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Prediction model of hypertensive disorders in pregnancy with the sFlt-1/PlGF ratio

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Objective

A precise diagnosis of preeclampsia (PE) and other hypertensive pregnancy disorders is necessary in order to prevent the potential devastating outcome for mother and child. Serum metabolite analysis of soluble fms-like tyrosine kinase 1 (sFlt-1), placental growth factor (PlGF) and their ratio (sFlt-1/PlGF) are used to accomplish the differential diagnostic process. The aim of this study was to generate reference ranges of sFLT, PlGF and the sFLT/PlGF ratio in uneventful singleton pregnancies measured with the Kryptor® immunoassay and compare them with pregnancies with PE and associated pregnancy complications to clarify the value of sFLT/PlGF ratio to predict pregnancy complications.

Methods

Observational case-control study covered the period between June 2016 and December 2020. We included pregnant women with presenting clinical signs and symptoms contributing to suspicion of PE. The exclusion criterion was manifest PE or HELLP syndrome. As a control group, we used blood samples from uncomplicated singleton pregnancies. Measurements were performed for sFlt-1 and PlGF on the fully automated Kryptor compact Plus system (Brahms Kryptor® Thermo Fisher Scientific). Our primary outcome was to generate reference ranges of sFLT, PlGF and the sFLT/PlGF ratio in uneventful singleton pregnancies, assess the relationship between gestational age and compare its distribution to women with clinical signs and symptoms contributing to suspicion of PE. Secondary outcomes were to derive the sFlt-1/PlGF ratio cut-off point for the prediction model to predict the presence of adverse outcomes in women with clinical signs and symptoms contributing to suspicion of PE within 1 and 2 weeks.

Results

869 (45.2%) women showed clinical signs and symptoms contributing to suspicion of PE and 1052 (54.8%) were controls. The median gestational age for inclusion between the groups did not differ. There were significant differences in age, BMI, parity, conception type and MAP between the groups. Of the 869 women with clinical PE signs and symptoms 343 (39.5%) developed PE or HELLP syndrome. A proportion of 101 (11.6%) pregnancies resulted in SGA or FGR (early or late). Only 74 (8.5%) pregnancies in the suspicion cohort had an uncomplicated course of pregnancy. In the control group 95.7% of pregnancies were uncomplicated. Figure S1 in the supplementary appendix shows the relatively stable sFlt-1 level until 32-34 weeks and an increase thereafter. Among women with blood sample drawn in the same gestational week interval, those who showed signs and symptoms contributing to suspicion of PE had significantly lower (mean: 3.6 times) and higher (mean: 2.5 times) median concentrations of PlGF and sFlt-1 than those who did not. Among pregnant women with uncomplicated pregnancy outcome the sFlt/PlGF ratio did not differ statistically (.315) from that with isolated excessive oedema or weight gain. In women with chronic hypertension the median sFlt/PlGF ratio was statistically elevated in comparison to uncomplicated pregnancy outcome cohort (.000). Gestational hypertension cohort showed statistically higher median sFlt/PlGF ratio in comparison to chronic hypertension cohort (.013). Women with gestational hypertension did not differ subsequently from late SGA/FGR cohort (.705). In cohorts with a high sFlt/PlGF ratio, we noticed following differences: pregnant women who developed preeclampsia during pregnancy and who delivered early SGA/FGR newborn, the high ratio did not differ significantly (.212). Women with HELLP syndrome differ significantly from preeclampsia pregnancies (.007). For the in pregnancy associated hypertensive disorders complication selected simple gestational age dependent sFlt-1/PlGF ratios prediction cutoff model the AUCs for 1 week rule out were 0.917% and 0.935% for 2 week rule out. The NPV and PPV for 1 and 2 week was 98.7%, 33.9%. For the in pregnancy associated hypertensive disorders complication selected complex gestational age dependent sFlt-1/PlGF ratios cutoff and MAP prediction model the AUCs were for 1 week rule out 0.934% and 0.952% for 2 week rule out. For the complex model the NPV and PPV for 1 week was 98.7% and 38.8 % and for 2 week 98.7% and 40.7%.

Conclusion

This study provides insight into the gestational age dependent reference ranges of sFLT, PlGF and the sFLT/PlGF ratio in uneventful singleton pregnancies measured with the Kryptor® immunoassay and clarify the value of sFLT/PlGF ratio in prediction of PE and associated pregnancy complications. Present study identified gestational age dependent sFLT/PlGF ratio cut-of points for the short-term (one week, two weeks) absence of PE and PE associated complications in women with singleton pregnancies and clinical signs that are suggestive of the disorder. The NPV of a sFLT/PlGF ratio at or below this gestational age dependent cut off points is 98.7%. Using a single sFLT/PlGF ratio value for the entire pregnancy does not appear to be methodologically correct. A promising option is the individualization of risk based on a combination of factors: age, BMI, parity, conception type and MAP.