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COMMENTARY

Venous thromboembolism still leads on maternal death

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It is concerning that venous thromboembolism (VTE) remains the leading cause of maternal mortality in the United Kingdom. The 2024 Mother and Babies; Reducing Risk through Audits and Confidential Enquiries across the UK (MBRRACE-UK) State of the Nation report indicates that VTE accounted for 16% of maternal deaths during and up to 6 weeks after the end of pregnancy between 2020 and 2022 [1]. This has increased since the previous MBRRACE-UK report, which reflected 2017-2019 data, and VTE is now responsible for the same number of maternal deaths as the next 3 most common direct causes put together: suicide, hemorrhage, and sepsis. These data support the conclusion of other datasets, including that of the World Health Organization, that the United Kingdom is an outlier when compared with other European countries. There are 1.5 VTE deaths per 100,000 live births, with the next highest of 0.8 per 100,000 live births in the Netherlands, being nearly half that of the United Kingdom [2]. The message is clear: more needs to be done in the United Kingdom to prevent, recognize, and treat VTE in pregnancy.

For 65% of women who died from pregnancy-related VTE, opportunities to improve care were identified, with assessors concluding that better care may have made a difference to the outcome. A number of common themes for improvement were identified. Notably, 1 in 4 women who died from VTE were in the first trimester, challenging the misconception among clinicians that early pregnancy represents a lower risk period for VTE than late pregnancy. Of the women who died from VTE in the first trimester, the majority had 1 or more recognized risk factors (previous VTE, severe hyperemesis, obesity, and age ≥35 years). The lack of clear and effective pathways for rapid assessment and prescription of prophylactic low-molecular-weight heparin (LMWH) during pregnancy for eligible women is likely to have been a contributing factor to these deaths, and pre-pregnancy counseling is rarely considered. MBRRACE-UK recommends that rapid access pathways for prescribing thromboprophylaxis, particularly in the first trimester, be more clearly defined.

There was also evidence of confusion among clinicians about when and how to use VTE risk assessment tools and how to interpret them, particularly a failure to appreciate the dynamic nature of VTE risk and the need to repeat risk assessment throughout pregnancy and postpartum. A consensus is required on common causes of inconsistency between assessors, such as how weight gain in pregnancy should be included and how to consider the most recent pregnancy in the parity calculation for postnatal VTE risk assessment. The second recommendation from MBRRACE-UK is therefore that existing VTE risk assessment tools be revised to make them clearer and less complicated to use.

MBRRACE-UK also identified confirmation bias among clinicians assessing pregnant women with VTE, with over attribution of VTE symptoms to the pregnancy, resulting in women being denied or receiving inappropriate imaging or treatment. The Royal College of Obstetricians and Gynaecologists (RCOG) 2015 guidance [3] that pregnant and postpartum women presenting to the emergency department should be discussed with the obstetrics team, and those with signs of an acute pulmonary embolus should have an electrocardiogram and chest X-ray was not followed for several of the cases assessed and is likely to have changed the outcome for these women. Thus, improvements in current guidelines are called for, as well as understanding, implementation, and uptake of them.

Current UK practice for VTE prevention in pregnancy is based on RCOG guidance from 2015 (Table) [3]. This recommends that all women have a documented VTE risk assessment in early pregnancy or prepregnancy, repeated in the event of hospital admission, the development of intercurrent problems, and immediately postpartum. LMWH is the method of choice for thromboprophylaxis, both antenatally and postnatally, and is safe in breastfeeding. The approach

TABLE Risk assessment and recommended low-molecular-weight heparin prophylaxis in the antenatal and postnatal periods, based on Royal College of Obstetricians and Gynaecologists' guidelines.

Antenatal	Risk factors	VTE prophylaxis with LMWH
	Any previous VTE except a single event related to major surgery	Required
	Hospital admission Single previous VTE related to major surgery High-risk thrombophilia without VTE Medical comorbidities Surgical procedure Ovarian hyperstimulation syndrome (first trimester only)	Consider
	BMI >30 kg/m^2 Age >35 y Parity ≥3 Smoker Gross varicose veins Current preeclampsia Immobility Unprovoked/estrogen-provoked VTE in first-degree relative Low-risk thrombophilia Multiple pregnancies IVF/ART	≥4 risk factors: from the first trimester ≥3 risk factors: from 28 wk ≤2 risk factors: during hospital admission
	Transient: Dehydration/hyperemesis Current systemic infection Long-distance travel	
	Lower risk	Mobilization and avoidance of dehydration
Postnatal	**Risk factors**	**VTE prophylaxis with LMWH**
	Any previous VTE Anyone requiring antenatal LMWH High-risk thrombophilia Low-risk thrombophilia and family history	At least 6 wk
	Cesarean section in labor BMI ≥40 kg/m^2 Readmission or prolonged admission in the puerperium Surgical procedure in puerperium except for immediate repair of the perineum	At least 10 d
	Medical comorbidities BMI >30 kg/m^2 Age >35 y Parity ≥3 Smoker Elective cesarean section Family history of VTE Low-risk thrombophilia Gross varicose veins Current systemic infection Immobility Current preeclampsia Multiple pregnancies Preterm delivery in this pregnancy (<37^{+0} wk) Stillbirth in this pregnancy Midcavity rotational or operative delivery Prolonged labor for >24 h Postpartum hemorrhage of >1 L or blood transfusion	≥2 risk factors: at least 10 d (If persisting or >3 risk factors, consider extending) <2 risk factors: lower risk (see below)
	Lower risk	Mobilization and avoidance of dehydration

ART, assisted reproductive technology; BMI, body mass index; IVF, *in vitro* fertilisation; LMWH, low-molecular-weight heparin; VTE, venous thromboembolism.

taken by the RCOG has several advantages. The risk assessment tool is comprehensive and directly links to prescribing recommendations, making it useful in daily clinical practice. The concise way the information is presented in the guideline, particularly in image format, enables quick reference and straightforward incorporation into local guidelines.

MBRRACE-UK makes 3 suggestions for a new tool.

First, it should "be easy to use, clear and accurate," with their assessors having found "evidence of confusion" over use and interpretation of the existing tool. Use of the word "consider" and the umbrella term "medical comorbidities" enables clinical judgment but permits variation and potential confusion, particularly among less experienced clinicians. In practice, VTE prophylaxis often falls to the most junior doctor on the ward, who may have little obstetric experience.

Second, the tool should "take into account factors that may arise during pregnancy or in the postnatal period." A person deemed low-risk at booking may subsequently develop further risk factors, such as preeclampsia or cesarean section. If clinicians fail to repeat the assessment, thromboprophylaxis may be incorrectly omitted or curtailed. The existing tool also does not consider the potential synergistic effect of combined risk factors. A recent Norwegian case-control study [4] provides an example of this, describing the multiplicative effect on VTE risk from body mass index >25 and immobilization (strict bed rest >1 week). The adjusted odds ratio of VTE from body mass index >25 is 1.8 antepartum and 2.4 postpartum; with immobilization, it is 7.7 antepartum and 10.8 postpartum, but in combination, it increases to 62.3 antepartum and 40.1 postpartum.

Third, the tool should "be based on research evidence." The grading of evidence quality used in the RCOG guideline varies significantly, with a small minority of recommendations based on grade 1 evidence (meta-analysis) and the majority between grades 2 (case-control and cohort studies, or systematic reviews thereof) and 4 (expert opinion).

International differences in practice reflect the paucity of high-quality evidence on which to base recommendations. The incidence of VTE in pregnancy is similar in the United Kingdom, United States, and Canada, although the United States and Canada have a higher risk threshold for starting LMWH postpartum [5]. The RCOG recommends LMWH for 10 days following emergency cesarean alone or elective cesarean plus 1 other risk factor, whereas Canadian guidelines recommend this for emergency cesarean plus 2 other risk factors or elective cesarean plus 3 other risk factors [6]. RCOG recommends postnatal thromboprophylaxis for all with prior VTE, whereas the American College of Obstetricians and Gynecologists recommends surveillance without anticoagulation unless additional risk factors are present [7]. The American Society of Hematology [8] aligns with the RCOG, except where the RCOG recommends considering prophylaxis following a single previous VTE related to major surgery, while the American Society of Hematology does not recommend antenatal prophylaxis following previous VTE with a temporary nonhormonal provoking factor. These differences reflect the lack of evidence to guide management, and the benefits of LMWH are by no means certain. In a Cochrane systematic review, a meta-analysis of 4 studies, including 476 women in total, found no statistically significant difference between antenatal ± postnatal prophylaxis with heparin vs no treatment or placebo (pooled relative risk, 0.39; 95% CI, 0.08-1.98). Caution is required when interpreting these data, however, due to a small number of trials in comparisons and few or no events [9].

So, where does this leave us now? Should we enhance the guidelines with more evidence of individual risk factors and their synergism when in combination, or, in an era moving toward personalized medicine, should we slacken guidelines to encourage clinical judgment, acumen, and individualized care? The reality is that strengthening the evidence base will take time and will not be straightforward. Large randomized controlled trials would be needed. It would be difficult to match cohorts given the numerous and varying VTE risk factors present alone and in combination, and recruitment of pregnant women into clinical trials is challenging. Is the solution, then, to look retrospectively, utilizing registries where available and collecting data on outcomes in practice? Comparison of outcomes between countries with different guidelines may also be helpful.

Public health initiatives and education in primary care, schools, and the media could make a significant impact on acquired and reversible risk factors such as obesity while having additional benefits for general health and the economy. Obesity affects more than one-fifth of the pregnant population in the United Kingdom, and the high associated risk of VTE is often underestimated [10]. There is also a need to raise awareness and empower nonobstetric clinicians to ask for specialist input when reviewing pregnant women with suspected VTE.

The worrying trend of increasing maternal deaths from VTE highlights the need for updated approaches to the prevention, recognition, and treatment of VTE in pregnancy to ensure that every woman receives the individualized and equitable care they need.

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