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## Reply to: Twin-twin transfusion syndrome: need for mechanistic studies

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Reply to: Twin-twin transfusion syndrome: Need for mechanistic studies

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**Title: Reply to: Twin-twin transfusion syndrome: Need for mechanistic studies**

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We thank Professor Ross et al. for their interest in our publication 'Early prognostic factors of outcomes in monochorionic twin pregnancy: systematic review and meta-analysis' (Mackie 2018), and for kindly highlighting important areas of future research.

We agree that unbalanced placental vascular anastomoses are pivotal to the pathophysiology of twin-twin transfusion syndrome (TTTS). Computational and mathematical studies, including those performed by Professor Ross, have demonstrated that fluid mechanics are involved in TTTS and have improved knowledge surrounding TTTS. However, to our knowledge there have been no studies able to translate the models' findings into real-life measurable parameters as it is very difficult to visualise placental anastomoses, irrespective of type, using colour flow or power Doppler, especially in the first trimester. Professor Christoph Lees is examining the use of advanced dynamic flow (ADF) and superb micro-vascular imaging (SMI) Doppler, although this is an early-stage research tool (personal communication).

The study by Nakata et al. (Nakata 2004) that Professor Ross et al. reference that evaluates invasive intra-amniotic Doppler placental anastomoses blood flow measurement received criticism regarding the lack of validation of the technique and the findings (Taylor 2004), and as far as the authors are aware, these findings have not been validated in real-life, nor have the findings of the computational modelling studies. Thus the search continues for novel first trimester predictive markers for

TTTS, which is hampered by the lack of animal models. We are exploring other aspects of TTTS pathogenesis, by investigating the use of maternal serum analytes and microRNA as predictive tests, which would be evaluated in conjunction with ultrasound assessment (Mackie 2017). Currently, as there is no prevention for TTTS, even with the identification of a 'high-risk' group, sequential ultrasound monitoring of the amniotic fluid deepest vertical pools would be required.

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