

Maternal serum concentrations of soluble endoglin and soluble Vascular Endothelial Growth Factor Receptor 2 may predict the severity of villous hypoplasia in severe early-onset fetal growth restriction

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Research question

Can levels of angiogenic and antiangiogenic factors in maternal serum predict mid-trimester placental histomorphometry and so identify different placental pathological phenotypes?

Conclusion

If the association between maternal serum levels of endoglin and VEGFR2 and villous hypoplasia is confirmed, it could help to target future therapies

Methods

Maternal serum was collected from pregnancies ending in intrauterine fetal demise (IUFD) as a result of:

- 1) Severe early-onset fetal growth restriction (FGR, estimated fetal weight <3rd centile)
- 2) Feticide (TOP) for fetal structural anomalies with an estimated fetal weight >10th centile

- We measured angiogenic factors [placental growth factor, vascular endothelial growth factor A (VEGFA), VEGFD] signalling receptors [VEGF receptor2 (VEGFR2), neuropilin1] and antiangiogenic factors [soluble fms-like tyrosine kinase1, endoglin]
- A single assessor, blinded to clinical outcome and gestation, analysed multiple images from two areas of each placenta using ImageJ (Fig 1)
- Univariate and multivariable associations were investigated using generalised linear models

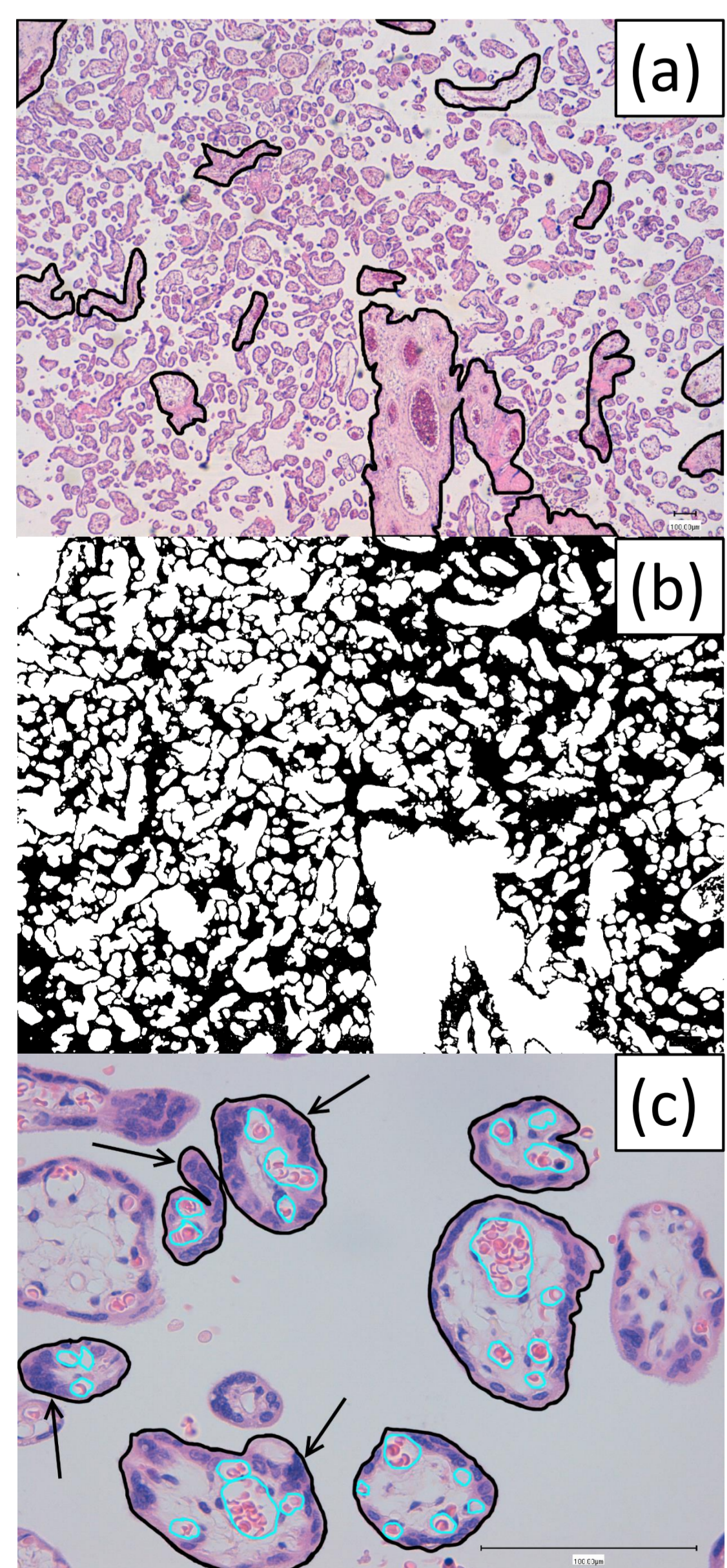


Fig 1: In 40x magnification images the percentage area made up of (a) stem villi and (b) intervillous space was measured, allowing calculation of the percentage area made up from intermediate and terminal villi (ITVp). In 400x magnification images (c): the mean terminal villous area; mean villous vascular area (mVVA); percentage of villi containing syncytial knots; and percentage of villi containing nucleated red cells (NRp) were calculated.

Results

- Gestation at serum collection was comparable in the two groups (FGR n=9, median 22+4 weeks, range 20+3-24+3 vs. TOP n=8, median 23+1 weeks, range 22+3-30+0, p=0.31)
- Gestation of IUFD (GAFD) was significantly lower in the TOP vs. FGR group, since feticide occurred on the day of serum collection (FGR, median GAFD 26+5 weeks, range 22+6-29+0, p=0.034)

- In the FGR group, all angiogenic factors and signalling receptors were significantly lower and both antiangiogenic factors were significantly higher than in the TOP group
- Both mVVA and NRp increased significantly with increasing GAFD (p=0.028, p=0.0004). Other measurements showed no association.

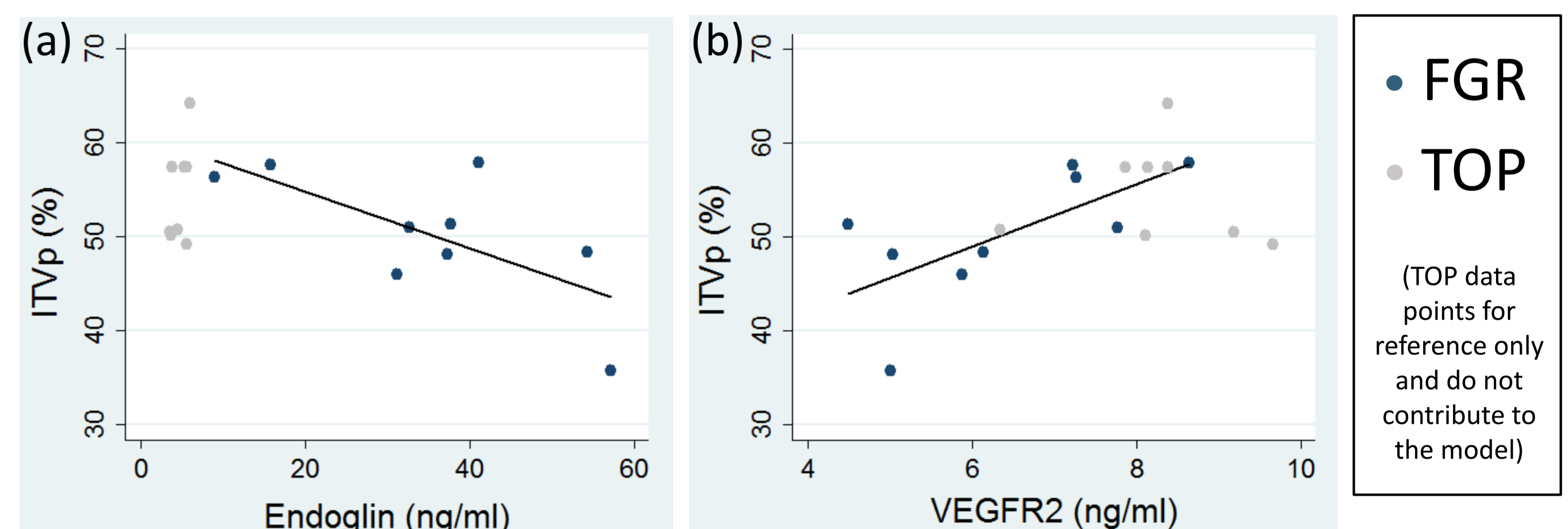


Fig 2: The linear association between maternal serum concentration of (a) endoglin (b) VEGFR2 and ITVp in pregnancies affected by FGR.

- Increasing serum concentration of endoglin and decreasing serum concentration of VEGFR2 predicted decreasing ITVp, but only in the FGR group (Fig 2)
- These associations persisted after adjusting for GAFD and umbilical artery pulsatility index at the time of serum collection (3.58 percentage point decrease in ITVp per 10ng/ml increase in endoglin, p=0.026, 4.91 percentage point decrease in ITVp per 1ng/ml decrease in VEGFR2, p<0.00005)

