SAFETY OF PREGNANCY FOLLOWING CEREBRAL VENOUS THROMBOSIS:

ISCVT2 - PREGNANCY

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STUDY PROTOCOL

RATIONALE FOR THE RESEARCH PROJECT:

Cerebral venous thrombosis (CVST) is a type of stroke involving dural sinus and veins of the brain. CVST is less common than other types of stroke, with a prevalence estimated to range from 0.22 to 1.23/100 000/year.

International Study of Cerebral Vein and Dural Sinus Thrombosis (ISCVT) was a prospective multinational observational study that included consecutive patients (aged >15 years) with symptomatic CVST. This multicentre, multinational collaboration provided new and robust information on many clinical questions but, despite the information provided there are several important clinical questions on this disease that remain to be answered in order to strength of evidence on the management of patients with CVST.

Pregnancy and the puerperium carry an increased risk of venous thrombotic events (VTE) including CVST but there are no precise data regarding relapse rate during pregnancy and puerperium in women with history of CVST, being the number of reported cases scarce and often with incomplete information regarding the regimen followed during pregnancy. As CVST is nowadays largely a disease of younger women and hormonal factors such as the intake of oral contraceptives or pregnancy are important risk factors in a large proportion of female patients, counselling of such women regarding future pregnancies remains a problem in clinical practice.
METHODS / DESIGN:

- **Study aims:**
  We aim to study the course and complications of pregnancy and puerperium, including the risk of recurrence of CVST and other thrombotic venous events, in women at childbearing age with previous cerebral venous occlusive disease.

- **Study design and setting:**
  Retrospectively assess the relapse rate of CVST and the incidence of venous thrombosis during subsequent pregnancies in female patients included in ISCVT who suffered a CVST at childbearing age.

- **Participants:**
  In ISCVT all participants committed themselves to provide data on consecutive cases diagnosed at their institutions and to perform at least a 6-month follow-up observation. Case report forms with inclusion and follow-up data were sent to the coordinating center in Lisbon, Portugal. All data were cross-checked and validated at the end of the follow-up period. Inclusion started in May 1998 and continued until May 2001. Patients were followed up from diagnosis to December 31, 2002. Most of the participants were neurologists. The diagnosis of CVT had to be confirmed by conventional angiography, CT venography, MRI combined with MR venography, surgery, or autopsy, following established diagnostic criteria. Demographic data, symptoms and signs, imaging data, risk factors including screening for thrombophilic state, treatment and outcome of CVST were previously recorded, with a median follow-up of 13.9 months.

  A total of 314 female patients in childbearing age (defined as less than 45 years at the time of CVST) were included in ISCVT and survived the acute phase, being eligible for the study.

  Data from the selected patients will be retrieved, namely demographic data, inclusion center and risk factors including thrombophilia.

  All the centers that included eligible patients will be invited to participate. Ethical Committee approval will be obtained in all participating centers.

  Informed consent is required for all participating women.
**Primary and secondary endpoint/outcome(s):**

The primary outcome is recurrence of CVST or other VTE associated with subsequent pregnancy.

The secondary outcomes are the pregnancy outcome and use and duration of antithrombotic prophylaxis during pregnancy and puerperium.

**Data collection and management:**

The questionnaire focuses on subsequent pregnancies asking for (1) recurrence of CVST (including its delay to the previous episode and how the diagnosis was established); (2) incidence of other VTE; (3) incidence of other pregnancy related complications and (4) use and duration of anticoagulation with heparin.

This data can be obtained in presentational consultation or by phone interview, using the standardised questionnaire. If questions are not or are equivocally answered in the mailed questionnaires, the patients or the treating physicians should be contacted by phone for clarification or completion of data (Figure 1).

Whenever the patient reported any pregnancy occurring after CSVT, the following information should be obtained: maternal outcomes (CVT, non-cerebral VTE; non-thrombotic complications associated with pregnancy/puerperium), fetal outcomes (spontaneous abortion, induced abortion, fetal death, preterm birth, full term birth,
congenital anomalies), antithrombotic prophylaxis (1st, 2nd and 3rd trimester of pregnancy and puerperium, defined as the first 6 weeks after delivery).

Imaging confirmation is required for the diagnosis of recurrent CVT or other venous thrombotic events. Imaging studies obtained elsewhere should be requested if there is concern about a new neurological event. If a patient was deceased, relatives of deceased patients should be contacted and outside data will be obtained.

- Synthesis of results

Simple comparisons of the baseline characteristics were made among the participants and non-participants of the cohort. The crude rates of recurrent CVT (per 1,000 pregnancies), non-cerebral VT (per 1,000 pregnancies) and spontaneous abortion (%) were calculated. In a secondary analysis these rates were stratified according to antithrombotic therapy. A p-value of 0.05 was considered statistically significant. 95% confidence intervals (95%CI) were calculated by the Wilson method.

**ANTICIPATED SIGNIFICANCE:**

*ISCVT-2 Pregnancy* aims to be the largest retrospective study to assess the safety of pregnancy in women with history of CVST.