Placenta 103 (2021) 76–81

Contents lists available at ScienceDirect

Placenta

journal homepage: http://www.elsevier.com/locate/placenta

Serum leukotriene B4 and hydroxyeicosatetraenoic acid in the prediction of pre-eclampsia

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ARTICLE INFO

Keywords:
LTB4
15(S)-HETE
Eicosanoids
Leukotriene
Biomarker
Pre-eclampsia

ABSTRACT

Introduction: Pre-eclampsia (PE) affects 2–8% of pregnancies worldwide. Despite identification of numerous possible biomarkers, accurate prediction and early diagnosis of PE remain challenging. We examined the potential of leukotriene B4 (LTB4) and 15-hydroxyeicosatetraenoic acid (15(S)-HETE) as biomarkers of PE by comparing serum levels at three gestational age (GA) groups between normotensive pregnancies and asymptomatic women who subsequently developed preterm or term-PE.

Methods: This is a case-control study drawn from a prospective study of adverse pregnancy outcomes with serum samples collected at 19–24 weeks (n = 48), 30–34 weeks (n = 101) and 35–37 weeks (n = 54) GA. LTB4 and 15 (S)-HETE levels were determined by ELISA. Serum level multiples of the median (MoM) were compared between normal and PE-pregnancies. Association between LTB4 and 15(S)-HETE and GA at delivery was investigated with Cox proportional-hazards models.

Results: Serum LTB4 levels were lower in women of East-Asian ethnicity, higher in women with PE history, and increased with GA in normotensive pregnancies, but not in PE. LTB4 was elevated at 19–24 weeks in women who developed preterm-PE. There was a negative association between LTB4 MoM and interval between sampling and delivery with PE at 19–24 weeks only. Serum 15(S)-HETE levels were not influenced by GA at testing and were elevated in women of South-Asian ethnicity. Median 15(S)-HETE levels were unchanged in preterm and term-PE at any GA.

Discussion: LTB4 was higher at 19–24 weeks in pregnancies that developed preterm-PE versus unaffected pregnancies, suggesting it is a potentially useful predictive marker of preterm PE in the second trimester.

1. Introduction

Pre-eclampsia (PE) is a leading cause of maternal and perinatal morbidity and mortality and affects 2–8% of pregnancies worldwide [1]. To date, there is no definitive treatment except the delivery of the baby and placenta. The severity of PE and fetal maturity are important considerations in the timing of the delivery and, as such, prediction of disease onset and intervention to prevent the development of severe PE are paramount to improve maternal and perinatal outcomes.

The current best available test for first trimester prediction of PE combines maternal characteristics and history with the results of mean arterial pressure (MAP), mean uterine artery pulsatility index (UtA-PI) and serum placental growth factor (PlGF) and/or serum pregnancy-associated plasma protein-A (PAPP-A) and detects about 75% of

Abbreviations: 15(S)-HETE, 15-hydroxyeicosatetraenoic acid; LC-MS/MS, Liquid chromatography with tandem mass spectrometry; LOX, lipoxygenase; LTB4, leukotriene B4; MAP, mean arterial pressure; PAPP-A, serum pregnancy-associated plasma protein-A; PlGF, serum placental growth factor; sFLT-1, serum soluble fms-like tyrosine kinase-1; UtA-PI, mean uterine artery pulsatility index.

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https://doi.org/10.1016/j.placenta.2020.10.007
Received 10 August 2020; Received in revised form 21 September 2020; Accepted 9 October 2020
Available online 10 October 2020

Table 1
Maternal characteristics of normotensive controls and pre-eclamptic women included in the study.

Characteristic	Controls (n = 114)	PE (n = 89)
Maternal age in years, mean ± SD	32.6 ± 0.5	31.1 ± 3.4
Maternal weight in kg, mean ± SD	70.5 ± 1.8	79.9 ± 9.2 *
Maternal height in cm, mean ± SD	163.7 ± 0.7	165.2 ± 17.5
Body mass index in kg/m^2, mean ± SD	29.4 + 5.6	32.4 + 7.3 *
Body mass index ≥ 30 kg/m^2, n (%)	41 (36.0)	51 (57.3) *
Racial origin		
White, n (%)	55 (48.2)	42 (47.2)
Black, n (%)	42 (36.8)	38 (42.7)
South Asian, n (%)	6 (5.3) *	8 (9.0)
East Asian, n (%)	7 (6.1) *	0 (0)
Mixed, n (%)	4 (3.5)	1 (1.1)
Parity		
Nulliparous, n (%)	45 (39.5)	49 (55.1)
Parous with no previous PE, n (%)	64 (56.1)	27 (30.3)
Parous with previous PE, n (%)	5 (4.4) *	13 (14.6)
Cigarette smoker, n (%)	11 (9.6)	6 (6.7)
Family history of PE, n (%)	6 (5.3)	4 (4.5)
Conception		
Spontaneous, n (%)	109 (95.6)	82 (92.1)
Assisted, n (%)	5 (4.4)	7 (7.9)
Mean arterial pressure in mmHg, mean + SD	88.0 + 8.9	100.9 + 13.1 **
Chronic hypertension, n (%)	3 (2.6)	16 (18.0) **
History of SLE/APS, n (%)	1 (0.9)	1 (1.1)
History of Diabetes (type 1 or 2), n (%)	3 (2.6)	0 (0)

PE: pre-eclampsia; SD: standard deviation; SLE: Systemic Lupus Erythematosus; APS: antiphospholipid syndrome; *P < 0.05, **P < 0.001.

preterm PE at a 10% false positive rate; however, the detection rate of this combined multimarker screening test for term PE is lower at about 45%, and term PE accounts for two thirds of all cases [2,3]. Similarly, studies have investigated potential biomarkers for the prediction of PE at the second trimester. These include MAP, UtA-PI, PIGF and serum soluble fms-like tyrosine kinase-1 (sFlt-1) and in late third trimester MAP, PIGF and sFlt-1 [4–7]. For the screening of asymptomatic women during the second and third trimesters, the Fetal Medicine Foundation (FMF) algorithm showed the best predictors to be MAP, UtAPI and PlGF [8] with sFlt-1 performing similarly to PIGF in predicting mid pregnancy PE. In the early and late third trimester, MAP, PIGF and sFlt-1 have been useful predictors [4,5,7,9].

Identification of other potential biomarkers to add to the current screening panel may add the extra value required to further improve accuracy. The eicosanoids leukotriene B4 (LTB4) and hydroxyeicosatetraenoic acid (HETE) have long been studied in PE but their potential as useful predictors of the disease is yet to be fully realised [10]. These molecules are derived from arachidonic acid via the lipoxygenase (LOX) pathway, are operative during inflammation to promote bronchoconstriction and are potent immunoregulatory lipid mediators of immune responses [11–13] with additional roles in vascular function and angiogenesis [13,14]. These properties and the contribution of excessive systemic inflammation to PE make these metabolites potential candidates as biomarkers for PE.

The objective of this study is to compare serum levels of LTB4 and 15 (S)-HETE in asymptomatic women who later developed preterm or term PE with those of unaffected pregnancies in the second and third trimesters of pregnancy.

2. Methods

2.1. Study design and population

This is a case-control study drawn from a prospective cohort study of screening for adverse pregnancy outcomes. Informed consent was obtained from women with singleton pregnancies attending routine second and third trimester hospital visits at the Harris Birthright Unit for Fetal Medicine, King's College Hospital, London, between July 2011 and January 2016. The study was approved by the UK National Research Ethics Committee (reference number: 02-03-033).

The following maternal characteristics were obtained: age, height, weight, racial origin, conception method (spontaneous or assisted with ovulation drugs or *in vitro* fertilization), cigarette smoking during pregnancy, history of chronic hypertension, systemic lupus erythematosus, antiphospholipid syndrome, pre-gestational diabetes (type 1 or 2), family history of PE in the maternal side of the patient and obstetric history including parity (parous or nulliparous-no previous pregnancies at or beyond 24 weeks), and any previous pregnancy with PE.

Pre-eclampsia was defined as per criteria established by the International Society for the Study of Hypertension in Pregnancy [15], as the presence of hypertension (≧ 140/90 mmHg) developing after 20 weeks of gestation with significant proteinuria (>0.3 g/24 h) or other maternal organ dysfunction in a previously normotensive woman. PE in cases of women with pre-existing chronic hypertension (present before conception or before 20 weeks of gestation without trophoblastic disease) was defined as worsening of hypertension and significant proteinuria as compared to baseline levels, after 20 weeks of gestation.

2.2. Blood collection and analysis

Blood samples were obtained from 203 women: 48 samples at 19–24 weeks (25 controls, 11 with preterm PE and 12 with term PE), 101 samples at 30–34 weeks (49 controls, 27 with preterm PE and 25 with term PE), and 54 samples at 35–37 weeks of gestation (40 controls and 14 with term PE). Serum was collected and stored at −80 °C until analysis. The cases were independent, with no collection of longitudinal samples.

Serum LTB4 and 15(S)-HETE were determined using commercial LTB4 and 15(S)-HETE enzyme-linked immunosorbent assay (ELISA) kits (Cayman Chemical, Ann Arbor, MI, USA) according to the manufacturer's protocol. Serum samples were tested neat for LTB4 ELISA and diluted 1/50 or 1/25 for the 15(S)-HETE ELISA. The standard curve ranges for each analyte were 3.9–500 pg/ml (LTB4) and 78-10,000 pg/ml (15(S)-HETE). The laboratory operator was blinded to pregnancy outcome when testing samples.

In some cases, samples were excluded due to levels being non-readable (too high or too low) for the sensitivity of the assay. In case of LTB4 assay at 19–24 weeks, 4/25 controls, 2/11 preterm PE and 1/12 term PE were excluded; at 30–34 weeks, 12/49 controls, 10/27 preterm PE and 6/25 term PE were excluded; at 35–37 weeks, 7/40 controls and 2/14 term PE were excluded. In case of 15(S)-HETE assay at 19–24 weeks, 7/25 healthy, 2/11 preterm PE and 1/12 term PE were excluded; at 30–34 weeks, 12/49 healthy, 2/25 term PE were excluded; at 35–37 weeks, 8/40 healthy and 3/14 term PE were excluded.

2.3. Statistical analysis

Categorical baseline variables are presented as absolute numbers and proportions and compared between the groups with the Chi-squared or Fisher's exact test, as appropriate. Continuous baseline variables are summarized as means and standard deviations and, due to the sample size, distributions were compared between the groups with the Wilcoxon rank-sum test. Multiple linear regression with stepwise backward elimination was applied on logarithmically transformed LTB4 and 15 (S)-HETE control values to determine the influence of gestational age at blood sampling and maternal characteristics that significantly impact on each eicosanoid value. Results were then expressed in multiples of the expected median (MoM), adjusting for covariates found to significantly influence LTB4 and 15(S)-HETE results. Eicosanoid levels were compared between normotensive pregnancies and those affected by preterm or term PE using the Wilcoxon rank-sum test. To investigate a possible association of eicosanoid levels with severity of PE, Cox

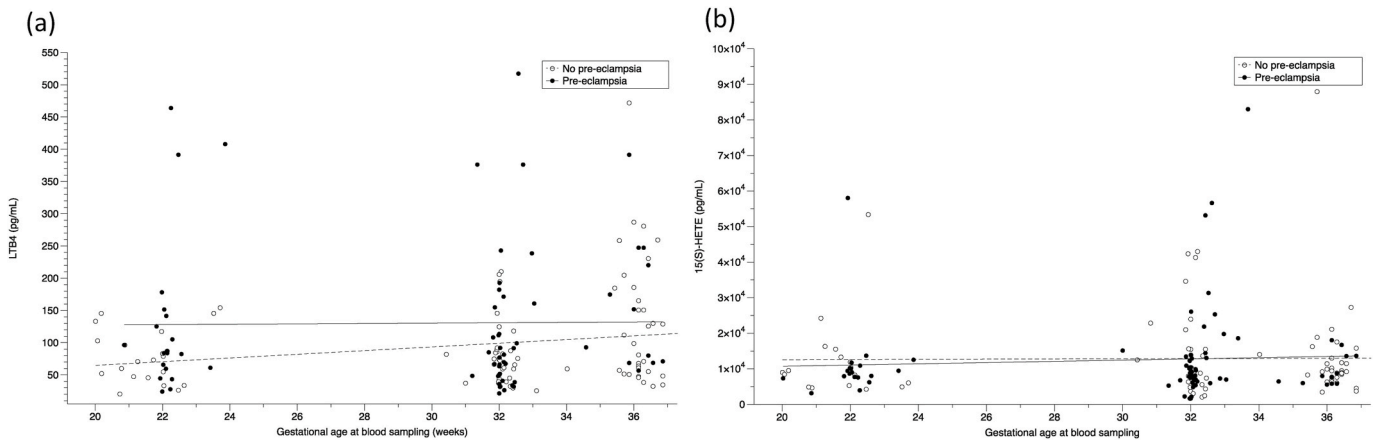

Fig. 1. Serum LTB4 (a) and 15(S)-HETE (b) levels at 19–24, 30–34 and 35–37 weeks of gestation in controls (open circles and dashed regression line) and PE cases (closed circles and solid regression line).

regression analysis was then applied in each gestational window to investigate the relationship between LTB4 and 15(S)-HETE MoM results and interval between sampling and delivery with PE, censoring deliveries without PE. Between-group comparisons were considered statistically significant at a 0.05 significance level. Statistical analysis was performed with SPSS Statistics (IBM Corp. Released 2019. IBM SPSS Statistics for Macintosh, Version 26.0 Armonk, NY: IBM Corp). Where potential differences were encountered, receiver operating characteristics (ROC) curves were produced, and the area under the ROC curve (AUC) was calculated.

3. Results

The baseline characteristics of the study population are listed in Table 1. Compared to normotensive controls, women who later developed PE had significantly higher maternal body weight, had more commonly a history of PE in a previous pregnancy, as well as higher rates of chronic hypertension.

3.1. Serum LTB4

Detectable serum LTB4 levels significantly increased with gestational age in normotensive controls (P = 0.011), while levels in PE women remained relatively unchanged throughout the second and the third trimesters (Fig. 1a). In addition, LTB4 values in normotensive pregnancies were higher in women with a previous history of pre-eclampsia (P = 0.026) and lower in those of East Asian racial origin compared to White women (P = 0.031) (Table 1).

The median LTB4 raw and MoM values in each group at different gestational age intervals at blood sampling are summarized in Table 2.

At 19–24 weeks, LTB4 was significantly increased in preterm PE (median raw 151.4 pg/ml, median MoM 2.12) compared to normotensive controls (median raw 73.2 pg/ml, median MoM 1.05) (Fig. 2a and b). At 30–34 weeks, there was a trend to higher serum LTB4 levels in cases in preterm PE (median raw 99.1 pg/ml, median MoM 1.21; normotensive controls median raw 66.3 pg/ml, median MoM 0.9) (Fig. 2a and b). No significant differences in LTB4 levels were found between normotensive pregnancies and cases of term PE, at any gestational age tested (Fig. 2a and b).

Cox regression analysis demonstrated a statistically significant negative association of LTB4 MoM values with time to delivery with PE at 19–24 weeks (P = 0.005), but not at 30–34 weeks or at 35–37 weeks (P = 0.609, P = 0.718, respectively) (Fig. 3a).

Supplementary Figure 1 shows the ROC curves for the prediction of preterm PE with LTB4 measured at 19–24 (AUC 0.78, 95% CI 0.60 to 0.96, p = 0.018) and at 30–34 weeks (AUC 0.66, 95% CI 0.48 to 0.83, p = 0.067).

3.2. Serum 15(S)-HETE

Serum 15(S)-HETE levels were not influenced by gestational age at blood sampling in normotensive and PE pregnancies (Fig. 1b) and were significantly higher in women of South Asian than in those of White racial origin (Table 1). The median 15(S)-HETE raw and MoM values in each group at different gestational age intervals at blood sampling are summarized in Table 3. Raw and MoM values of 15(S)-HETE (Fig. 2c and d) in pregnancies affected by PE did not differ from those of normotensive controls. There were no associations between 15(S)-HETE MoM values and interval between sampling and delivery with PE (Fig. 3b) in all gestational age windows studied.

Table 2
Comparison of median LTB4 values according to different outcome groups at 19–24, 30–34 and 35–37 weeks.

	LTB4 (pg/mL) Median (IQR)	P value	LTB4 MoM, Median (IQR)	P value
19–24 weeks				
Control (n = 21)	73.2 (46.5–110.1)	–	1.05 (0.67–1.83)	–
Preterm PE (n = 9)	**151.4 (74.8–399.7)**	**0.011***	**2.12 (1.11–4.95)**	**0.018***
Term PE (n = 11)	82.4 (43.4–96.4)	0.751	0.99 (0.62–1.46)	0.463
30–34 weeks				
Control (n = 37)	66.3 (40.2–86.6)	–	0.90 (0.52–1.09)	
Preterm PE (n = 17)	**99.1 (53.4–171.5)**	**0.052**	**1.21 (0.66–2.10)**	**0.067**
Term PE (n = 19)	67.4 (48.3–113.5)	0.556	0.79 (0.45–1.41)	0.539
35–37 weeks				
Control (n = 33)	98.7 (53.4–185.1)	–	1.08 (0.66–2.16)	–
Term PE (n = 12)	115.9 (68.7–240.5)	0.342	1.27 (0.65–2.61)	0.758

Comparisons between groups were performed with one-way ANOVA on logarithmically transformed values with post-hoc Dunnett's adjustment for multiple comparisons, using the control group as the reference category.

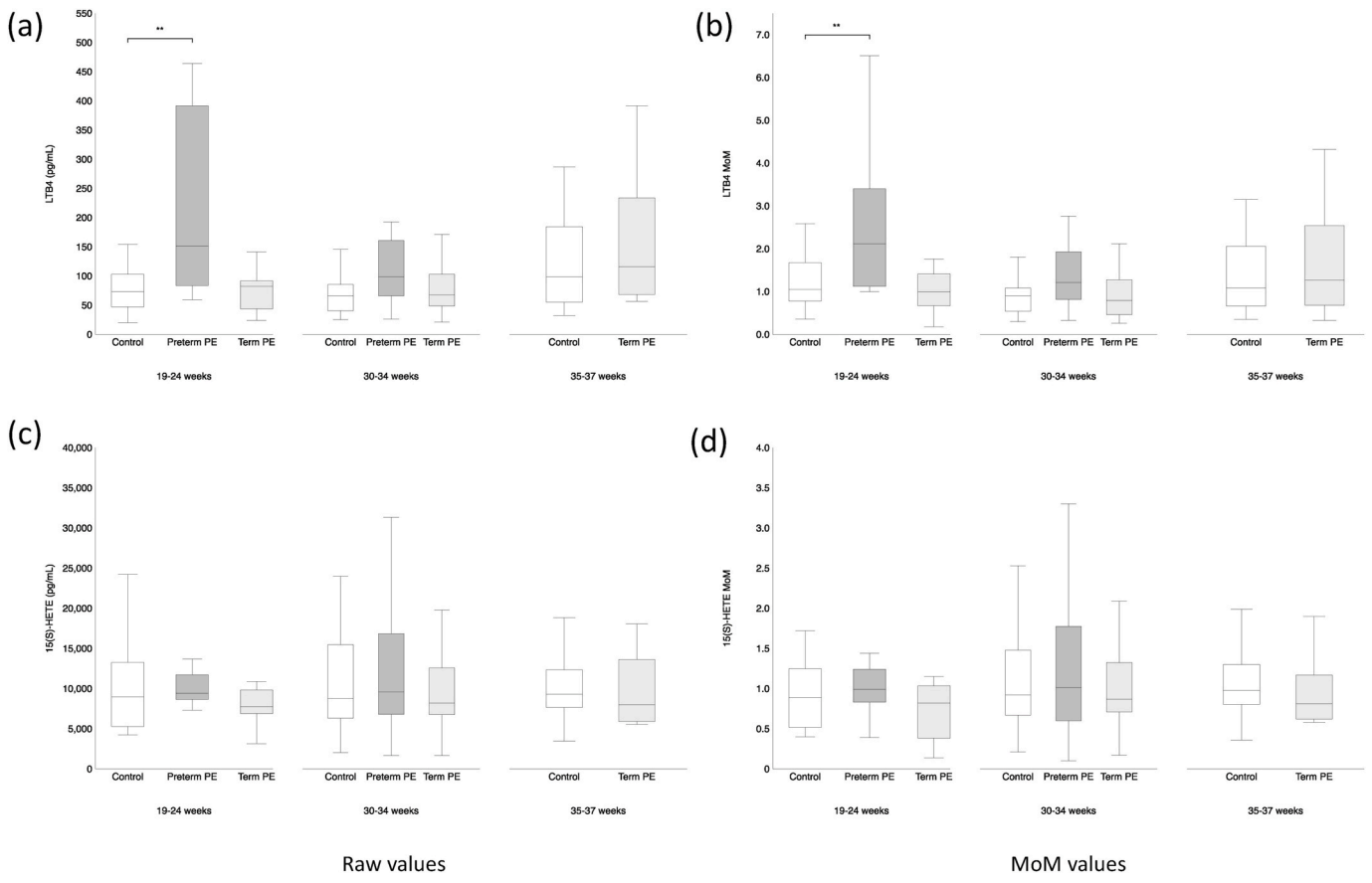

Fig. 2. Serum LTB4 raw (a), multiples of the median (MoM) values (b) and 15(S)-HETE raw (c), multiples of the median (MoM) values (d) and at 19–24, 30–34, and 35–37 weeks of gestation. At 19–24 weeks, healthy vs preterm PE LTB4 raw and MoM values have P = 0.011 and 0.018, respectively.

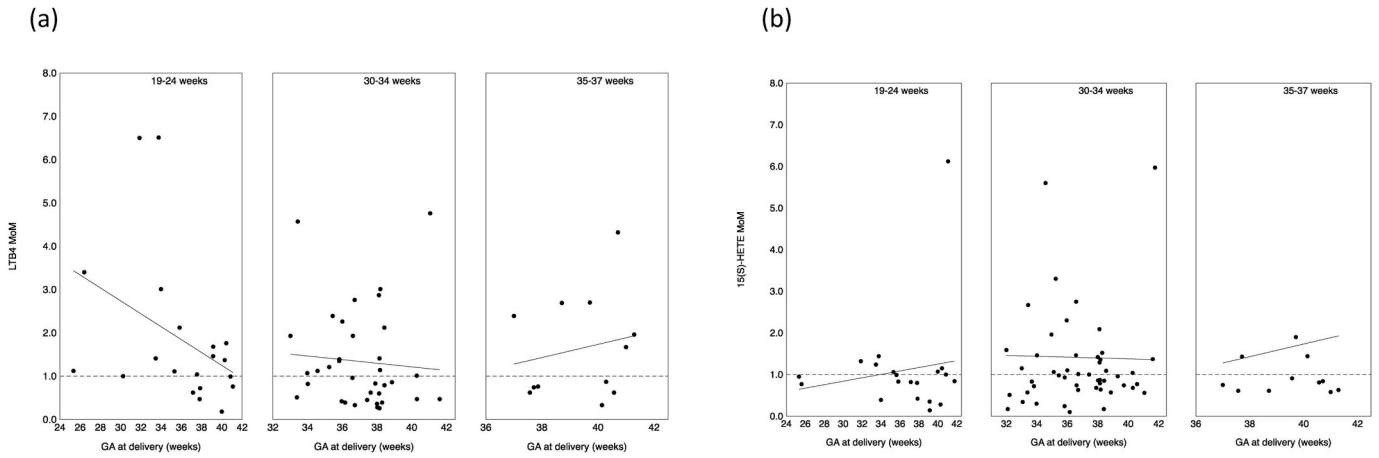

Fig. 3. Serum LTB4 (a) and 15(S)-HETE (b) multiples of the median at 19–24, 30–34, and 35–37 weeks of gestational age and the interval between sampling and delivery in pregnancies with pre-eclampsia. Regression lines are shown (LTB4 P values 0.005 at 19–24 weeks, 0.609 at 30–34 weeks and 0.718 at 35–37 weeks of gestational age; 15(S)-HETE P values 0.569 at 19–24 weeks, 0.949 at 30–34 weeks and 0.792 at 35–37 weeks of gestation).

4. Discussion

4.1. Main findings

Serum LTB4 levels increased with gestational age in normal pregnancies but remained stable in women who developed PE. Women with preterm PE had significantly higher LTB4 at 19–24 weeks and a trend to higher levels at 30–34 weeks, and in the second trimester these levels seem to correlate with the severity of disease. In women with term PE, LTB4 levels were comparable to those of normotensive controls. Serum 15(S)-HETE levels remained stable during gestation in normotensive controls and in women with preterm or term PE were not significantly different when compared to controls. Our findings suggest that LTB4 levels are significantly increased in women with preterm PE in the second and early third trimesters, whilst 15(S)-HETE values are not altered in women who later develop PE.

Table 3
Comparison of median 15(S)-HETE values according to different outcome groups at 19–24, 30–34 and 35–37 weeks.

	15(S)-HETE (pg/mL), Median (IQR)	P value	15(S)-HETE MoM, Median (IQR)	P value
19–24 weeks				
Control (n = 17)	8982.5 (5109.3–14413.9)	–	0.89 (0.52–1.33)	–
Preterm PE (n = 9)	9419.4 (8285.4–12136.9)	0.686	0.99 (0.80–1.28)	0.808
Term PE (n = 11)	7753.0 (6222.3–10198.8)	0.438	0.82 (0.35–1.07)	0.269
30–34 weeks				
Control (n = 37)	8776.7 (6160.1–15492.8)	–	0.92 (0.65–1.55)	
Preterm PE (n = 27)	9586.8 (6778.1–18603.7)	0.698	1.01 (0.57–1.96)	0.812
Term PE (n = 23)	8214.3 (6462.4–12916.6)	0.744	0.87 (0.68–1.36)	0.861
35–37 weeks				
Control (n = 32)	9321.8 (7628.1–12689.1)	–	0.98 (0.80–1.34)	–
Term PE (n = 11)	7987.8 (5819.7–13646.9)	0.404	0.81 (0.61–1.43)	0.164

Comparisons between groups were performed with one-way ANOVA on logarithmically transformed values with post-hoc Dunnett's adjustment for multiple comparisons, using the control group as the reference category.

4.2. Results of previous studies

The current study reports increased LTB4 with advancing gestational age in women with normal pregnancy. This is likely explained by physiological changes in a typical pregnancy that are conducive to increased production of arachidonic acid metabolites [16–18]. Other case-control studies have similarly reported an association of increased LTB4 with PE. However, the women in these studies were sampled late in their pregnancy (34–35 weeks), after PE diagnosis, and LTB4 was measured in plasma. Nevertheless, plasma LTB4 levels, measured by immunoassay [19] (n = 21 PE and 20 normotensive controls) and Liquid chromatography with tandem mass spectrometry (LC-MS/MS)-based metabolomics [20] (n = 10 PE and 10 normotensive controls) were elevated in women with PE compared to gestational age-matched controls. In addition, clotting has been shown not to affect LTB4 concentration [21]. Moreover, Long et al. sampled women before and after PE diagnosis and found LTB4 to be elevated in both samples compared to controls (n = 49 total PE and 26 normotensive controls) [10]. This same study also reported that severe PE cases had increased LTB4 levels compared to mild PE and normotensive controls. Interestingly, serum LTB4 in women with mild PE was comparable to normotensive controls [10]. In the case of 15(S)-HETE, this metabolite has been reported to be both significantly increased (n = 49 PE and 26 normotensive controls) [10] and trended to be higher (n = 10 PE and 10 normotensive controls) [20] in PE compared with normotensive pregnancies. Most studies did not account for possible confounders such as gestational age at sampling or examine the interval between sampling and delivery with PE. Consequently, it is difficult to accurately interpret the data and its usefulness in validating the predictive value of these metabolites.

Differential levels of LTB4 in preterm PE and term PE may be reflective of the phenotypic differences between these disease presentations [22] further highlighting the importance of accounting for covariates that may affect eicosanoid levels. Moreover, while it is yet to be proven, it has been suggested that PE may represent two different pathophysiological mechanisms depending on the time of diagnosis [23], with more predominating proinflammatory factors in preterm PE compared to term PE and normotensive pregnant women that maybe causative of elevated LTB4 levels in these patients [17,24].

4.3. Limitations and strengths

The main limitation of the current study is its case-control design with a relatively small number of cases included. Some samples were below the detection limit of the assays. PE is a heterogeneous disorder in terms of maternal phenotype, pathophysiology and severity, and as such the total number of normal and pathological pregnancies examined will likely need to be increased in additional studies to evaluate the predictive ability of LTB4 and 15(S)-HETE in screening for PE.

To avoid introduction of bias, blood samples for this study were prospectively collected and the assays were performed blinded to pregnancy outcomes. In addition, we adjusted the LTB4 and 15(S)-HETE results for possible confounders (such as ethnicity and history of pregnancy complications) and accounted for the changes in biomarker values throughout gestation. Variable reports on the levels of these and other metabolites are possibly due to lack of adjustment for gestational age and other maternal characteristics that may influence metabolite levels.

4.4. Clinical implications and further research

Given that LTB4 is elevated in the second and possibly in the third trimester of pregnancies destined to develop preterm PE it might be capable of improving the detection rates of previously developed second trimester predictive models for preterm PE. 15(S)-HETE, on the other hand, does not appear to be altered in pregnancies that go on to develop PE, and is unlikely to be useful in PE prediction. Apart from LTB4 other products of the lipooxygenase pathway might be altered in patients with PE as well, however currently no valid ELISA kits are available to test other eicosanoids. Although first trimester prediction is ideal to identify a high-risk group that benefits from preventive interventions such as aspirin prophylaxis, second and third trimester prediction is useful to screen women who missed the optimal first trimester prediction, and to reassess previously estimated risks and to individualize antenatal care.

While anti-inflammatory use could theoretically affect LTB4 and 15 (S)-HETE levels, non-steroidal anti-inflammatories are usually avoided in pregnancy. Aspirin is commonly prescribed to patients at high risk of PE, but its use became more common after the publication of the Aspirin for Evidence-Based Prevention of Pre-eclampsia (ASPRE) trial in 2017 [25], and in the doses normally utilized in pregnancy (below 300 mg), aspirin selectively inhibits the cyclooxygenase 1 (COX-1) enzyme, with no significant effects on the lipooxygenase pathway.

As with most biomarkers, poor discrimination ability (demonstrated in the ROC curves) will likely preclude the use of LTB4 in isolation as a predictive tool in clinical practice. Future larger cohort studies are necessary to evaluate the possible benefit of combining LTB4 measurement with currently established risk factors and biomarkers such as sFlt-1 and PlGF in predictive algorithms. Such studies should take into account the effect of gestational age and maternal characteristics on LTB4 results, the interaction of LTB4 with other biomarkers, and the relationship between LTB4 results with severity of the disease.

5. Conclusion

Serum LTB4 is increased during the second and early third trimester in women who will develop preterm PE and is a potentially useful predictive biomarker in the prediction for PE. Serum 15(S)-HETE is not altered in pregnancies affected by PE in the second or in the third trimester before disease onset and is unlikely to be useful in PE prediction.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

ED was supported by a senior research fellowship from the National Health and Medical Research Council of Australia (grant numbers 1117033 and 1098332). DW was supported by a grant from the Paracelsus Medical University Salzburg, Austria (PMU Research Fund – PMU FFF Number: L-18/02/006-WET) and by Drs Haackert Foundation, Germany.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.placenta.2020.10.007.

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