Serum Fatty Acid Binding Protein 4 (FABP4) Predicts Pre-eclampsia in Women With Type 1 Diabetes

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OBJECTIVE

To examine the association between fatty acid binding protein 4 (FABP4) and pre-eclampsia risk in women with type 1 diabetes.

RESEARCH DESIGN AND METHODS

Serum FABP4 was measured in 710 women from the Diabetes and Pre-eclampsia Intervention Trial (DAPIT) in early pregnancy and in the second trimester (median 14 and 26 weeks' gestation, respectively).

RESULTS

FABP4 was significantly elevated in early pregnancy (geometric mean 15.8 ng/mL [interquartile range 11.6–21.4] vs. 12.7 ng/mL [interquartile range 9.6–17]; $P < 0.001$) and the second trimester (18.8 ng/mL [interquartile range 13.6–25.8] vs. 14.6 ng/mL [interquartile range 10.8–19.7]; $P < 0.001$) in women in whom pre-eclampsia later developed. Elevated second-trimester FABP4 level was independently associated with pre-eclampsia (odds ratio 2.87 [95% CI 1.24–6.68], $P = 0.03$). The addition of FABP4 to established risk factors significantly improved net reclassification improvement at both time points and integrated discrimination improvement in the second trimester.

CONCLUSIONS

Increased second-trimester FABP4 independently predicted pre-eclampsia and significantly improved reclassification and discrimination. FABP4 shows potential as a novel biomarker for pre-eclampsia prediction in women with type 1 diabetes.

Pre-eclampsia, defined as new-onset hypertension and proteinuria occurring after 20 weeks of gestation, is associated with significant perinatal morbidity and mortality (1,2). Pre-eclampsia is two to four times more likely to develop in women with type 1 diabetes than in the background population (3,4).

Fatty acid binding protein 4 (FABP4), or adipocyte FABP, is an intracellular lipid chaperone involved in coordination of lipid transportation (5). FABP4 is expressed mainly in adipocytes and can be released into the circulation (6). In the nonpregnant state, FABP4 is associated with the following known pre-eclampsia risk factors: obesity, hypertension, and diabetes (6,7).

Several studies have reported elevated FABP4 levels in women with pre-eclampsia (8,9) or in those in whom pre-eclampsia later developed (10), compared with those in whom it did not, although all studies excluded women with diabetes.

Our objective was to examine the role of FABP4 as a potential biomarker for pre-eclampsia alone, and in tandem with established clinical risk factors, in women with type 1 diabetes.

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RESEARCH DESIGN AND METHODS

The population comprised 710 of the 762 women from the Diabetes and Pre-eclampsia Intervention Trial (DAPIT), a randomized, multicenter, double-blind, placebo-controlled trial investigating vitamin C and E supplementation and the risk of pre-eclampsia in women with type 1 diabetes (11). Pre-eclampsia, the primary end point, was defined using international guidelines (1,12). Women provided written informed consent. West-Midlands Multicenter Research Ethics Committee approved the study (MREC 02/7/016).

Blood samples were collected at randomization (8–22 weeks, median gestation 14 weeks) and in the second trimester (median gestation 26 weeks). Serum samples were batch analyzed, blind to pre-eclampsia status, using a commercially available ELISA (Biovendor, Modrice, Czech Republic). Interassay and intra-assay coefficients of variation were 8.3% and 3.8%, respectively.

Intervention and control groups were analyzed together as supplementation did not reduce pre-eclampsia risk (risk ratio 0.81 [95% CI 0.59–1.12], $P = 0.20$) (11); FABP4 levels were not different between groups, and the effect of supplementation on pre-eclampsia risk did not depend on FABP4 level.

Statistical Analysis

FABP4 concentrations were positively skewed and therefore logarithmically transformed. Values are reported as geometric mean and interquartile range. χ^2 and independent samples *t* tests were used for group comparisons. Logistic regression analysis investigated the association between FABP4 and pre-eclampsia before and after adjusting for the following risk factors: age, BMI, gestational age, blood pressure, parity, duration of diabetes, smoking status, history of pre-eclampsia, HbA_{1c} level, renal status, and DAPIT treatment group. The area under the receiver operating characteristic curve (AUROC) was used to assess the predictive value of FABP4 for pre-eclampsia (13). Integrated discrimination improvement (IDI) and net reclassification improvement (NRI) indices were calculated to determine the clinical utility of the addition of FABP4 to established risk factors and the ability of FABP4 to improve pre-eclampsia prediction (for calculation of AUROC, NRI and IDI, see Supplementary Data) (14). Statistical analysis was performed using SPSS version 20 (IBM Corp., Armonk, NY), Stata release 14 (StataCorp, College Station, TX), and the Hmisc package in R version 3.1.3 (R Core Team, Vienna, Austria).

RESULTS

Serum from one or both time points was available for 710 women, among whom pre-eclampsia developed in 120 (17%) (for maternal and clinical characteristics, see Supplementary Table 1).

FABP4 levels at randomization (median gestation 14 weeks) and 26 weeks were significantly higher in women in whom pre-eclampsia later developed compared with those in whom it did not (Table 1). Of the 319 women with blood samples at ≤13 weeks' gestation, FABP4 levels were elevated in those in whom pre-eclampsia later developed compared with those in whom it did not ($P = 0.02$).

For each doubling of serum FABP4 levels, the adjusted risk of pre-eclampsia increased by 40% (odds ratio 1.4 [95% CI 1.0–2.0], $P = 0.031$) and 60% (1.6 [1.1–2.3], $P = 0.017$) at 14 and 26 weeks, respectively. The independent ability of FABP4 to predict pre-eclampsia, in relation to quarters of FABP4 in combination with established risk factors, is shown in Supplementary Table 2. In the second trimester, the highest quarter of FABP4 was a significant independent predictor of pre-eclampsia compared with the lowest (odds ratio 2.87 [1.24–6.68], $P = 0.03$).

AUROCs for FABP4 alone were 0.622 and 0.646, respectively, at 14 and 26 weeks (Table 1). When FABP4 was added to the model containing established risk factors, AUROCs were 0.801 and 0.825, respectively, at 14 and 26 weeks (both nonsignificant from established risk factors alone).

The NRI statistic showed that the addition of FABP4 to established risk factors significantly increased the correct reclassification of case patients and non–case patients at both 14 and 26 weeks. The IDI statistic showed that the FABP4 level significantly increased discrimination between case patients and non–case patients in the second trimester (Table 1).

CONCLUSIONS

We believe that this is the first study to date to investigate FABP4 levels in relation to the development of pre-eclampsia and to investigate its clinical utility in pregnant women with type 1 diabetes. Maternal FABP4 levels were significantly elevated in women in whom pre-eclampsia later developed compared with those in whom it did not, both at 14 and 26 weeks of gestation. Furthermore, the addition of FABP4 to established risk factors improved the NRI at both time points and the IDI in the second trimester.

Only one previous study has measured FABP4 levels prior to the onset of pre-eclampsia. In line with our findings, Scifres et al. (10) reported significantly elevated FABP4 levels before 13 weeks and at 26 weeks of gestation in women without diabetes in whom pre-eclampsia later developed.

Table 1—Serum FABP4 concentrations at randomization and in the second trimester with AUROC, NRI, and IDI analyses

	Maternal serum FABP4 concentration* (ng/mL)		AUROC					
	Pre-eclampsia	No pre-eclampsia	FABP4 alone	Established risk factors without FABP4	Established risk factors with FABP4	Incremental area (*P*)†	NRI (*P*)	IDI (*P*)
Randomization	15.8 (11.6–21.4)	12.7 (9.6–17.0)	0.622	0.793	0.801	0.008 (0.17)	0.306 (0.003)	0.009 (0.11)
Second trimester	18.8 (13.6–25.8)	14.6 (10.8–19.7)	0.648	0.819	0.825	0.006 (0.34)	0.251 (0.02)	0.012 (0.048)

*Reported as geometric mean and interquartile range. †Comparison of AUROCs: established risk factors without FABP4 level vs. established risk factors with FABP4 level.

FABP4 levels may play a role in the development of pre-eclampsia. Shangguan et al. (9) reported increased third trimester FABP4 levels in women with pre-eclampsia compared with healthy pregnant and nonpregnant women, suggesting no effect of pregnancy on FABP4 level, thus implicating FABP4 in the development of pre-eclampsia.

This study explores both the predictive properties and clinical utility of FABP4 in relation to pre-eclampsia in women with type 1 diabetes. FABP4 level remained significantly associated with pre-eclampsia after controlling for established risk factors. FABP4 level, when added to established risk factors, did not significantly increase the AUROC. However, the NRI and IDI, which are proposed as superior methods to determine the clinical utility of a biomarker (14), showed that FABP4 level, in addition to clinical risk factors, improved the prediction of pre-eclampsia. This was significant for NRI at 14 weeks, and for both NRI and IDI at 26 weeks.

The strengths of this study include the study size, with DAPIT being the largest prospective data set reported of thoroughly characterized women with type 1 diabetes, together with the strict definition of pre-eclampsia, as each potential case was reviewed independently by three clinicians (11,15). In addition, women with essential hypertension or any existing renal disease were included, making our study more representative of the typical population. The study has the limitation that trial participants may not be entirely representative of all pregnant women with type 1 diabetes because they were self-selecting. Randomization samples also represented a range of gestational ages from 8 to 22 weeks.

In summary, we believe that this is the first study to investigate FABP4 level in relation to the development of pre-eclampsia in pregnant women with type 1 diabetes. FABP4 levels in both the first and second trimester were significantly associated with the development of pre-eclampsia. Elevated second trimester FABP4 independently predicted pre-eclampsia, significantly improving reclassification and discrimination. Although further studies are now needed to replicate these findings, our data suggest that FABP4 level shows potential as a novel biomarker for pre-eclampsia prediction in women with type 1 diabetes.

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Author Contributions. A.C.W. carried out laboratory analysis and researched and wrote the manuscript. I.S.Y., D.R.M., M.J.A.M., D.W.M.P., J.D.W., and V.A.H. reviewed and edited the manuscript. C.C.P. supervised the statistical analysis and reviewed and edited the manuscript. V.A.H. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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