing CVST in pregnancy and/or puerperium. Studies were included in our pooled analysis if they included individual patient symptoms, management approach, and discharge or follow-up condition. Patients were excluded if they presented with symptoms greater than 6 weeks from delivery postpartum based on the literature definition of puerperium [31]. Patients were additionally excluded if they were lacking clinical outcome, lacking intervention data, or if they presented with comorbidities that confounded the outcome.

2.2. Data extraction

The following variables were extracted: (1) patient age, (2) pregnant vs. puerperal, (3) gestational age or postpartum length, (4) presence of pre-eclampsia or associated thrombophilia, (5) clinical presentation, (6) radiographic evidence of cerebral infarction or hemorrhage, (7) the duration from symptom onset to diagnosis, (8) method of diagnosis, (9) location of thrombus, (10) intervention strategy and complications, (11) duration from intervention to symptom improvement, (12) radiographic evidence of sinus recanalization, (13) time and clinical condition at last follow-up, (14) vaginal vs. caesarean section delivery, (15) use of epidural or spinal analgesia during delivery, and (16) fetal outcome. Intervention strategy was categorized into one of the three categories including anticoagulation (heparin, warfarin, enoxaparin, or nadroparin sodium), intra-arterial (IA) thrombolysis with urokinase (UK) or tissue plasminogen activator (tPA) alone, and IA thrombectomy with thrombolysis. The need for decompressive craniectomy was also noted. Patients were included in the IA thrombolysis alone group if they received IA tPA or UK without thrombectomy, regardless of anticoagulation therapy. The primary outcome was measured utilizing the modified Rankin Scale (mRS) with excellent outcome defined as mRS 0; in some cases, mRS was deduced based on descriptions in the articles. All outcome data was utilized for this study regardless of follow-up length.

2.3. Statistical analysis

We initially performed a univariate analysis to determine variables significantly associated with the main outcome (mRS 0 or mRS >0, dependent categorical variable). Categorical variables were organized into contingency tables against the outcome variable for analysis using either a chi-squared test or Fisher's exact test. A Fisher's exact test was utilized in cases when the expected counts in any of the cells within a contingency table were less than 5. Continuous variables were initially tested for normality using a Kolmogorov–Smirnov test. To assess for differences in continuous variables according to outcome, we utilized a two-tailed student's t-test in cases of normality and a Wilcoxon signed-rank test in cases of non-normal data. We subsequently performed a multivariate logistic regression analysis using the variables identified in the univariate analysis as inputs to assess the odds ratio for excellent clinical outcome. Chi-squared and Fisher exact tests were utilized in sub-group analyses to determine differences in outcome across treatment modalities. mRS 0 and mRS 0-2 outcomes were considered for sub-group analyses. Statistical significance was always defined as $p < 0.05$ and continuous variables are reported as averages with 95% confidence intervals unless otherwise mentioned.

3. Results

3.1. Study selection

Our search identified 425 potential articles for review. After title and abstract examination for relevance to the current study, we screened out 352 articles. Of the 73 titles remaining, 12 were excluded due to lacking clinical outcome; 5 due to lacking intervention data; 4 due to CVST occurrence more than 6 weeks postpartum; and 2 due to comorbid terminal cancer that confounded the follow-up outcome data. Fifty articles (5 case series, 45 case reports) were included in the final analysis, which included 66 patients for data extraction (Fig. 1) [32–81]. Individual studies are described in further detail in Supplemental Table 1.

3.2. Baseline patient information, presentation, and diagnosis

The mean age of patients at presentation was 26.5 (95% confidence interval, 25.3–27.7) years. Of 66 patients in the cohort, 24 (36%) were pregnant, 42 (64%) were puerperal. Forty-six patients (70%) were primigravid (Table 1). The most prevalent signs and symptoms were headache (74%), seizure (50%), motor weakness (38%), coma or obtundation (45%), and visual disturbances (24%). Other less frequent signs and symptoms included nausea (17%), vomiting (23%), paresthesias/numbness (8%), neck stiffness (8%), photophobia (5%), and dysarthria/aphasia (8%). CVST was diagnosed most frequently with MRI (magnetic resonance imaging) and MRV (MR-venography) although there were six cases of false negatives (5-MRI, 1-MRV) on initial imaging that resulted in a delay in diagnosis [41,42,65,73,79]. Other common delays in diagnosis resulted from presumptive or concurrent diagnoses of postdural puncture headaches after epidural analgesia (12%) and the onset of eclampsia (5%) [35,36,38,41,49,50,52,59,71,77,80]. Thrombi were most frequently localized to the superior sagittal (70%) and transverse/sigmoid sinuses (58%), although most often (56%), patients presented with clots involving multiple elements of the venous sinus system. Concurrent thrombophilia was elicited from patient history or further lab studies in 38% of patients.

3.3. Intervention outcomes and complications

Of the total patient cohort, 60 (91%) patients were anticoagulated; 17 (26%) received IA thrombolysis alone; 5 (8%) received IA thrombectomy. Five patients ultimately required decompressive craniectomy (8%) (Table 2). We observed a high frequency of comatose patients within the IA thrombolysis alone (76%), IA thrombectomy (80%), and decompressive craniectomy (83%) groups (Table 1).

Regardless of treatment approach, 59% of patients achieved an excellent clinical outcome (mRS 0), with the majority (94%) of patients achieving a good clinical outcome (mRS 0-2). Mortality