Reduced circulating levels of kisspeptin (KP), human chorionic gonadotropin (hCG), placental-like growth factor (PLGF), soluble fms-like tyrosine kinase-1 (FLT-1) and soluble endoglin (ENG) but not prokineticin-1 (PK1) are associated with miscarriage risk

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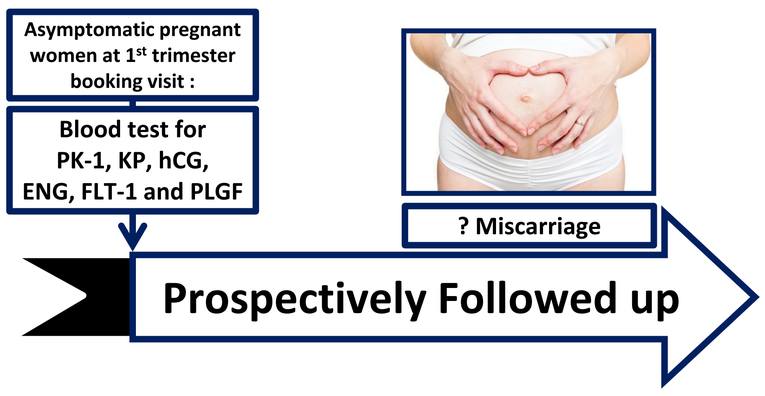
Introduction

Miscarriage (spontaneous loss of pregnancy occurring prior to 24 weeks of gestation) occurs in 20% of clinical pregnancies and can be devastating for affected couples.
Abnormal placental development is observed in two-thirds of miscarriages and may be secondary to defects in the regulation of angiogenesis and foetal trophoblast invasion. Recently, the circulating placental markers prokineticin-1 (PK-1), kisspeptin (KP), human chorionic gonadotropin (hCG), soluble endoglin (ENG), soluble fms-like tyrosine kinase-1 (FLT-1) and placental growth factor (PLGF) have been identified as putative markers of placental function. KP, PLGF, and PK-1 are highly expressed in syncitiotrophoblast cells of the placenta. KP is an anti-metastatic factor; PLGF, PK-1 are angiogenic factors; whilst ENG and FLT-1 are anti-angiogenic peptides.
This study evaluated the predictive value of these putative circulating markers of placental function in identifying miscarriage risk in asymptomatic pregnant women.

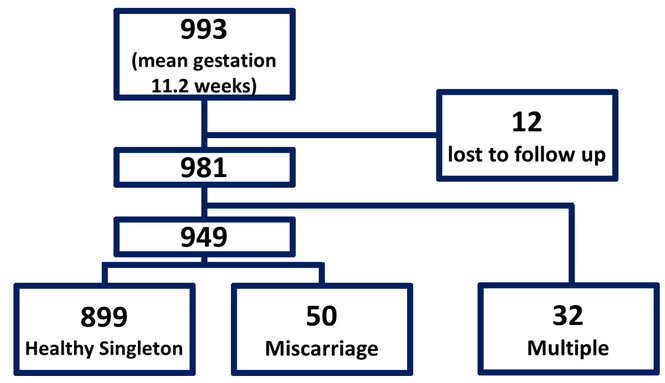
Aims

To determine whether PK-1, KP, hCG, ENG, FLT-1 and PLGF were able to identify asymptomatic pregnant women at risk of subsequent miscarriage.

Methods



Prospective cohort study (n=981) asymptomatic women attending antenatal booking visit (8-12 weeks gestation) at Imperial College NHS Healthcare trust. A single measurement of serum PK-1, KP, hCG, ENG, FLT-1 and PLGF was made, and pregnancy outcome prospectively monitored. KP was measured using an in-house radioimmuno-assay and hCG with an automated immunometric assay. Serum PLGF, sEng, sFLT-1, and plasma PK-1 was performed using enzyme-linked immunosorbent assay (ELISA). Multiples of gestation specific medians (MOM) levels were calculated to correct for gestational age.



Results 1: Levels of PK-1, KP, hCG, ENG, FLT-1 and PLGF with Gestation

In women with singleton pregnancy unaffected by miscarriage, KP and PLGF levels rose with increasing gestation, whilst hCG peaked at 8.5 weeks before falling again (see Figure 1). To account for the changes in levels with gestation, multiples of gestation-specific medians (MOM) were used for further analyses.

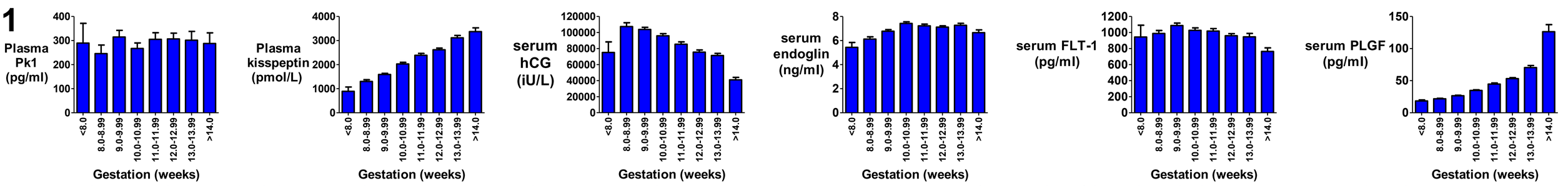
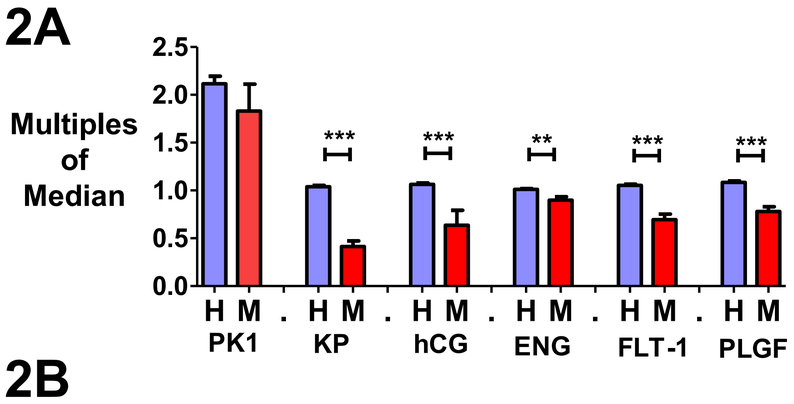
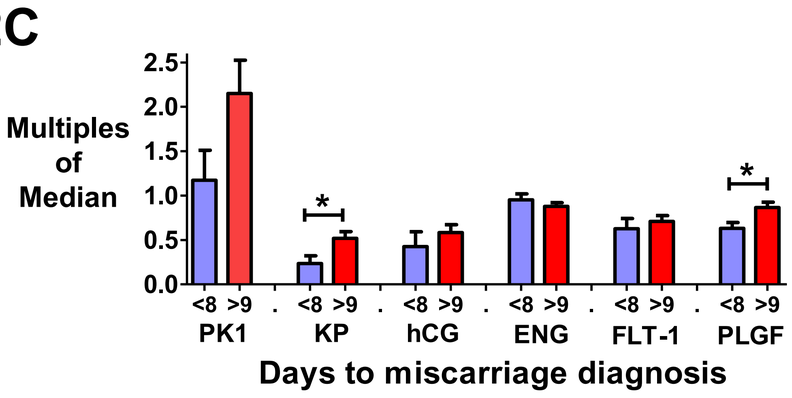


Figure 1: Changes in plasma levels of plasma PK1, plasma Kisspeptin, Serum hCG, Serum Endoglin, Serum FLT-1 and Serum PLGF with gestation (mean and SEM) for each week of gestation in women with singleton pregnancy which did not end in miscarriage (n=899).

Results 2: Levels of PK-1, KP, hCG, ENG, FLT-1 and PLGF with miscarriage



Levels of MOM of studied blood markers were all significantly lower in asymptomatic pregnant women who later suffered miscarriage, except for PK-1 (see Figure 2A). KP had the most discriminatory value in identifying asymptomatic women at risk of subsequent miscarriage with an area under the ROC curve of 0.86 (see Figure 2B). Both KP and PLGF were lower still in women who miscarried imminently (within 8 days of blood sampling) when compared with women who miscarried later (see Figure 2C).



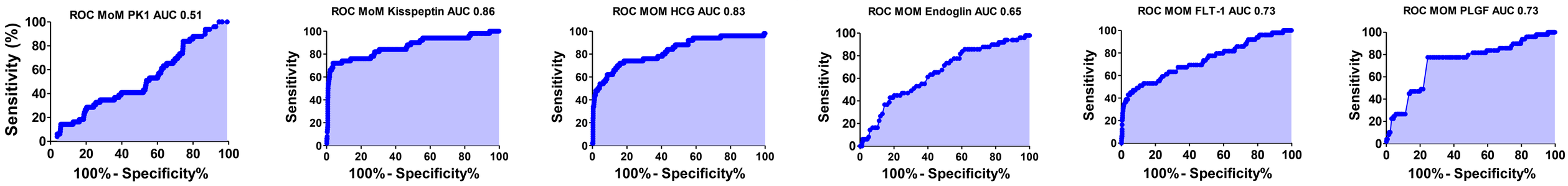


Figure 2: 2A Multiples of median (MOM) of PK-1, KP, hCG, ENG, FLT-1, and PLGF in women with healthy singleton pregnancy (H) not resulting in miscarriage (n=899) were compared with women with singleton pregnancy subsequently ending in miscarriage (M) (n=50). 2B Time to miscarriage- MOM of PK-1, KP, hCG, ENG, FLT-1, and PLGF are shown for women who miscarried within 8 days compared to those who miscarried 9 days or later following blood sampling. 2C Receiver operating curves (ROC) for MOM of PK-1, KP, hCG, ENG, FLT-1, and PLGF in identifying women with singleton pregnancy at risk of miscarriage. Pairs of groups were compared with unpaired t test. *P<0.05; ***P<0.001.

Results 3: Levels of PK-1, KP, hCG, ENG, FLT-1 and PLGF in multiple pregnancy

MOM of KP, hCG, FLT-1 and PLGF were higher in healthy twin and triplet pregnancies, but similar to healthy singleton pregnancy in women with multiple pregnancy affected by miscarriage of one twin (see Figure 3).

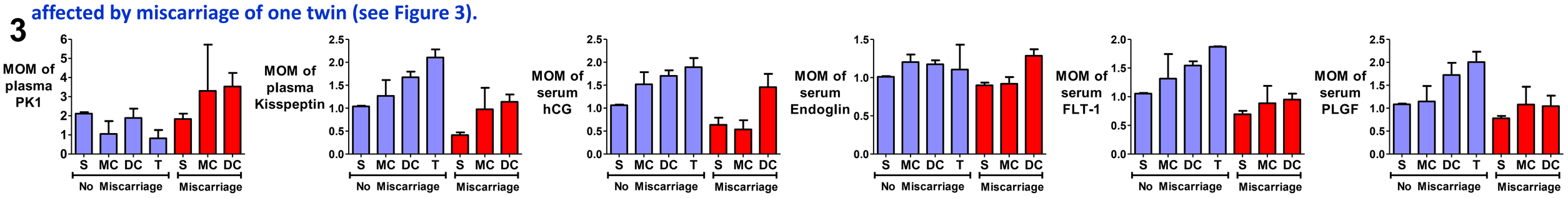


Figure 3: Multiples of gestation specific medians of KP, hCG, PLGF, FLT-1, ENG and PK-1 in S (singleton), MC (monochorionic), DC (dichorionic), and T (triplet) pregnancies resulting in healthy live birth and those affected by miscarriage of one foetus.

Conclusion

Although a number of putative markers of placental function predicted miscarriage in asymptomatic pregnant women in our study, plasma kisspeptin-54 had the highest discriminatory value, identifying women at high risk of miscarriage with greatest accuracy, whilst also detecting how imminently miscarriage was due to occur.
Furthermore kisspeptin-54 rose predictably with multiple pregnancy in accordance with the number of foeto-placental units, and was reduced to the level of singleton pregnancy if multiple pregnancy was affected by miscarriage. Future studies will assess whether identifying women at increased risk of miscarriage may allow for targeted investigations or therapies to be trialled in order to help such women.