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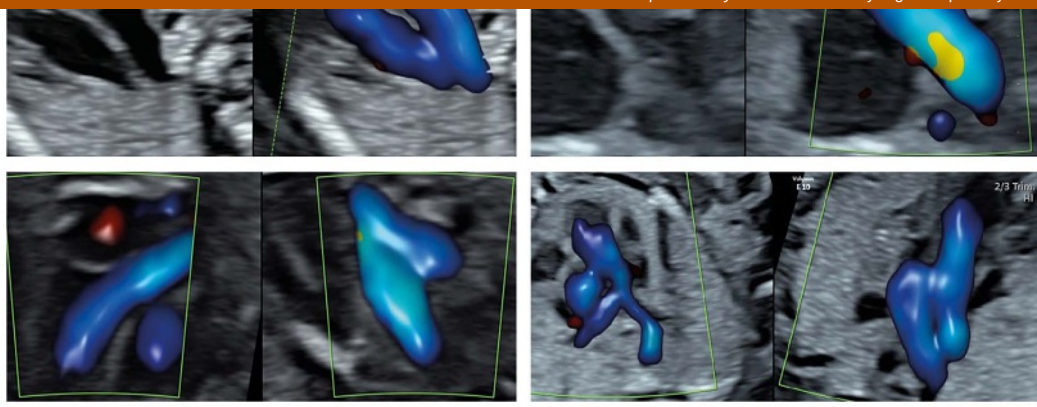

Cardiac advanced online series

Course chair: *Dr. Simon Meagher (Australia)*

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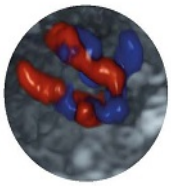
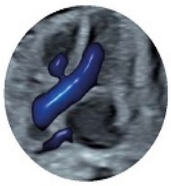


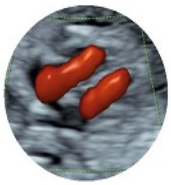
Malformation of the Fetal Semilunar Valves

12 September 2020



Override Anomalies (Conotruncal part 1)

14 November 2020



Transposition of the great arteries (Conotruncal part 2)

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Angiogenic markers are elevated in women with acute fatty liver of pregnancy

Acute fatty liver of pregnancy (AFLP) is a life-threatening, pregnancy-specific condition with an estimated global incidence of 1 in 7000 to 15 000 pregnancies[1]. Despite several clinical characteristics unique to the disorder, distinguishing AFLP from other liver diseases of pregnancy, such as hemolysis, elevated liver enzymes and low platelet count (HELLP) syndrome or pre-eclampsia (PE), may be challenging. Recent studies established an imbalance in angiogenic factors, characterized by elevated levels of soluble fms-like tyrosine kinase-1 (sFlt-1) and low placental growth factor (PlGF) levels, as a key pathogenic mechanism underlying PE and HELLP syndrome[2]. However, the role of these factors in the pathophysiology of AFLP remains unknown. In this study, we measured serum levels of sFlt-1 and PlGF in women with AFLP, and compared them to those in women with suspected PE, confirmed PE or HELLP syndrome.

We conducted a secondary analysis of a prospective multicenter cohort study, in which women with AFLP, suspected or confirmed PE or HELLP syndrome were enrolled at three Dutch hospitals, originally aimed at evaluating the diagnostic value of sFlt-1, PlGF and sFlt-1/PlGF ratio. Serum samples were collected and stored at −80°C upon study entry, and were measured at the end of the study. We aimed to compare three gestational-age matched women with suspected PE, confirmed PE or HELLP syndrome, for each woman with AFLP.

Overall, 53 singleton and 25 twin pregnancies were included. A total of 11 women diagnosed with AFLP were evaluated, of whom six had singleton pregnancy and five had twin pregnancy. In women diagnosed with AFLP, median gestational age at study entry was 36 (range, 34–38) weeks in those with singleton pregnancy and 33 (range, 30–34) weeks in those with twin pregnancy. In singleton pregnancies with HELLP syndrome, gestational age was lower than in those with suspected PE, confirmed PE or AFLP (Tables S1 and S2). In singleton pregnancies, women with AFLP displayed higher serum sFlt-1 levels than women with suspected or confirmed PE (Figure 1). When comparing

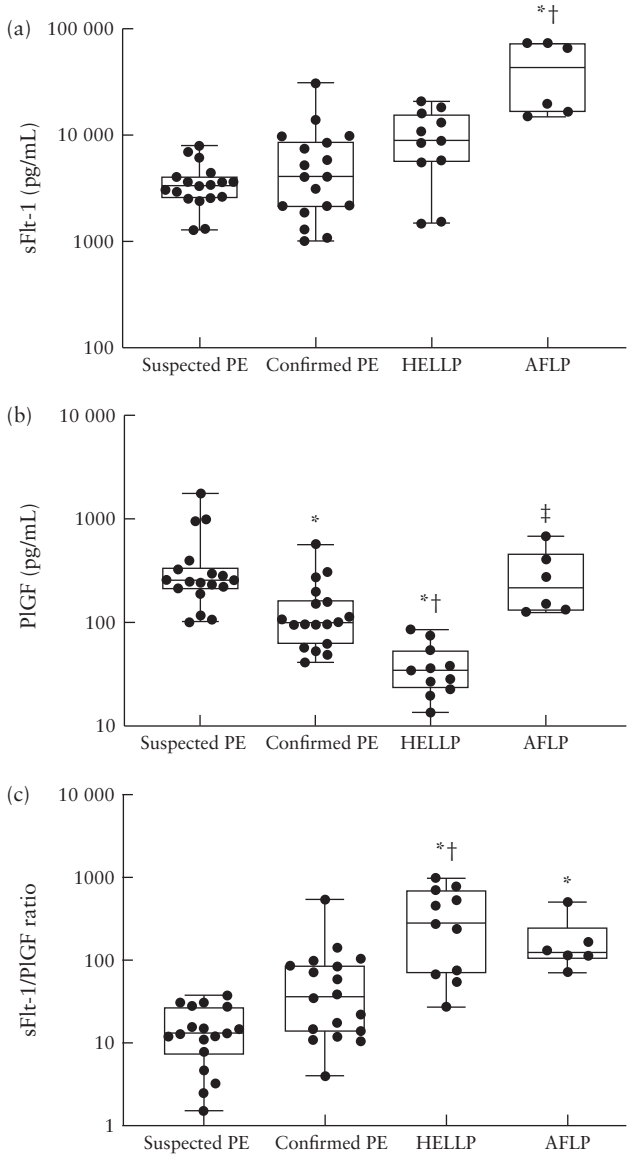

Figure 1 Box-and-whiskers plots showing circulating levels of soluble fms-like tyrosine kinase-1 (sFlt-1) (a), placental growth factor (PlGF) (b) and sFlt-1/PlGF ratio (c) in 53 singleton pregnancies, according to clinical diagnosis. $P < 0.05$ for comparison with: *suspected pre-eclampsia (PE) group; †confirmed PE group; and ‡hemolysis, elevated liver enzymes and low platelet count (HELLP) syndrome group. Boxes show median and interquartile range, and whiskers are range. AFLP, acute fatty liver of pregnancy.

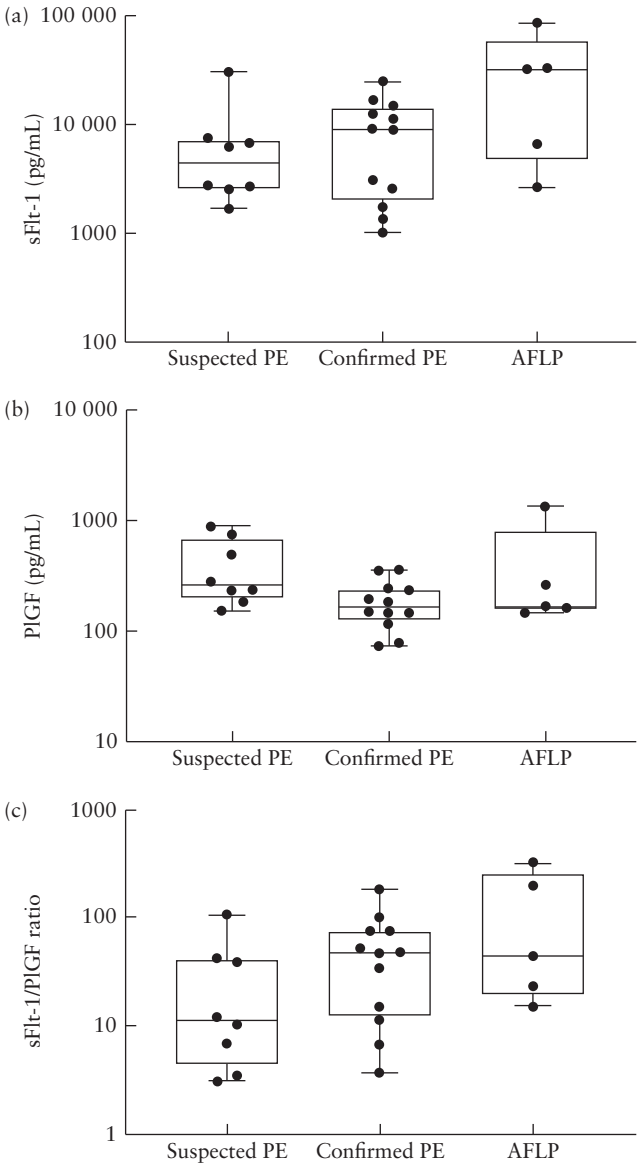

Figure 2 Box-and-whiskers plots showing circulating levels of soluble fms-like tyrosine kinase-1 (sFlt-1) (a), placental growth factor (PlGF) (b) and sFlt-1/PlGF ratio (c) in 25 twin pregnancies, according to clinical diagnosis. There were no significant differences between groups. Boxes show median and interquartile range, and whiskers are range.

PlGF levels in singleton pregnancies, women diagnosed with HELLP syndrome displayed lower levels than women with suspected PE, confirmed PE or AFLP, whereas the sFlt-1/PlGF ratio was higher in both women with HELLP syndrome and AFLP, when compared with the suspected PE group, and higher in women with HELLP syndrome when compared to the confirmed PE group. No differences in sFlt-1 or PlGF levels or sFlt-1/PlGF ratio were observed between twin pregnancies with suspected PE, confirmed PE and AFLP (Figure 2). Our previous observation that non-pre-eclamptic twin pregnancies exhibit higher sFlt-1 levels than non-pre-eclamptic singleton pregnancies due to increased placental mass[3], may provide an explanation for this lack of difference.

Our results, together with the observations of Suzuki *et al.*[4], who reported an elevated sFlt-1/PlGF ratio in a woman with AFLP in comparison to 14 women with HELLP syndrome, imply a potential role for sFlt-1 in the pathophysiology of AFLP. One could suggest that the mechanisms underlying PE, HELLP syndrome and AFLP are all a consequence of an antiangiogenic state, which may explain why these disorders coexist in 20% of cases[1]. This is indirectly supported by preclinical studies in which tyrosine-kinase inhibitors were used as an antiangiogenetic treatment, resulting in impaired hepatic mitochondrial oxidation[5]. Nonetheless, we encourage future studies to investigate the role of angiogenic factors, particularly sFlt-1, in the pathogenesis of AFLP.

R. I. Neuman[1,2], E. R. M. Hesselink[1,2], L. Saleh[1,2], A. H. van den Meiracker[1], A. H. J. Danser[1] and W. Visser[1,2]*
[1]*Department of Internal Medicine, Division of Pharmacology and Vascular Medicine, Erasmus Medical Center Rotterdam, Rotterdam, The Netherlands;*
[2]*Department of Obstetrics and Gynecology, Division of Obstetrics and Prenatal Medicine, Erasmus Medical Center Rotterdam, Rotterdam, The Netherlands*
**Correspondence.*
(e-mail: willy.visser@erasmusmc.nl)
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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Table S1 Patient characteristics and outcome in 53 singleton pregnancies, according to clinical diagnosis

Table S2 Patient characteristics and pregnancy in 25 twin pregnancies, according to clinical diagnosis