Author contributions

SKI, LN and JRH all analysed the data and wrote this manuscript.

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Thrombin generation assays for optimizing low molecular weight heparin dosing in pregnant women at risk of thrombosis – response to Ismail *et al*

We thank Ismail *et al* for their interest in our study (Chowdary *et al*, 2015) and for raising some important issues on this controversial topic. We acknowledge the limitation in our study: that this was a real life exercise and hence, the relatively wide time frame between low molecular weight heparin (LMWH) injection and blood sampling.

Ismail *et al* reported typical anti-Xa pharmacodynamic profiles after fixed dose Tinzaparin in patients post-Caesarean section. However this is not really comparing like with like, because these are postpartum patients and observations post-surgical procedure are a study in themselves. It is interesting to note that Ismail *et al* reported very low peak anti-Xa levels with a concomitant reduction of thrombin-antithrombin (TAT). It would be interesting to see TAT levels in patients with a contraindication for LMWH as a control.

The main message from our study is that there appears to be a considerable inter-individual variation between the anti-Xa levels, the currently recommended way of monitoring LMWH in pregnancy, and thrombin generation results. The data shows that, at lower levels of anti-Xa (<0·7 iu/ml), there is an exponential reduction of thrombin generation and thus the baseline thrombin generation has an impact on this reduction, unlike the situation at higher levels of anti-Xa (>0·7 iu/ml) where there is absolute reduction in thrombin generation. The timing of the injection remains relevant because the LMWHs used were Tinzaparin and Enoxaparin, which have different anti-IIa and anti-Xa activities and the thrombin generation assay is able to reflect both (Samama *et al*, 1994). Given that the half-life of the anti-IIa effect is shorter than that of the anti-Xa effect (Samama *et al*, 1994), it is possible that the thrombin generation assay may be more influenced by the anti-IIa effect of the LMWHs (Gerotziafas *et al*, 2007) and, in these instances, a higher reduction of thrombin generation would be expected for a given anti-Xa level. In our study, 83% of the samples were from patients treated with enoxaparin, which has much lower anti-IIa effect. This serves to strengthen our argument that perhaps the anti-Xa assay is not the ideal method of LMWH concentration measurement and one should not rely on this estimate, especially with levels <0·7 iu/ml in complex patients.

We agree with Ismail and colleagues that a weight-based dosing might yield a better anticoagulant effect but ideally this needs to be verified in clinical outcome trials. Another important observation arising from our study is that the thrombin generation parameters become more hypercoagulable as pregnancy progress (Chowdary *et al*, 2015). This, coupled with the fact that the elimination of LMWH increases progressively with gestation, suggests that incremental dosing

according to the individual trimester rather than a fixed dose, whether weight-based or not, may be considered.

As our colleagues explain, various factors need to be considered when making decisions regarding thromboprophylaxis. We believe that prospective studies that include both *in vivo* and *ex vivo* assays of thrombin generation as surrogate markers and clinical endpoints are required to help us deliver individualized care, particularly for complex patients.

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