Tranexamic acid for the prevention of postpartum hemorrhage in women undergoing cesarean delivery: an updated meta-analysis

To the Editors:

We read with interest the meta-analysis performed by Bellos and Pergialotis.[1] The authors included 36 randomized controlled trials involving 10,659 women. The authors judged that none of the included trials were at high risk of bias, with 21 (58.3%) trials judged to be at low risk and 15 (41.7%) trials to be at moderate risk of bias, and the remainder rated as unclear. The fact that no trials were judged to be at high risk of bias, was included as a strength of the meta-analysis and apparently informed the conclusions. We, however, strongly disagree.

We have previously systematically reviewed randomized trials assessing the effects of TXA for preventing post-partum hemorrhage.[2] The included trials were all small with significant methodological flaws as well as other serious deficiencies, including absence of ethical approval, reporting errors, and subversion of the randomization process, that rendered them unreliable. The only clear exception is the TRAAP2 trial,[3] which stands alone as a large, multicenter, randomized trial that was designed and executed to minimize bias (e.g. prospectively registered, adequately concealed, double-blind, minimal missing outcome data).

The primary outcome of the review was 'total blood loss'. Blood loss was measured either gravimetrically or was estimated based on hematocrit peripartum change and the woman's weight (EBL). Blood loss data were pooled across trials irrespective of the method used, the appropriateness of which is questionable. Moreover, in the case of the TRAAP2 trial, both methods to measure blood loss were used, yet EBL was used in the meta-analysis. As TRAAP2 observed a statistically significant reduction in EBL but not gravimetrical blood

loss, this raises the possibility of selective reporting bias in favor of TXA affecting the results of the meta-analysis.

The results of the TRAAP2 trial also stand out. Unlike the other, poorer quality trials, TRAAP2 did not observe any evidence for a beneficial effect of TXA on gravimetrically measured blood loss or other related outcomes such as blood transfusion. Yet, in this meta-analysis the reliable evidence generated by the TRAAP2 trial has been distorted by the numerous substandard clinical trials that pervade this important research topic. TRAAP2 is the only trial completed to date to reliably assess the effects of TXA for preventing PPH. The evidence from all other trials is unreliable as are the results of meta-analyses they contribute data to.

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