NAME OF PROJECT

Guidance on the management of women with type 2B von Willebrand disease during pregnancy and postpartum

Subcommittee

Women’s Health Issues in Thrombosis & Hemostasis SCC
VWF SSC

Person responsible (Chair / Principal Investigator): Dr Predrag Miljic/ Dr Maha Othman/ Dr Michelle Lavin.

Description Abstract

State the application’s broad, long-term objectives and specific aims, making reference to the health relatedness of the project. Suggested length is 2-3 paragraphs.

Type 2B VWD accounts for about 5% of all cases of von Willebrand disease (VWD). As a result of single amino acid substitution in A1-domain of VWF leading to a gain-of-function mutation leading to single amino acid substitution in A1-domain of VWF, enhanced binding to platelet GPIb is exhibited. This increased affinity of dysfunctional VWF to platelets leads to accelerated uptake of VWF/platelet complex by macrophages and reduced lifespan of platelets. Thrombocytopenia is present in about 30% of patients at baseline, and in 57% of patients in stress conditions or during bleeding episodes. Type 2B VWD is usually characterized by moderate to moderate-severe bleeding tendency due to a combination of the qualitative defect in VWF as well as variable thrombocytopenia. Furthermore, beside the functional defect of plasma VWF and thrombocytopenia, it has been more recently demonstrated that a third mechanism explains bleeding in type 2_B. A well characterized thrombocytopathy as a result of dysregulated platelet signaling is a consequence of variant VWF binding to platelets (Casari C, JCI 2013). This dysregulated signaling impairs platelet aggregation, platelet secretion, and platelet spreading and could contribute to the need for platelet transfusion and the lack of efficacy of VWF concentrates alone in some cases. The heterogeneity of the disease at the clinical, laboratory and genetic levels has been described in literature and has added complexity to the diagnosis and management.

Management of women with type 2B VWD during pregnancy or postpartum is clinically challenging due to dysfunctional VWF whose physiological increase in plasma during pregnancy may exacerbate thrombocytopenia. In addition, in the event of antenatal or postnatal bleeding therapeutic options such as desmopressin (DDAVP) may be unsuitable for use in type 2B VWD due to release of dysfunctional VWF and worsening of thrombocytopenia. Hemostatic cover at time of delivery is often warranted, but the optimal therapeutic targets for both VWF levels and platelet count for delivery in women with type 2B VWD remain ill defined.
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In the current literature there are only 18 well described cases of management of pregnancy in women with type 2B VWD reported between 1987-2018. In all these cases, reported as case reports or small case series, management varied significantly. Use of VWF/FVIII concentrates was reported in all 18 cases, with variable use of platelet transfusion. Importantly, despite treatment, bleeding complications were still observed in approximately 1/3 of reported cases, highlighting the need for improved management strategies for women with this condition. The lack of evidence base regarding the management of women with type 2B VWD in pregnancy has hampered clinical guidelines in providing specific guidance for this subtype. As a result, management of women with type 2B VWD during pregnancy and postpartum mainly reflects a pragmatic approach based on this limited literature or expert opinions and hence are highly variable. The rarity of type 2B VWD limits the possibility of clinical studies in this area. Given all of the above, an ISTH guidance document for the management of women with type 2B VWD during pregnancy and postpartum is expected to enhance the fetal and maternal outcomes. This guidance document will be developed in coordination with both the Women’s Health and VWF SSC of the ISTH.

Both SSCs will work initially on a well-organized international registry to collate data and improve our understanding of the current practices and the pregnancy outcomes and management for women with type 2B VWD. This registry will aim to engage with clinicians worldwide and collect sufficient amount of high quality data on management and outcomes in women with type 2B VWD during pregnancy and postpartum.

Efforts will then be combined to extract data from the SSC on VWF’s recent ISTH supported survey of clinicians on the management of VWD in pregnancy. This data is already collected by Dr. Michelle Lavin; the specific responses in relation to management of type 2B VWD will be extracted, providing information on the current clinical management practices internationally.

This registry and current data from the VWD project would help inform and enable generation of recommendations from the ISTH on management of type 2B VWD during pregnancy, reducing variability in care worldwide.

Design and methodology (Data expected to collect, sample size and statistical analysis):

Describe concisely the research design and methods for achieving these goals. Suggested length 2-3 paragraphs

The plan of the ISTH guidance document will be based on data collection on the pregnancy outcomes for women with type 2B VWD via the following systematic tripartite approach:

1. To develop an international registry through the ISTH using the REDCap tool. This would provide an easily accessible platform for practitioners (hematologists, gynecologists, anesthesiologists) to document details of management and outcomes of cases of women with type 2B VWD during pregnancy and postpartum. Data can be collected in both a prospective and retrospective manner. Clinicians will be actively invited to participate in the registry through international conferences, mailing lists and social media outreach. Housing the registry in REDCap, with the support of the ISTH,
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would allow participation of practitioners worldwide, contributing to accrual of data for this relatively rare condition. Each of participating practitioners will be responsible for ethic’s approval according to local guidelines at individual institution.

2. Systematic review of the literature to date of all published cases of pregnancy in women with type 2B VWD with extraction of details related to management and outcomes.

3. Extraction of data related to management of type 2B VWD during pregnancy from the recent ISTH supported survey of clinicians on the management of VWD in pregnancy. This data is already collected by Dr. Michelle Lavin; the specific responses in relation to management of type 2B VWD will be extracted, providing information on the current clinical management practices internationally.

Following completion of these steps, a joined panel of experts from SSC for Women’s Health Issues in Thrombosis & Hemostasis and SSC for VWF will analyze data and draft the guidance document and generate recommendations for management of this rare condition during pregnancy and postpartum.

Study population (Inclusion, exclusion, eligibility) (patient population; recruitment of participating institutions/physicians and subjects; minimum number needed; expected number):

Suggested length 2-3 paragraphs

The study population would include pregnant women who met diagnostic criteria for type 2B VWD. Pregnancy will be defined as a positive pregnancy test and/or presence of the fetal heartbeat on ultrasound. In this manner, data will also be collected on the rate of pregnancy loss and frequency of bleeding complications after miscarriage or abortion. In the registry following data will be collected:

a. Baseline demographics (age, country of residence, parity),

b. Bleeding phenotype before pregnancy, treatment to date,

c. Diagnosis of type 2B (personal and family bleeding history with proven mutation within exon 28 and/or reduced ratio (<0.7) of VWF platelet-binding activity to VWF antigen (VWF:Act/vWF:Ag <0.7 or low VWF:CB/VWF:Ag ratio) associated with enhanced RIPA with exclusion of platelet type-VWD).

d. Known family history, age at diagnosis and source of referral if known,

e. Level of VWF:Ag, VWF:Act, FVIII and platelets count before, during pregnancy and postpartum with specification of the method that has been used to obtain results of VWF:Act.

f. Management during pregnancy and postpartum (VWF/FVIII concentrate and platelet substitution, antifibrinolytics),
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g. Outcome of pregnancy,

h. Mode of delivery, use of neuroaxial analgesia and VWF/FVIII levels at which administered,

i. Complications in mother and baby.

Women who don't fulfilled diagnostic criteria for 2B variant, with other types of VWD or other causes of thrombocytopenia will not be included. Keeping in the mind rarity of condition, our intention is to collect data for 50 women during pregnancy, including 18 well described cases published so far. For women already included in publications, the clinicians will be asked to provide the publication reference to avoid duplication of records. This data set will allow a descriptive analysis of factors influencing outcome of pregnancy and enable outlining of recommendations for management pregnancy in women with 2B VWD.

Expected timeline:

- Project stage/set up: 3 months from approval
- Launch: Once set up is complete
- Duration: 3 years
- Finalization/analysis: 6 months
- Reporting: 3 months

Expected outcomes (ie. publications):

Guidance document from the ISTH SSC (Women’s Health and VWF), original publication, potential change to existing guidance documents.

Description of project set up and management, needed infrastructure and resources (summary):

If approval is granted, we would work with the relevant SSCs to create the REDCap registry and with relevant collaborators to input data over time.

Each clinician wishing to add data into the registry would be responsible for obtaining consent from the patient. Data could be entered directly to the REDCap registry through an online link.

Investigators will perform thorough review of current literature and input in the registry data for cases with 2B VWD in pregnancy where full set of data was provided.

Predrag Miljic (Faculty of Medicine, University in Belgrade, Belgrade), Dr Maha Otman (Queen’s University, Kingston, Canada) and Michelle Lavin (RCSI, Dublin, Ireland) will analyze the data, report to SSC and write the publication.
Possible references:


