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Pharmacologic Thromboprophylaxis in Obstetrics: Broader Use Demands Better Data

Dr. Baha M. Sibai, MD and

Department of Obstetrics, Gynecology and Reproductive Sciences UT Health- University of Texas Medical School at Houston

Dr. Dwight J. Rouse, MD, MSPH [Associate Editor]

(Obstetrics) for Obstetrics & Gynecology

Baha M. Sibai: Baha.M.Sibai@uth.tmc.edu; Dwight J. Rouse: drouse@greenjournal.org

Venous thromboembolism (VTE), a serious complication comprising deep vein thrombosis (DVT) and pulmonary embolism, occurs infrequently during pregnancy and the postpartum period, with an estimated incidence of 1-2 per 1,000 deliveries[1]. This incidence is substantially higher in women with a prior VTE and in those with high risk genetic or acquired thrombophilias.[1,2] For many years, the American College of Obstetricians and Gynecologists (the College)[3] , the American College of Chest Physicians (ACCP)[2], and the Royal College of Obstetricians and Gynaecologists (RCOG)[4] have recommended that pregnant women who meet certain criteria receive thromboprophylaxis with either unfractionated heparin or low molecular weight heparin (LMWH) during pregnancy, postpartum, or both, based on their risk status[2-4]. In addition, the College recommends universal perioperative use of pneumatic compression devices (mechanical prophylaxis) for all women undergoing cesarean delivery until they are ambulatory[3].

During the past decade, several organizations and expert panel groups, including the RCOG and ACCP, published clinical guidelines recommending universal screening and risk scoring of all pregnant women to identify those who are at even slightly increased risk for VTE. For risk scoring, some of the suggested risk factors have included one or more of the following: family history of VTE, low-risk thrombophilias, obesity, cesarean delivery, increased parity, advanced maternal age, prolonged immobilization, and various obstetric and medical disorders. Based on results of the scoring, both the RCOG and ACCP recommend either clinical surveillance or thromboprophylaxis in certain patients. Recommendations differ, however, regarding the scoring system to be used, the risk threshold for prophylaxis, and the prophylactic method (mechanical or pharmacologic). These inconsistencies are not surprising, as there is no level I or level II evidence to validate these scoring systems, and since the benefits and risks of pharmacologic thromboprophylaxis in pregnancy and postpartum are uncertain, College guidelines do not endorse these nonspecific scoring systems; rather, their recommendations for pharmacologic prophylaxis apply only to a small percentage of pregnant or postpartum women (< 5%).[3] In contrast, the most recent RCOG

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guidelines recommend pharmacologic prophylaxis in a large percentage of antepartum women and almost all women who undergo cesarean delivery[5,6].

This issue of the journal (see page XXX) includes consensus recommendations on preventing VTE during pregnancy and postpartum from authors representing the National Partnership for Maternal Safety.[7,8] The impetus for these recommendations is observational data suggesting that during the past decade there has been an increased rate of VTE with no change in maternal death from VTE in the United States, whereas there was a significant reduction in maternal deaths from VTE in the UK after publication of the RCOG guidelines[4]. They put forward four major recommendations: 1) All pregnant women undergo risk assessment for VTE throughout pregnancy, during any antepartum hospitalization, intrapartum, and again in the postpartum period; 2) Based on results of this assessment, providers should calculate a patient's risk for VTE using a modified Caprini or Padua score; 3) Expanded antenatal prophylaxis with unfractionated heparin or LMWH in women hospitalized for ≥ 3 days; 4) Expanded use of prophylaxis (mechanical or pharmacologic or both) during and after vaginal delivery, and expanded use of pharmacologic prophylaxis to most women after cesarean delivery.

We applaud the Partnership for taking on the important issue of obstetric VTE, and view their focus on and commitment to lowering severe maternal morbidity and maternal mortality as admirable. However, we are concerned that the marked expansion of pharmacologic prophylaxis that would occur with implementation of their recommendations[7] is not justified by the available data, and has the very real potential of doing more harm than good. We have four major specific concerns:

1) The modified Padua or Caprini scoring systems are based mostly on low-quality evidence from studies conducted in internal medicine and surgery patients. As such, they should be adopted in obstetric patients with caution, if at all. Most of the patients from which these scores were derived were older than 60 years and had associated serious medical conditions such as active cancer (44%), prolonged hospital immobility (average of 9 days), and active cardiorespiratory failure or stroke (20%). For a Padua score of ≥ 4, the authors cite an 11% risk of VTE for patients not receiving thromboprophylaxis. In contrast, a multi-center prospective study conducted in the United States found a rate of VTE of 0% without the use of prophylaxis among 290 pregnant women with prothrombin gene or factor V Leiden mutation.[9,10] (These patients would have a modified Padua score of at least 4). It also bears mention that neither the Caprini nor the Padua score have been prospectively validated in any population.

2) The evidence provided to support the recommendations for the use of antepartum prophylaxis with unfractionated heparin for women with hospital stay of ≥ 3 days is also based on low-quality evidence from nonobstetric populations. Indeed, a recent Cochrane review on the subject concluded that there is insufficient evidence on which to base recommendations for thromboprophylaxis with heparin during pregnancy.[11] Moreover, the recommended prophylactic dose of unfractionated heparin (5,000 units every

12 hours) has never been shown to reduce rate of VTE for gravid women with the conditions that lead to such hospitalizations (eg, preterm premature rupture of membranes, preterm labor, preeclampsia).

3) The authors state that pharmacologic prophylaxis with LMWH or unfractionated heparin may be considered after vaginal delivery in women at high risk for venous thromboembolism based on RCOG criteria or a Padua score of ≥ 4. The validity of the use of this score in obstetrics aside, this statement is unclear as to what dose of heparin to use, and for how long. Since most women will be discharged 48 hours after vaginal delivery, do they recommend 2 days or 6 weeks of prophylaxis? The duration of prophylaxis will have implications regarding the fraction of VTE cases to be prevented.

4) We are most troubled by the authors' recommendation that pharmacologic prophylaxis be used after cesarean delivery in women with risk factors based on the RCOG criteria, which would apply to more than half of all cesarean deliveries in the United States based on data from the Maternal-Fetal Medicine Units Network cesarean delivery registry (Sibai et al, unpublished data available on request), and their statement that hospitals may choose a strategy in which all women undergoing cesarean birth (approximately 1.2 million cesarean deliveries per year in the United States) receive postoperative prophylaxis with unfractionated heparin or LMWH. Their rationale for the latter recommendation relates to poor compliance with mechanical devices and challenges in identifying women at high risk. This rationale is at odds with the conclusions of Clark et al,[12] who reported only one maternal death due to pulmonary embolism among 465,880 women who underwent cesarean delivery after implementation of a universal mechanical thromboprophylaxis policy. This finding implies that mechanical prophylaxis is effective in clinical practice irrespective of risk stratification. Even if adding pharmacologic prophylaxis to mechanical prophylaxis further reduced the rate of fatal pulmonary embolism by half (an effectiveness yet to be demonstrated), then approximately 1 million women would require pharmacologic prophylaxis to prevent even one maternal death from cesarean delivery–associated pulmonary embolism. At Women & Infants Hospital (WIH), the cost (to the hospital) of a syringe containing 40 units of LMWH is $13.07 (personal communication, Jennifer Swawicki, WIH pharmacist). Ignoring administration costs, a 4-day course of prophylactic LMWH therefore costs $52, and a 4-day course is likely not adequate prophylaxis. Even if it were, and we ignored the morbidity of the 1,000 women per million who would experience severe hemorrhage with such a dose (and the associated costs),[1,13,14] and the many more who would experience lesser morbidities, the absolute minimum cost for preventing a maternal death by adding pharmacologic to mechanical prophylaxis would then be $52,000,000. If a 10-day course were used, the absolute minimum cost would be $130,000,000. Nor is it improbable that the addition of pharmacologic prophylaxis would to some extent undo the benefits of

mechanical prophylaxis by occasioning a reduced commitment to ensuring proper and consistent use of the latter.

In summary, these new recommendations, although well-intentioned and aimed at a life-threatening complication, in fact derive from sparse data of questionable applicability to obstetric patients. In large measure, pharmacologic prophylaxis for obstetric patients is of unproven benefit, and even if it proved effective, the recommendations do not take into account the potential for harm in the vast majority of women who would be unnecessarily exposed to anticoagulants in order to prevent a single VTE under the proposed strategy. Adoption of the recommendations in this bundle would lead in just a few years to the exposure of millions of pregnant women to pharmacologic prophylaxis of speculative benefit, recognized harms, and significant costs. Viewed objectively, it is our opinion that current evidence is of insufficient quality to so broaden current College recommendations for pharmacologic prophylaxis of VTE.

What, then, to do about obstetric VTE? On a clinical level, all obstetric units should maximize compliance with postcesarean mechanical thromboprophylaxis. As Clark et al have demonstrated,[12] this simple and safe intervention has been associated with an exceedingly low of rate of fatal pulmonary embolism. By extension, pregnant women who are hospitalized, and those who have delivered vaginally and are at high-risk of VTE should receive mechanical prophylaxis liberally while in the hospital, and ambulate regularly. On an academic level, at a minimum, we need prospective data from large, well-characterized cohorts of pregnant and post-partum women in whom mechanical thromboprophylaxis has been implemented and used extensively. With the increased use of electronic medical records, assembling such cohorts could be done relatively quickly and efficiently. The rate of VTE in such women would provide a much needed baseline against which to compare the potential benefits, harms, and costs of the addition of pharmacologic prophylaxis, both for pregnant and postpartum women overall, and for selected subgroups. Starting with such an approach would represent a reasonable middle ground between doing nothing, and doing too much.

Biography

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