

## COMMENTARY

# Standardizing definitions for bleeding events in studies including pregnant women: A call to action

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Venous thromboembolism (VTE) is a leading cause of death in pregnancy and during the postpartum period.<sup>1</sup> Weight-adjusted low molecular weight heparin (LMWH) is used to prevent and to treat VTE during pregnancy. The stakes are very high: a maternal death from a pulmonary embolism (PE) is a devastating event with wide-reaching consequences for the woman's family, friends, and society. VTE may also impose lifelong disability. VTE risk rises during pregnancy and peaks in the postpartum period, with reported pooled incidence rates of 1.2 (95% confidence interval [CI]: 1.0–1.4) and 4.2 (95% CI: 2.4–7.6) per 1000 person-years during the antenatal and postpartum periods respectively.<sup>2</sup> Consequently, optimal VTE prevention and treatment is of crucial importance.

Postpartum hemorrhage (PPH) is also a leading cause of global maternal death: in a 2014 World Health Organization systematic review analyzing global, regional, and subregional estimates of the causes of maternal death during 2003–2009, hemorrhage accounted for 27.1% (19.9%–36.2%) of global maternal deaths.<sup>3</sup> Anticoagulation administered for VTE treatment is known to be associated with a bleeding risk, which may be relevant during pregnancy, in the peripartum period and postpartum.<sup>4–7</sup>

Despite these high competing risks, the precise effect of therapeutic anticoagulation on bleeding risk in pregnancy is poorly characterized. Randomized controlled trials (RCTs) evaluating a range of LMWH doses have provided some data: for example, in both prophylactic LMWH and no-LMWH RCT arms, the risk of major bleeding has been reported to be low.<sup>8</sup> Although minor bleeding appears

common (but variable) in women in heparin and no-heparin RCT arms, it remains uncertain whether LMWH significantly affects this risk.<sup>9</sup>

In this issue of RPTH, Simard and colleagues tackled this important knowledge gap. They conducted a systematic review according to a prespecified protocol registered on PROSPERO (CRD42021276771) and conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, the aim of which was to evaluate the risk of antepartum and postpartum bleeding in women receiving therapeutic anticoagulation for VTE during pregnancy.<sup>10</sup> Studies were included if they involved use of therapeutic anticoagulation for treatment of acute pregnancy-associated VTE with weight-adjusted LMWH and if they reported a defined bleeding outcome. Studies were excluded if the main LMWH indication was not VTE. Five studies (representing 611 patients receiving therapeutic LMWH and 876 controls) were included, comprising four retrospective cohort studies<sup>5–7,11</sup> and one prospective cohort study.<sup>12</sup> The risk of bias of most studies ranged from serious to critical because of issues including absence of controls in some of the include studies and the absence of a standardized assessment method for bleeding.

Importantly, the authors identified an important quality issue: variability in bleeding definitions used in individual studies. Two studies used the International Society on Thrombosis and Haemostasis (ISTH) definition of major bleeding, one used a composite endpoint of major complications and the final two used PPH

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as a bleeding endpoint. This limitation challenged firm conclusions and permitted only a descriptive report of outcomes: major bleeding risk (according to the ISTH definition) was reported in 2.9%–5.0% and risk estimates of PPH were 12%–30% in women receiving therapeutic anticoagulation for VTE treatment during pregnancy. One study suggested a higher PPH risk in women receiving therapeutic anticoagulation compared with controls (30.0% vs. 18.0%, odds ratio [OR] 1.9, 95% CI 1.1–3.5),<sup>5</sup> whereas another suggested no significant difference between groups (18.0% vs. 22.0%, relative risk [RR] for PPH 0.8, 95% CI 0.5–1.4).<sup>6</sup> Importantly, the authors highlighted the dearth of high-quality data despite the clear importance to patients' lives and health of therapeutic anticoagulation for VTE in pregnancy.

Therefore, this systematic review, in addition to its importance in its own right, serves as a crucial call to action for higher quality studies and funding prioritization in this area. Both VTE and maternal bleeding are major global health priorities that kill thousands of pregnant women every year.<sup>1,3</sup> PPH accounts for almost one quarter of all maternal deaths worldwide<sup>13</sup> and is the second leading cause of direct maternal mortality in the UK and Ireland.<sup>14</sup> PPH is also a significant contributor to severe maternal morbidity and long-term disability.<sup>15</sup> Alarming, the incidence of PPH is increasing.<sup>15,16</sup> The four main drivers of PPH have traditionally been described as the “the four Ts”: Tone (failure of the uterus to contract), Tissue (retained placenta/membranes), Trauma (lacerations/uterine rupture), and Thrombin (abnormal coagulation). Anticoagulation may therefore be hypothesized to influence PPH risk by affecting the fourth “T.” As the authors point out, further challenges arise from the fact that variability in peripartum clinical practices also likely influence bleeding risks and obstetric intervention can differ widely by center, in particular the routine use of active management of the third stage of labor and the time interval between the last dose of LMWH and delivery. Further challenges arise from the way that PPH is measured and defined.<sup>10</sup>

There has indeed been a shameful lack of a clear bleeding definition as a safety outcome in past studies evaluating LMWH during and after pregnancy. In a 2019 systematic review of RCTs addressing this issue, and including a range of LMWH doses and indications, only 34% of the 2690 women included in a trial evaluating the effect of LMWH had bleeding events prospectively recorded using a standardized definition.<sup>9</sup>

Arising from this unmet clinical need, a new classification of bleeding during and after pregnancy for use in clinical trials has recently been proposed by the Scientific and Standardization Subcommittee (SSC) on Control of Anticoagulation of the ISTH<sup>9</sup> (Figure 1). In particular, specific definitions of gynecological

bleeding events are provided, with a focus on what kind of management they require and whether the events are frequently associated with the normal childbirth process. An adaptation of the CRNMB definition to the context of pregnancy and postpartum is proposed, and a downgrade of some events to minor bleeding. For example, antepartum minor vaginal bleeding events are very common (occurring in 20%–30% of women), and also frequently lead to an unscheduled contact with a health care professional. Traditionally therefore, these would have been classified as clinically relevant nonmajor bleeding (CRNMB) events. However, in the new ISTH SSC classification for bleeding during and after pregnancy, such events are classified as minor bleeding events. Another example is primary PPH (<1000 ml) not requiring intervention (other than a prophylactic uterotonic), which is suggested to be reported as a minor bleeding event unless it requires additional treatments/interventions (Figure 1).

Standards have already risen for evaluation of bleeding outcomes in pregnant women in world-class clinical trials: the recently completed multicenter, multinational Highlow RCT (NCT01828697) has included the use of an independent adjudication committee to validate both thromboembolic and bleeding events. We hope that the adoption of such standards and the use of the proposed ISTH definitions by future studies will reward the huge efforts of trialists with safety outcomes that provide meaningful data for the patients that we serve. Moreover, more high-quality data will in coming years be available from ongoing well-designed prospective cohort studies that are addressing the effect of peripartum anticoagulation on patient outcomes including bleeding outcomes. For example, the prospective, multicentre “PREP and GO” study (PRospective Evaluation of Peripartum Anticoagulation manaGement for thromboembolism; prepandgo.ca; led by Dr Leslie Skeith) is an international cohort study that will evaluate peripartum anticoagulation management across centers for pregnant women with VTE and will include bleeding and VTE outcome assessment using standardized definitions and adjudicated outcomes.

In conclusion, bleeding complications arising from the use of therapeutic anticoagulation for VTE management in pregnancy are poorly characterized (Figure 2). Simard and colleagues, in their systematic review, provided an estimate for bleeding risks in this context, cognizant of a high risk of bias. They highlight the challenges and knowledge gaps that contribute to this phenomenon, including a lack of standardized definition for bleeding events in studies including pregnant women and call for future studies to adopt the new ISTH classification for bleeding in pregnancy and postpartum. Such standardization will be crucial for trials to achieve the best possible impact for patient care in the future.

**FIGURE 1** Proposed definition of bleeding events in studies evaluating antithrombotic therapy in pregnant women from ISTH SSC on Control of Anticoagulation (reproduced with permission). Colors correspond to the criteria selected for each class of bleeding: red for major bleeding, orange for clinically relevant nonmajor bleeding, and green for minor bleeding, respectively. (A) Proposed classification for antepartum and secondary postpartum (24 h to 6 weeks after delivery) periods. (B) Proposed classification for primary postpartum (first 24 h of delivery) period.

(A)		Major bleeding	CRNMB	Minor bleeding
<b>Antepartum and secondary postpartum periods</b>				
Vaginal bleeding	Prompting a face-to-face evaluation			■
	Leading to hospitalization		■	
	Leading to antithrombotic therapy modification		■	
	Related to early pregnancy loss <sup>c</sup>		■	
Placenta praevia	■			
Placenta abruption	■			
Fetal or neonatal death (for example bleeding because of placenta abruption)	■			
Any sign or symptom of hemorrhage <sup>c</sup> including bleeding found by imaging alone			■	
Acute clinically overt bleeding	Prompting a face-to-face evaluation		■	
	Leading to hospitalization or increased level of care		■	
	Requiring medical intervention by health-care professional		■	
Acute clinically overt bleeding	Leading to death	■		
	That occurs in a critical organ: intracranial, intraspinal, intraocular, retroperitoneal, pericardial, intra-articular, intramuscular with compartment syndrome	■		
	Associated to a fall in hemoglobin level of 2 g/dL or more	■		
	Leading to transfusion of two or more units of whole blood or red cells to	■		

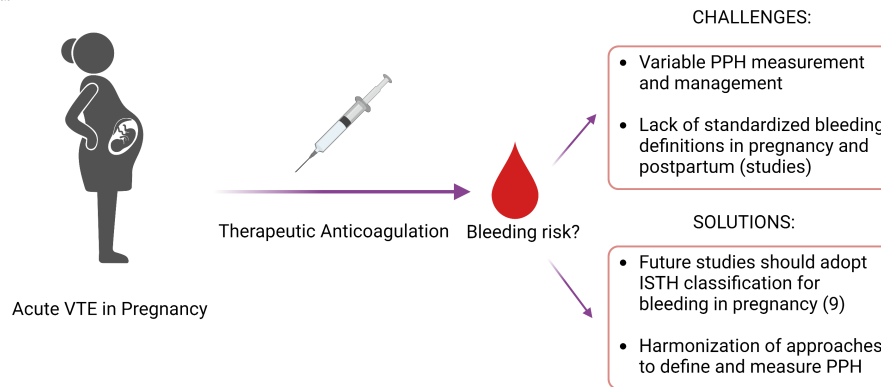
<sup>a</sup>Early pregnancy loss before the 13th gestational week (first trimester).

<sup>b</sup>Placenta praevia requiring delivery.

<sup>c</sup>Defined as any overt, actionable sign of hemorrhage (vaginal and nonvaginal) that does not fit the criteria of major bleeding (including spontaneous subcutaneous hematoma >25 cm<sup>2</sup> or >100 cm<sup>2</sup> if provoked).

(B)		Major bleeding	CRNMB	Minor Bleeding
<b>Primary postpartum period<sup>a</sup></b>				
Blood loss <1000 mL	Alone (including one prophylactic administration of uterotonics)			■
	Leading to Uterus intervention to stop bleeding (eg curettage)		■	
	A first line of treatment with uterotonics and/or tranexamic acid		■	
Blood loss ≥1000 mL	Transfusion of two or more units of whole blood or red cells to maintain hemoglobin level >7-9 g/dL	■		
	Alone			■
Leading to	A first line of treatment with uterotonics and/or tranexamic acid		■	
	Uterine intervention to stop bleeding (eg curettage)	■		
	A second line of treatment with uterotonics	■		
	Transfusion of two or more units of whole blood or red cells to maintain hemoglobin level >7-9 g/dL	■		
	Balloon tamponade	■		
	Embolization	■		
	Conservative surgery	■		
	Hysterectomy	■		
	Death	■		

<sup>a</sup>In case of hemorrhage of nongynecological origin, refer to the Table 3.



**FIGURE 2** Bleeding complications arising from the use of therapeutic anticoagulation for VTE management in pregnancy are poorly characterized. Challenges and knowledge gaps that contribute to this phenomenon should be addressed, including a lack of a standardized definition for bleeding events in studies including pregnant women. Solutions include the adoption of the ISTH classification for bleeding in pregnancy and postpartum<sup>9</sup> in future studies.

### AUTHOR CONTRIBUTIONS

Both KS and FNA wrote the paper and contributed equally.

### RELATIONSHIP DISCLOSURE

The authors report no conflicts of interest relevant to this work.

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