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Plasma oxylin levels associated with preterm birth in preterm labor

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ABSTRACT

Introduction Preterm labor is a common clinical problem in obstetrics. Since the majority of women with preterm labor eventually deliver at full term, biomarkers are needed to more accurately predict who will deliver preterm. Oxylipins, given their importance in inflammation regulation, are highly interesting in this respect since labor is an inflammatory process.

Methods Eighty women with preterm labor before 34 weeks of gestation were enrolled in a prospective observational multi-center cohort study. Oxylipin levels of 67 analytes in plasma samples were analyzed by liquid chromatography coupled to tandem mass spectrometry.

Results Twenty-one (26%) of the women delivered before 34 weeks of gestation, and of those women, fourteen delivered within 48 hours of admission. Logistic multivariate regression showed that lower levels of 9,10-DiHODE were associated with delivery before 34 weeks of gestation (aOR 0.12 (0.024-0.62)) and within 48 hours ((aOR 0.13 (0.019-0.93)). Furthermore, higher levels of 11,12-DiHETrE were associated with delivery before 34 weeks of gestation ((aOR 6.19 (1.17-32.7)) and higher levels of 8-HETE were associated with delivery within 48 hours ((aOR 5.01 (1.13-22.14)).

Conclusions The oxylipin 9,10-DiHODE may be protective in preterm labor, both for delivery after 34 weeks of gestation and for delivery later than 48 hours of admission, whereas 11,12-DiHETrE and 8-HETE display the opposite effect. Larger studies are needed to validate these mediators as biomarkers for prediction of preterm birth following preterm labor.

KEYWORDS

Preterm labor, preterm birth, oxylipins, eicosanoids, biomarker, prediction

SUMMARY

Labor is an inflammatory process. Oxylipins, which are important regulators of inflammation, are therefore highly relevant to explore as biomarkers in preterm labor in order to distinguish women with subsequent preterm birth from the majority of women with subsequent birth at full term, thereby avoiding unnecessary treatments. Plasma levels of 67 oxylipins were measured by liquid chromatography coupled to tandem mass spectrometry in 80 women with preterm labor before 34 weeks of gestation. Logistic multivariate regression showed that 9,10-DiHODE was protective both for delivery before 34 weeks of gestation and for delivery within 48 hours, whereas 11,12-DiHETrE had the opposite effect in relation to delivery before 34 weeks, and 8-HETE for delivery within 48 hours. Larger studies are needed to evaluate these compounds as potential predictive biomarkers for preterm birth following preterm labor.

1. INTRODUCTION

Preterm labor is a clinical condition with regular uterine contractions and cervical ripening before 37 weeks of gestation, which potentially leads to preterm birth (PTB). PTB, defined as birth before 37 weeks of gestation, affects 11% of infants globally and is the leading cause of neonatal morbidity and mortality, and also the leading cause of death in children under the age of five [1-3]. However, a substantial proportion of women with preterm labor deliver at full term [4, 5]. From a clinical point of view, preterm labor therefore constitutes a major problem, since it is crucial to correctly identify and treat women with imminent PTB, but also to avoid hospital admissions, hazardous transports to tertiary centers, and potentially injurious treatments for women who will eventually deliver at term. Although a short cervical length, as measured by transvaginal ultrasound, is associated with increased risk of PTB [6], more accurate prediction models are needed to improve clinical decision-making. In order to develop potential biomarkers, a better understanding of the underlying mechanisms is needed.

In this context, the changes in the immune system and its regulatory role during pregnancy are of great importance. Generally, pregnancy is associated with a shift toward immune tolerance [7] in order to avoid rejection of the semi-foreign fetus. This immune tolerance is broken at term and replaced by an inflammatory state that contributes to the initiation of labor. It is assumed that a lack, or preterm break, of tolerance is a basis for the inflammation that is involved in various pregnancy complications, including spontaneous PTB [8]. Due to the pivotal regulatory role of oxylipins in inflammation, these compounds might be relevant in immune regulation of pregnancy and highly relevant to explore as biomarkers in preterm labor.

Oxylipins are fatty acid metabolites that are important for a broad variety of conditions with an inflammatory component. They are derived from polyunsaturated fatty acids such as arachidonic acid (AA), linoleic acid (LA), eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), dihomo- γ -linolenic acid (DGLA), and α -linolenic acid (ALA). The most important enzymatic cascades involved in the formation of oxylipins are catalyzed by cyclooxygenase (COX), lipoxygenase (LOX), and cytochrome P450 (CYP) [9]. AA-derived oxylipins are also known as eicosanoids. The most well-known group of oxylipins in relation to labor and pregnancy are found among the eicosanoids, namely the prostanoids, including prostaglandins, derived from AA by COX. Prostanoids are elevated in amniotic fluid before the onset of labor, both preterm and at term [10-12]. Furthermore, prostanoids and other oxylipins have been associated with gestational age at birth [13], and they are involved in

multiple physiological processes of importance in pregnancy, for instance immune activation [14, 15], endothelial cell activation [16], resolution of inflammation [17, 18], and coagulation [19].

DHA supplementation in pregnancy and the impact on oxylipins and precursor fatty acids have been studied in the context of PTB, and it has been suggested that a subset of oxylipins might serve as potential early biomarkers for spontaneous PTB [20]. Furthermore, it has been proposed that low circulating levels of omega-3 polyunsaturated fatty acids are a risk factor for early PTB [21]. However, these findings do not reflect the specific situation of a woman presenting with symptoms of preterm labor, and it is not known how oxylipins are involved in the underlying mechanism of preterm labor, nor if oxylipin signatures might have the potential to predict PTB in women with preterm labor.

We therefore performed an exploratory study in women with preterm labor to investigate the signature of oxylipins in association with delivery before and after 34 weeks of gestation, and within and after 48 hours of hospital admission. The chosen time points (34 weeks and 48 hours, respectively) were based on clinical importance [22].

2. MATERIALS AND METHODS

2.1. Study design and collection of samples

A prospective observational multi-center cohort study was performed during 2014-2017 as previously described in a study of inflammatory proteins [5]. From that study, a sub-cohort of 80 women with preterm labor was included in the current study. Preterm labor was defined as regular painful uterine contractions before 34 weeks of gestation with cervical shortening (cervix <25 mm), measured by transvaginal ultrasound, or a cervical dilatation of more than one cm, assessed by digital examination. All 80 women had intact membranes and were clinically assessed as having a high risk of delivery before 34 weeks of gestation.

Accordingly, they were hospitalized and treated for preterm labor. The women were recruited from three different hospitals in the south-east region of Sweden. Two of the hospitals were secondary level centers (Jönköping and Kalmar) and one was a tertiary center (Linköping). All women had singleton pregnancies. Gestational age was determined by a standardized routine transabdominal ultrasound performed in the second trimester (week 12-19).

Blood samples (EDTA tubes) were drawn immediately after admission to hospital, before initiation of any medical treatment. After being left for one-two hours at room temperature the

tubes were centrifuged at 2500g for ten minutes and the plasma was immediately frozen in aliquots at -70°C. In the two secondary level centers (n=39 and n=26) pneumatic tube transport of the EDTA tubes was used, which was not the case in the tertiary center (n=15).

2.2. Ethical approval

The study was approved by the Regional Ethical Review Board in Linköping, Sweden (2013/417-31 and 2016/421-32), and all women gave written informed consent to participate. The work was carried out according to the principles of the declaration of Helsinki.

2.3 Analysis of oxylipins by a liquid chromatography tandem mass spectrometry method

Unesterified oxylipins were isolated from plasma with solid phase extraction using Waters Oasis HLB cartridges (60 mg of sorbent, 30 µm particle size), and then 67 individual analytes (Figure 1) were probed for by liquid chromatography (LC) coupled to tandem mass spectrometry (MS/MS) according to previously published protocols [23] with an additional set of ALA-derived epoxides and diols synthesized in-house. Separation of the analytes was performed using an Agilent Infinity 1290 (Agilent Technologies, CA, USA) LC equipped with a Waters BEH C18 column (2.1 mm×150 mm, 130 Å, 1.7 µm particle size) using a gradient of water (0.1% acetic acid) and acetonitrile:isopropanol (90:10) as mobile phases. An Agilent 6495 triple quadrupole mass spectrometer was used in negative electrospray ionization mode for dynamic multiple reaction monitoring of fragment ions (two for each analyte, one for quantification and one for qualification purposes). Chromatograms were evaluated manually using an in-house script and quantification of oxylipins was performed using external calibration curves as described previously [24]. The abbreviations of each oxylipin are explained in supplementary table S1.

2.4 Data analyses

For comparison of clinical characteristics, non-parametric analyses were made for continuous variables (Mann-Whitney *U*-test) and a Chi-2 test or Fisher's exact test were used when appropriate for categorical variables. P-values <0.05 were considered significant.

The Mann-Whitney *U*-test, or Chi-2 test when appropriate, was used for screening of differences in oxylipin concentrations between groups and also for investigations of systematic differences between hospitals.

Oxylipins with a difference in concentrations between groups at a p-value <0.1 were further analyzed with logistic quantile regression in univariate and multivariate models. Here, only oxylipins with at least 40% of values above the limit of detection (LOD) were taken into consideration, and values below LOD were substituted with $\text{LOD}/\sqrt{2}$ [25]. Multivariate logistic quantile regression models were adjusted for usage of pneumatic tube systems for sample transport, as this may affect oxylipin levels [26]. Adjacent quartiles of statistically significant variables were combined if the actual frequencies were similar or opposite to the significant trend.

The software Statistica v.13.5.0.17 (TIBCO Software Inc., Palo Alto, CA, USA) and GraphPad Prism v. 8.3.0 for Windows (GraphPad Software, San Diego, CA, USA) were used for all analyses.

3. RESULTS

Of the 80 women included in the study, 21 (26%) delivered before 34 weeks of gestation. Of those, 14 women delivered within 48 hours after admission to hospital. Hence, 59 women (74%) delivered after 34 weeks, whereas 66 (82%) women delivered later than 48 hours after admission (Figure 2).

Clinical characteristics have been reported previously, in the context of inflammatory proteins [5]. Briefly, women who delivered <34 weeks ($n = 21$) had higher BMI (median 25 (range 20-46) versus 22 (16-41), $p=0.011$), a higher proportion of nulliparity (81% versus 27%, $p=0.010$), and shorter cervical length (7 mm (0-49) versus 16 mm (4-40), $p<0.001$) compared to women who delivered ≥ 34 weeks (Table 1). The women with delivery within 48 hours after admission had a higher BMI (25 (20-46) versus 22 (16-41), $p=0.022$) and a shorter cervical length (9 (0-40) versus 16 (0-40), $p=0.008$) than the women with delivery after 48 hours (Table 1). Regarding age, tobacco use, and gestational age at inclusion, there were no significant differences between either of the groups.

According to the initial non-stringent ($p<0.1$) screening, using a Mann-Whitney *U*-test (supplementary Table S2), women with delivery before 34 weeks of gestation had lower concentrations of 9-HOTrE ($p=0.09$), 9,10-DiHOME ($p=0.09$), and 9,10-DiHODE ($p=0.02$) and higher concentrations of 8-HETE ($p=0.02$) and 11,12-DiHETrE ($p=0.08$) compared to women with delivery after 34 weeks (Figure 3). Furthermore, women with delivery within 48

hours after inclusion displayed higher concentrations of 8-HETE ($p=0.05$) and lower concentrations of 9,12,13-TriHOME ($p=0.06$), 9,10-DiHOME ($p=0.08$), and 9,10-DiHODE ($p=0.02$) compared to women with delivery after 48 hours (Figure 4). The association between these oxylipins and time of delivery was further analyzed with univariate and multivariate logistic regression.

In the univariate logistic regression analysis, there was an association with delivery before 34 weeks of gestation and lower concentrations of 9,10-DiHOME, 9,10-DiHODE, and 9-HOTrE, as well as an association with higher concentrations of 8-HETE and 11,12-DiHETrE (Table 2). In the multivariate analysis, two oxylipins remained significantly associated with delivery before 34 weeks of gestation. Forty percent of women with concentrations of 9,10-DiHODE in the lowest two quartiles (<0.237 pmol/mL) delivered before 34 weeks compared to 10% of women with concentrations in the highest quartile (>0.441 pmol/mL) (adjusted OR 0.12 (0.024-0.62); $p=0.012$) (Table 2). The multivariate analysis also showed a significant association between delivery before 34 weeks and higher concentrations of 11,12-DiHETrE; 15% of women with concentrations in the lowest quartile (≤ 0.486 pmol/mL) gave birth before 34 weeks compared to 45% of women with concentrations of 11,12-DiHETrE in the highest quartile (>0.739) (adjusted OR 6.19 (1.17-32.7); $p=0.032$) (Table 2). Data for all quartiles is shown in Supplementary Tables S3 and S4.

Regarding delivery within 48 hours of hospital admission, there was a univariate association with lower concentrations of 9,10-DiHOME, and 9,10-DiHODE as well as an association with higher concentrations of 8-HETE (Table 3). After multivariate analysis, the two remaining oxylipins with a significant association with delivery within 48 hours were 9,10-DiHODE and 8-HETE. Concerning 9,10-DiHODE, 28% of women with concentrations in the two lowest quartiles (<0.237 pmol/mL) of this oxylipin delivered within 48 hours compared to 5% of women with concentrations in the highest quartile (>0.441 pmol/mL) (adjusted OR 0.13 (0.019-0.93); $p=0.042$). The corresponding numbers for 8-HETE were 7% delivery within 48 hours in the two lowest quartiles and 28% in the two highest quartiles (adjusted OR 5.01 (1.13-22.14); $p=0.034$) (Table 3).

Furthermore, since the sampling protocol and pneumatic tube transport have been reported to influence a subset of oxylipins [26], we investigated the potential impact of these factors on our data set. In the univariate logistic regression analysis there was a tendency to find a statistically significant association between not using pneumatic tube transport and delivery before 34 weeks ($p=0.053$); however, in the multivariate analysis an association was not

verified ($p=0.127$) (Table 2). Regarding delivery within 48 hours, the use of pneumatic tube transport had no impact on the results (Table 3).

There was a numerically higher proportion of women with delivery before 34 weeks (47%) and within 48 hours (27%) at the tertiary center compared to the two secondary centers (21% and 23%, respectively, for delivery before 34 weeks, and 13% and 19%, respectively, for delivery within 48 hours). However, this was not a significant difference ($p>0.05$). There were no significant differences regarding frequencies of detected analytes when comparing hospitals (data not shown).

4. DISCUSSION AND CONCLUSIONS

In this prospective multi-center observational cohort study, we report, for the first time that there are a few, but important, oxylipins that are significantly associated with PTB in women presenting with preterm labor. In particular, 9,10-DiHODE and 11,12-DiHETrE were independently associated with PTB before or after 34 weeks of gestation. Both compounds are dihydroxy fatty acids derived *via* the CYP pathway, although 9,10-DiHODE is derived from ALA while 11,12-DiHETrE is derived from AA. Interestingly, 9,10-DiHODE and 11,12-DiHETrE showed opposing effects; 9,10-DiHODE being protective and 11,12-DiHETrE being harmful in relation to PTB. For delivery within 48 hours of hospital admission, again 9,10-DiHODE showed a protective effect, and here 8-HETE was associated with an increased risk of impending PTB. Although oxylipins are mechanistically relevant to the pro-inflammatory state of PTB, and the findings support a role of selected oxylipins as biomarkers, further studies are needed to establish their clinical utility.

In the present study, we chose 34 weeks of gestation as a cut-off for clinically relevant PTB. In guidelines [22] it is recommended that corticosteroids are given to pregnant women with preterm labor and a high risk of delivery before 34 weeks of gestation in order to decrease respiratory distress complications in the neonate. It is also generally considered that the full effect of corticosteroids is achieved after 48 hours. Therefore, the gestational age of 34 weeks and the time interval of 48 hours after admission are very important in the clinical setting.

High levels of 9,10-DiHODE were associated with delivery after gestational week 34 and later than 48 hours of admission to the hospital, which implies a protective effect of 9,10-DiHODE in relation to spontaneous PTB. 9,10-DiHODE is an ALA-derived dihydroxy fatty

acid produced *via* the CYP pathway. It has been associated with pregnancy in analyses of bovine corpora lutea [27]. Furthermore, CYP products (together with LOX products) have been recognized as the most prominent among the oxylipins for identifying overall and spontaneous preterm birth [28], although 9,10-DiHODE was not included in that study. DiHODEs such as 9,10-DiHODE are not commercially available, which in part may have hampered investigations of their role in PTB. Our findings underline the need for a comprehensive panel of analytes in studies of preterm labor and PTB, including ALA-derived oxylipins such as DiHODEs.

High levels of another dihydroxy fatty acid, namely 11,12-DiHETrE (also known as 11,12-DHET), derived from AA *via* the CYP pathway, were associated with delivery before gestational week 34, which implies a harmful effect of 11,12-DiHETrE in terms of spontaneous PTB. Earlier studies of 11,12-DiHETrE have shown that it is significantly associated with increased odds of preterm birth, as stated in the review article by Aung *et al.* [28]; however, this was in asymptomatic women, hence not in the setting of preterm labor. The opposite association of the omega-6 AA-derived 11,12-DiHETrE compared to the omega-3 ALA-derived 9,10-DiHODE with PTB emphasizes the complexity of oxylipin pathways in which the same enzymes catalyze the conversion of a range of fatty acid parent compounds, some with anti-inflammatory properties, and others with pro-inflammatory properties. The finding of opposing effects is intriguing since in a protein screening [5] of 92 proteins, none was found to be protective in relation to PTB. Thus, it is relevant to consider mechanisms for protective effects with emphasis on the anti-inflammatory and pro-resolving effects of oxylipins. Interestingly, omega-3 supplementation has been associated with decreased risk of PTB [28, 29], and low plasma concentration of omega-3 EPA and DHA is a distinct risk factor for PTB [21]. In a recent study, Simmonds *et al.* [30] reported that women with singleton pregnancies and low total omega-3 PUFA status early in pregnancy had an increased risk of preterm birth before 34 weeks of gestation, and that omega-3 supplementation (DHA and EPA) could reduce that risk. Although the study population in Simmonds's work were asymptomatic women in early pregnancy, which are not clinically comparable to our study population of women with symptoms of PTL, it demonstrates the importance of PUFA status in relation to preterm birth, not only the potential effect of individual oxylipins. Ramsden *et al.* [20] investigated whether the protective effect of oxylipins was mediated by increasing levels of DHA-derived oxylipins, while reducing AA-derived oxylipins, such as prostaglandins and other prostanoids, which are implicated in

uterine contractility, or by modulation of immune activation, such as HETEs [20].

Unfortunately, they were not able to detect any prostanoids since the levels were below the limit of quantitation in all plasma samples. Levels of prostanoids were below the LOD also in our study, so it was not possible to investigate the effect of prostaglandins on PTB in preterm labor in the current study either. Other potential limitations include keeping blood samples at room temperature for an extended period of time prior to centrifugation, so potential *ex-vivo* formation and degradation processes cannot be excluded and thus data on platelet derived oxylin such as TXB₂ as well as 12-HETE need to be interpreted with caution [26].

Furthermore, pneumatic tube transport was used for sample delivery at two of the three hospitals in this study, a procedure with a potential impact on oxylin content [26]. Although pneumatic tube transport did not significantly affect oxylin levels, the use of pneumatic tube transport was adjusted for in the statistical analyses as an extra precaution.

Beyond the dihydroxy fatty acids, high levels of the 8-HETE were associated with delivery within 48 hours of admission to hospital. 8-HETE is a monohydroxy fatty acid derived from non-enzymatic oxidation of AA, or *via* the LOX pathway. 8-HETE was not associated with PTB in Aung *et al.* [28]. Moreover, in the univariate analysis, there was an association between higher levels of 8-HETE and delivery before 34 weeks. Other findings in the univariate analysis only were that 9-HOTrE seemed to have a protective effect regarding delivery before 34 weeks, as did 9,10-DiHOME, which was protective in relation to both delivery before 34 weeks and within 48 hours. In Aung *et al.* [28], 9,10-DiHOME was also a significant finding, but with an opposite effect, as it was associated with increased risk of spontaneous PTB. Comparison between the studies must be made with caution, as the study of Aung *et al.* was performed on asymptomatic women and not women with preterm labor, where inflammatory cascades are supposedly augmented. Interpretation of the results in the univariate regression model should be carried out cautiously as it is possible that one of the oxylin is dependent on another oxylin to exert its effect on the outcome. Furthermore, it is possible that clearance of investigated PUFA metabolites, at least in part, contributes to our results, in line with findings on glucuronidation of AA and LA metabolites [31]. Urine analysis needs to be included in future studies in order to investigate the significance of glucuronidation.

In conclusion, in this study of women with preterm labor before 34 weeks of gestation, 9,10-DiHOME and 11,12-DiHETrE were both associated with delivery before 34 weeks, but in opposite directions. 9,10-DiHOME was additionally associated with delivery later than 48

hours after hospital admission, whereas 8-HETE was associated with delivery within 48 hours. To our knowledge, there are no previous findings reporting on the association between preterm labor and these three oxylipins, implying that this is a novel and interesting finding, although it needs to be verified in larger studies whether 9,10-DiHODE, 11,12-DiHETrE, and 8-HETE can serve as biomarkers for PTB in preterm labor.

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TABLES

Table 1. Maternal characteristics of women with preterm labor presented separately for those who delivered at <34 and ≥34 weeks of gestation, and those who delivered within 48 hours and later, respectively. Non-parametric analyses were conducted for continuous parameters (Mann-Whitney *U*-test) and Chi-2 test or Fisher's exact test when appropriate for categorical variables.

Variable	Time of delivery			Time from inclusion to delivery		
	<34 weeks	≥34 weeks	Diff p	≤48 hours	>48 hours	Diff p
N	21	59		14	66	
Age						
Median (IQR)	27 (25-30)	27 (25-31)	1.000	28 (25-31)	27 (25-31)	0.797
Body mass index (kg/m²)						
Median (IQR)	25 (22-32)	22 (20-26)	0.011	25 (22-30)	22 (20-26)	0.022
Tobacco use during pregnancy (n; %)						
No	17 (85)	41 (71)		11 (85)	47 (72)	
Yes	3 (15)	17 (29)	0.249	2 (15)	18 (28)	0.496
Parity at inclusion (n; %)						
Nulliparous	17 (81.0)	27 (45.8)		10 (71.4)	34 (51.5)	
Parous	4 (19.0)	32 (54.2)	0.010	4 (28.6)	32 (48.5)	0.240
Gestational week at inclusion						
Median (IQR)	30 (28-33)	30 (28-32)	0.453	28 (28-33)	31 (28-32)	0.543
Cervical length (mm)						
Median (IQR)	7 (0-12)	16 (12-20)	<0.001	9 (0-13)	16 (12-20)	0.008
Time from inclusion to delivery (n; %)						
0-48 h	14 (66.7)	0 (0.0)		14 (100.0)	0 (0.0)	
2-7 d	6 (28.6)	2 (3.4)		0 (0.0)	8 (12.1)	
>7 d	1 (4.8)	57 (96.6)	<0.001	0 (0.0)	58 (87.9)	-
Time of delivery (n; %)						
<34 weeks	-	-		14 (100)	7 (11)	
≥34 weeks	-	-	-	0 (0)	59 (89)	<0.001

IQR=inter quartile range

Table 2. Oxylipins (pmol/mL) significantly associated with delivery before 34 weeks of gestation following preterm labor analyzed using logistic regression. In the multivariate model the variables were adjusted for pneumatic tube transport.

		Delivery ≤week 34		Univariate logistic regression		Multivariate logistic regression	
Variable	Total	n	%	OR (95% CI)	p	OR (95% CI)	p
Pneumatic tube transport							
No	15	7	47	1.00		1.00	
Yes	65	14	22	0.31 (0.10-1.03)	0.053	0.36 (0.10-1.35)	0.127
9,10-DiHOME Quartiles							
<2.859 (Q1+Q2)*	40	14	35	1.00		-	
2.859-4.872	20	5	25	0.49 (0.24-1.00)		-	
>4.872	20	2	10	0.24 (0.06-0.99)	0.049	-	
9,10-DiHODE Quartiles							
<0.237 (Q1+Q2)*	40	16	40	1.00		1.00	
0.237-0.441	20	3	15	0.37 (0.17-0.81)		0.35 (0.16-0.79)	
>0.441	20	2	10	0.14 (0.03-0.66)	0.014	0.12 (0.024-0.62)	0.012
9-HOTrE Quartiles							
≤702 (Q1+Q2)*	40	14	35	1.00		-	
0.703-1.521	20	5	25	0.49 (0.24-1.00)		-	
>1.521	20	2	10	0.24 (0.06-0.99)	0.049	-	
8-HETE Quartiles							
≤0.020 (Q1+Q2)*	41	6	15	1.00		-	
>0.020 (Q3+Q4)*	39	15	38	3.65 (1.22-10.92)	0.021	-	
11,12-DiHETrE Quartiles							
≤0.486	20	3	15	1.00		1.00	
0.487-0.739 (Q2+Q3)*	40	9	23	2.26 (1.04-4.90)		2.49 (1.08-5.72)	
>0.739	20	9	45	5.12 (1.09-24.05)	0.039	6.19 (1.17-32.74)	0.032

*Adjacent quartiles of statistically significant variables are combined when the actual frequencies were similar or opposite to the significant trend (see corresponding supplementary tables S3).

Table 3. Oxylipins (pmol/mL) significantly associated with delivery within 48 hours after admission to hospital due to preterm labor analyzed using logistic regression.

		Delivery < 48 hours		Univariate logistic regression		Multivariate logistic regression	
Variable	Total	n	%	OR (95% CI)	p	OR (95% CI)	p
Pneumatic tube transport							
No	15	4	27	1.00		1.00	
Yes	65	10	15	0.50 (0.13-1.93)	0.306	1.05 (0.23-4.82)	0.954
9,12,13-TriHOME Quartiles							
≤3.332 (Q1+Q2+Q3)*	60	13	22	1.00		-	
>3.332	20	1	5	0.19 (0.02-1.61)	0.126	-	
						-	
9,10-DiHOME Quartiles							
≤1.701	20	6	30	1.00		-	
1.701-2.858	20	4	20	0.55 (0.31-0.99)		-	
2.859-4.872	20	3	15	0.30 (0.09-0.98)		-	
>4.872	20	1	5	0.17 (0.03-0.97)	0.046	-	
9,10-DiHODE Quartiles							
<0.237 (Q1+Q2)*	40	11	28	1.00		1.00	
0.237-0.441	20	2	10	0.35 (0.13-0.93)		0.36 (0.14-0.97)	
>0.441	20	1	5	0.12 (0.017-0.87)	0.036	0.13 (0.019-0.93)	0.042
8-HETE Quartiles							
≤0.020 (Q1+Q2)*	41	3	7	1.00		1.00	
>0.020 (Q3+Q4)*	39	11	28	4.98 (1.24-19.95)	0.024	5.01 (1.13-22.14)	0.034

*Adjacent quartiles of statistically significant variables are combined when the actual frequencies were similar or opposite to the significant trend (see corresponding supplementary tables S4).

FIGURE LEGENDS

Figure 1. Overview of the oxylipins included in the analysis. Oxylipins marked in bold were significantly associated with delivery before 34 weeks of gestation and/or within 48 hours after inclusion in the study.

Figure 2. Flow chart (panels A and B) **and inclusion chart** (panel C) **of women with threatened preterm labor (PTL).** The bars in panel C represent gestational age at inclusion and at delivery for individual women. The red bars represent those who delivered before 34 weeks of gestation. The arrows indicate delivery within 48 hours.

Figure 3. Oxylipins associated with delivery before (n=21) and after (n=59) 34 weeks of gestation. A non-parametric Mann-Whitney *U*-test was used. Results are shown for oxylipins with p-values <0.1. Medians and inter-quartile ranges are noted.

Figure 4. Oxylipins associated with delivery within (n=14) and later than (n=66) 48 hours after study inclusion.

All figures are intended for color print.

SUPPLEMENTARY TABLES

Table S1. Abbreviation list of the oxylipin compounds analyzed in this study.

9,10,13-TriHOME	9,10,13-trihydroxy-octadecenoic acid
9,12,13-TriHOME	9,12,13-trihydroxy-octadecenoic acid
PGF2a	Prostaglandin F2a
Resolvin D1	7,8,17-trihydroxy-docosahexaenoic acid
Resolvin D2	7,16,17-trihydroxy-docosahexaenoic acid
TXB2	Thromboxane B2
LTB4	Leukotriene B4
PGD2	Prostaglandin D2
PGE2	Prostaglandin E2
9,10-DiHOME	9,10-dihydroxy-octadecenoic acid
12,13-DiHOME	12-hydroxy-eicosapentaenoic acid
9,10-DiHODE	9,10-dihydroxy-octadecadienoic acid
12,13-DiHODE	12,13-dihydroxy-octadecadienoic acid
15,16-DiHODE	15,16-dihydroxy-octadecadienoic acid
5,6-DiHETrE	5,6-dihydroxy-eicosatrienoic acid
8,9-DiHETrE	8,9-dihydroxy-eicosatrienoic acid
11,12-DiHETrE	11,12-dihydroxy-eicosatrienoic acid
14,15-DiHETrE	14,15-dihydroxy-eicosatrienoic acid
8,9-DiHETE	8,9-dihydroxy-eicosatetraenoic acid
11,12-DiHETE	11,12-dihydroxy-eicosatetraenoic acid
14,15-DiHETE	14,15-dihydroxy-eicosatetraenoic acid
17,18-DiHETE	17,18-dihydroxy-eicosatetraenoic acid
7,8-DiHDPE	7,8-dihydroxy-docosapentaenoic acid
10,11-DiHDPE	10,11-dihydroxy-docosapentaenoic acid
13,14-DiHDPE	13,14-dihydroxy-docosapentaenoic acid
16,17-DiHDPE	16,17-dihydroxy-docosapentaenoic acid
19,20-DiHDPE	19,20-dihydroxy-docosapentaenoic acid
9-HODE	9-hydroxy-octadecadienoic acid
13-HODE	13-hydroxy-octadecadienoic acid
9-HOTrE	9S-hydroxy-octadecatrienoic acid
13-HOTrE	13-hydroxy-octadecatrienoic acid
5-HETE	5-hydroxy-eicosatetraenoic acid
8-HETE	8-hydroxy-eicosatetraenoic acid
9-HETE	9-hydroxy-eicosatetraenoic acid
11-HETE	11-hydroxy-eicosatetraenoic acid
12-HETE	12-hydroxy-eicosatetraenoic acid
15-HETE	15-hydroxy-eicosatetraenoic acid
20-HETE	20-hydroxy-eicosatetraenoic acid
5-HEPE	5-hydroxy-eicosapentaenoic acid
12-HEPE	12,13-dihydroxy-octadecenoic acid
15-HEPE	15-hydroxy-eicosapentaenoic acid

17-HDoHE	17-hydroxy-docosahexaenoic acid
15-HETrE	15-hydroxy-eicosatrienoic acid
5-oxo-ETE	5-oxo-eicosatetraenoic acid
12-oxo-ETE	12-oxo-eicosatetraenoic acid
15-oxo-ETE	15-oxo-eicosatetraenoic acid
9-oxo-ODE	9-oxo-10,12-octadecadienoic acid
13-oxo-ODE	13-oxo-octadecadienoic acid
9(10)-EpOME	9(10)-epoxy-octadecenoic acid
12(13)-EpOME	12(13)-epoxy-octadecenoic acid
EKODE	12(13)-epoxy-9-keto-octadecenoic acid
9(10)-EpODE	9(10)-epoxy-octadecadienoic acid
12(13)-EpODE	12(13)-epoxy-octadecadienoic acid
15(16)-EpODE	15(16)-epoxy-octadecadienoic acid
8(9)-EpETrE	8(9)-epoxy-eicosatrienoic acid
11(12)-EpETrE	11(12)-epoxy-eicosatrienoic acid
14(15)-EpETrE	14(15)-epoxy-eicosatrienoic acid
8(9)-EpETE	8(9)-epoxy-eicosatetraenoic acid
11(12)-EpETE	11(12)-epoxy-eicosatetraenoic acid
14(15)-EpETE	14(15)-epoxy-eicosatetraenoic acid
17(18)-EpETE	17(18)-epoxy-eicosatetraenoic acid
7(8)-EpDPE	7(8)-epoxy docosapentaenoic acid
10(11)-EpDPE	10(11)-epoxy docosapentaenoic acid
13(14)-EpDPE	13(14)-epoxy docosapentaenoic acid
16(17)-EpDPE	16(17)-epoxy docosapentaenoic acid
19(20)-EpDPE	19(20)-epoxy docosapentaenoic acid

Table S2. Median values (pmol/mL) and quartiles (Q1-Q3) for all oxylipins in the study population of women with preterm labor grouped for delivery before or after 34 weeks and delivery within or after 48 hours, respectively. Values below limit of detection (LOD) were substituted with LOD/ $\sqrt{2}$. The Mann-Whitney *U*-test was used for non-parametric analyses. P-values <0.1 are marked in bold. DF, detection frequency (percentage of samples above LOD).

Variable	DF (%)	Delivery before or after 34 weeks			Delivery within or after 48 hours		
		<34 weeks	≥34 weeks	p	<48 h	≥48 h	p
N		21	59		14	66	
9,10,13-TriHOME	10	0.06 (0.06-0.06)	0.06 (0.06-0.06)	0.397	0.06 (0.06-0.06)	0.06 (0.06-0.06)	0.807
9,12,13-TriHOME	61	0.76 (0.02-2.49)	1.16 (0.02-4.05)	0.434	0.02 (0.02-1.09)	1.19 (0.02-4.05)	0.056
PGF2a	6	0.05 (0.05-0.05)	0.05 (0.05-0.05)	0.761	0.05 (0.05-0.05)	0.05 (0.05-0.05)	0.945
Resolvin D1	0	0.02 (0.02-0.02)	0.02 (0.02-0.02)		0.02 (0.02-0.02)	0.02 (0.02-0.02)	
Resolvin D2	0	1.01 (1.01-1.01)	1.01 (1.01-1.01)		1.01 (1.01-1.01)	1.01 (1.01-1.01)	
TXB2	53	0.12 (0.02-0.99)	0.12 (0.02-0.34)	0.610	0.12 (0.02-1.03)	0.12 (0.02-0.34)	0.411
LTB4	0	0.02 (0.02-0.02)	0.02 (0.02-0.02)		0.02 (0.02-0.02)	0.02 (0.02-0.02)	
PGD2	5	0.05 (0.05-0.05)	0.05 (0.05-0.05)	0.680	0.05 (0.05-0.05)	0.05 (0.05-0.05)	0.876
PGE2	0	0.05 (0.05-0.05)	0.05 (0.05-0.05)		0.05 (0.05-0.05)	0.05 (0.05-0.05)	
9,10-DiHOME	100	2.53 (1.44-3.12)	3.81 (1.85-5.46)	0.090	2.50 (1.35-3.12)	3.22 (1.85-5.24)	0.075
12,13-DiHOME	100	4.23 (2.77-7.25)	6.04 (3.34-10.61)	0.138	3.96 (2.52-7.25)	6.03 (3.95-10.26)	0.113
9,10-DiHODE	98	0.17 (0.13-0.25)	0.32 (0.16-0.48)	0.021	0.16 (0.12-0.25)	0.29 (0.17-0.45)	0.020
12,13-DiHODE	31	0.02 (0.02-0.02)	0.02 (0.02-0.68)	0.101	0.02 (0.02-0.02)	0.02 (0.02-0.67)	0.433
15,16-DiHODE	100	40.9 (23.1-57.1)	51.7 (37.8-95.6)	0.104	33.9 (23.1-61.1)	51.6 (33.4-85.0)	0.192
5,6-DiHETrE	16	0.06 (0.06-0.73)	0.06 (0.06-0.06)	0.138	0.06 (0.06-0.06)	0.06 (0.06-0.06)	0.778
8,9-DiHETrE	14	0.02 (0.02-0.02)	0.02 (0.02-0.02)	0.664	0.02 (0.02-0.02)	0.02 (0.02-0.02)	0.647
11,12-DiHETrE	94	0.64 (0.54-0.85)	0.55 (0.47-0.69)	0.082	0.62 (0.53-0.82)	0.56 (0.47-0.70)	0.260
14,15-DiHETrE	93	0.58 (0.45-0.73)	0.51 (0.44-0.58)	0.355	0.54 (0.44-0.70)	0.51 (0.45-0.61)	0.925
8,9-DiHETE	0	0.02 (0.02-0.02)	0.02 (0.02-0.02)		0.02 (0.02-0.02)	0.02 (0.02-0.02)	
11,12-DiHETE	4	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.931	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.817

14,15-DiHETE	0	0.00 (0.00-0.00)	0.00 (0.00-0.00)		0.00 (0.00-0.00)	0.00 (0.00-0.00)	
17,18-DiHETE	100	0.38 (0.30-0.48)	0.34 (0.28-0.43)	0.361	0.38 (0.32-0.58)	0.34 (0.28-0.43)	0.234
7,8-DiHDPE	15	0.05 (0.05-0.05)	0.05 (0.05-0.05)	0.712	0.05 (0.05-0.05)	0.05 (0.05-0.05)	0.603
10,11-DiHDPE	20	0.02 (0.02-0.02)	0.02 (0.02-0.02)	0.680	0.02 (0.02-0.02)	0.02 (0.02-0.02)	0.769
13,14-DiHDPE	9	0.02 (0.02-0.02)	0.02 (0.02-0.02)	0.948	0.02 (0.02-0.02)	0.02 (0.02-0.02)	0.915
16,17-DiHDPE	0	0.02 (0.02-0.02)	0.02 (0.02-0.02)		0.02 (0.02-0.02)	0.02 (0.02-0.02)	
19,20-DiHDPE	15	0.02 (0.02-0.02)	0.02 (0.02-0.02)	0.602	0.02 (0.02-0.02)	0.02 (0.02-0.02)	0.577
9-HODE	100	12.0 (9.3-19.7)	13.5 (8.9-23.2)	0.712	10.5 (8.6-15.3)	13.5 (9.7-23.2)	0.312
13-HODE	63	4.33 (0.00-8.16)	1.61 (0.00-9.15)	0.440	1.61 (0.00-8.16)	1.61 (0.00-9.15)	0.836
9-HOTrE	65	0.40 (0.00-1.00)	0.84 (0.00-1.72)	0.095	0.20 (0.00-1.00)	0.76 (0.00-1.60)	0.152
13-HOTrE	26	0.02 (0.02-0.02)	0.02 (0.02-2.53)	0.253	0.02 (0.02-0.02)	0.02 (0.02-2.43)	0.376
5-HETE	0	0.02 (0.02-0.02)	0.02 (0.02-0.02)		0.02 (0.02-0.02)	0.02 (0.02-0.02)	
8-HETE	49	0.17 (0.02-0.25)	0.02 (0.02-0.18)	0.020	0.18 (0.09-0.25)	0.02 (0.02-0.19)	0.050
9-HETE	0	0.02 (0.02-0.02)	0.02 (0.02-0.02)		0.02 (0.02-0.02)	0.02 (0.02-0.02)	
11-HETE	100	0.30 (0.15-0.49)	0.20 (0.14-0.30)	0.135	0.27 (0.15-0.44)	0.21 (0.14-0.32)	0.356
12-HETE	28	0.02 (0.02-0.38)	0.02 (0.02-0.02)	0.355	0.02 (0.02-5.29)	0.02 (0.02-0.02)	0.318
15-HETE	9	0.02 (0.02-0.02)	0.02 (0.02-0.02)	0.595	0.02 (0.02-0.02)	0.02 (0.02-0.02)	0.684
20-HETE	24	0.02 (0.02-0.49)	0.02 (0.02-0.02)	0.141	0.02 (0.02-0.49)	0.02 (0.02-0.02)	0.171
5-HEPE	10	0.06 (0.06-0.06)	0.06 (0.06-0.06)	0.385	0.06 (0.06-0.06)	0.06 (0.06-0.06)	0.788
12-HEPE	46	0.02 (0.02-0.75)	0.02 (0.02-0.38)	0.648	0.09 (0.02-0.88)	0.02 (0.02-0.41)	0.749
15-HEPE	0	0.06 (0.06-0.06)	0.06 (0.06-0.06)		0.06 (0.06-0.06)	0.06 (0.06-0.06)	
17-HDoHE	9	0.06 (0.06-0.06)	0.06 (0.06-0.06)	0.572	0.06 (0.06-0.06)	0.06 (0.06-0.06)	0.935
15-HETrE	3	0.02 (0.02-0.02)	0.02 (0.02-0.02)	0.837	0.02 (0.02-0.02)	0.02 (0.02-0.02)	0.866
5-oxo-ETE	0	0.06 (0.06-0.06)	0.06 (0.06-0.06)		0.06 (0.06-0.06)	0.06 (0.06-0.06)	
12-oxo-ETE	0	0.12 (0.12-0.12)	0.12 (0.12-0.12)		0.12 (0.12-0.12)	0.12 (0.12-0.12)	
15-oxo-ETE	16	0.02 (0.02-0.02)	0.02 (0.02-0.02)	0.871	0.02 (0.02-0.02)	0.02 (0.02-0.02)	0.494
9-oxo-ODE	0	2.59 (2.59-2.59)	2.59 (2.59-2.59)		2.59 (2.59-2.59)	2.59 (2.59-2.59)	
13-oxo-ODE	9	0.13 (0.13-0.13)	0.13 (0.13-0.13)	0.905	0.13 (0.13-0.13)	0.13 (0.13-0.13)	0.945
9(10)-EpOME	100	0.76 (0.51-1.43)	0.84 (0.62-1.19)	0.983	0.76 (0.51-1.34)	0.84 (0.62-1.20)	0.621
12(13)-EpOME	100	3.14 (2.09-5.00)	2.98 (1.99-5.32)	0.939	2.71 (2.09-3.95)	3.11 (1.99-5.32)	0.404

EKODE	100	7.88 (3.99-11.47)	6.31 (4.34-11.51)	0.974	5.84 (3.99-12.57)	6.53 (4.34-11.47)	0.836
9(10)-EpODE	9	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.618	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.712
12(13)-EpODE	0	0.02 (0.02-0.02)	0.02 (0.02-0.02)		0.02 (0.02-0.02)	0.02 (0.02-0.02)	
15(16)-EpODE	0	0.02 (0.02-0.02)	0.02 (0.02-0.02)		0.02 (0.02-0.02)	0.02 (0.02-0.02)	
5(6)-EpETrE	0	0.06 (0.06-0.06)	0.06 (0.06-0.06)		0.06 (0.06-0.06)	0.06 (0.06-0.06)	
8(9)-EpETrE	0	0.06 (0.06-0.06)	0.06 (0.06-0.06)		0.06 (0.06-0.06)	0.06 (0.06-0.06)	
11(12)-EpETrE	0	0.02 (0.02-0.02)	0.02 (0.02-0.02)		0.02 (0.02-0.02)	0.02 (0.02-0.02)	
14(15)-EpETrE	0	0.06 (0.06-0.06)	0.06 (0.06-0.06)		0.06 (0.06-0.06)	0.06 (0.06-0.06)	
8(9)-EpETE	0	0.12 (0.12-0.12)	0.12 (0.12-0.12)		0.12 (0.12-0.12)	0.12 (0.12-0.12)	
11(12)-EpETE	0	0.02 (0.02-0.02)	0.02 (0.02-0.02)		0.02 (0.02-0.02)	0.02 (0.02-0.02)	
14(15)-EpETE	0	0.02 (0.02-0.02)	0.02 (0.02-0.02)		0.02 (0.02-0.02)	0.02 (0.02-0.02)	
17(18)-EpETE	0	0.00 (0.00-0.00)	0.00 (0.00-0.00)		0.00 (0.00-0.00)	0.00 (0.00-0.00)	
7(8)-EpDPE	0	0.02 (0.02-0.02)	0.02 (0.02-0.02)		0.02 (0.02-0.02)	0.02 (0.02-0.02)	
10(11)-EpDPE	0	0.02 (0.02-0.02)	0.02 (0.02-0.02)		0.02 (0.02-0.02)	0.02 (0.02-0.02)	
13(14)-EpDPE	0	0.02 (0.02-0.02)	0.02 (0.02-0.02)		0.02 (0.02-0.02)	0.02 (0.02-0.02)	
16(17)-EpDPE	0	0.11 (0.11-0.11)	0.11 (0.11-0.11)		0.11 (0.11-0.11)	0.11 (0.11-0.11)	
19(20)-EpDPE	0	0.02 (0.02-0.02)	0.02 (0.02-0.02)		0.02 (0.02-0.02)	0.02 (0.02-0.02)	

Table S3. Oxylipins (pmol/mL) associated with delivery before 34 weeks of gestation following preterm labor analyzed using logistic regression. In the multivariate model the variables were adjusted for pneumatic tube transport. All quartiles shown.

		Delivery <week 34		Univariate logistic regression		Multivariate logistic regression	
Variable	Total	n	%	OR (95% CI)	p	OR (95% CI)	p
Pneumatic tube transport							
No	15	7	47	1.00		1.00	
Yes	65	14	22	0.31 (0.10-1.03)	0.053	0.38 (0.11-1.38)	0.137
9,10-DiHOME Quartiles							
≤1.701	20	7	35	1.00		-	
1.701-2.858	20	7	35	0.63 (0.39-1.02)		-	
2.859-4.872	20	5	25	0.40 (0.15-1.05)		-	
>4.872	20	2	10	0.25 (0.06-1.08)	0.062	-	
9,10-DiHODE Quartiles							
≤0.142	21	7	33	1.00		1.00	
0.142-0.236	19	9	47	0.58 (0.35-0.94)		0.53 (0.32-0.90)	
0.237-0.441	20	3	15	0.33 (0.13-0.89)		0.28 (0.10-0.81)	
>0.441	20	2	10	0.19 (0.04-0.84)	0.028	0.15 (0.03-0.73)	0.017
9-HOTrE Quartiles							
≤702 (Q1+Q2)	40	14	35	1.00		-	
0.703-1.521	20	5	25	0.49 (0.24-1.00)		-	
>1.521	20	2	10	0.24 (0.06-1.00)	0.050	-	
8-HETE Quartiles							
≤0.020 (Q1+Q2)	41	6	15	1.00		-	
0.020-0.194	19	8	42	1.81 (0.99-3.32)		-	
>0.194	20	7	35	3.28 (0.97-11.05)	0.055	-	
11,12-DiHETrE Quartiles							
≤0.486	20	3	15	1.00		1.00	
0.486-0.563	20	5	25	1.58 (0.98-2.55)		1.66 (0.99-2.78)	
0.564-0.739	20	4	20	2.49 (0.95-6.52)		2.75 (0.98-7.71)	
>0.739	20	9	45	3.94 (0.93-16.65)	0.062	4.57 (0.98-21.40)	0.050

Table S4. Oxylipins (pmol/mL) associated with delivery within 48 hours after admission to hospital due to preterm labor analyzed using logistic regression. In the multivariate model the variables were adjusted for pneumatic tube transport. All quartiles shown.

		Delivery < 48 hours		Univariate logistic regression		Multivariate logistic regression	
Variable	Total	n	%	OR (95% CI)	p	OR (95% CI)	p
Pneumatic tube transport							
No	15	4	27	1.00		1.00	
Yes	65	10	15	0.50 (0.13-1.93)	0.306	0.54 (0.13-2.18)	0.377
9,12,13-TriHOME Quartiles							
≤1.017 (Q1+Q2)	40	9	23	1.00		-	
1.018-3.332	20	4	20	0.52 (0.23-1.20)		-	
>3.332	20	1	5	0.27 (0.05-1.45)	0.121	-	
						-	
9,10-DiHOME Quartiles							
≤1.701	20	6	30	1.00		-	
1.701-2.858	20	4	20	0.55 (0.31-0.99)		-	
2.859-4.872	20	3	15	0.30 (0.09-0.98)		-	
>4.872	20	1	5	0.17 (0.03-0.97)	0.042	-	
9,10-DiHODE Quartiles							
≤0.142	21	6	29	1.00		1.00	
0.142-0.236	19	5	26	0.52 (0.29-0.94)		0.52 (0.29-0.95)	
0.237-0.441	20	2	10	0.27 (0.08-0.88)		0.27 (0.08-0.91)	
>0.441	20	1	5	0.14 (0.02-0.83)	0.028	0.14 (0.02-0.87)	0.031
8_HETE Quartiles							
≤0.020 (Q1+Q2)	41	3	7	1.00		-	
0.020-0.194	19	7	37	1.75 (0.88-3.51)		-	
>0.194	20	4	20	3.08 (0.77-12.29)	0.106	-	

	Name	Class	DF (%)
ALA 18:3(ω-3)	9(10)-EpODE	Epoxide	9
	12(13)-EpODE	Epoxide	0
	15(16)-EpODE	Epoxide	0
	9,10-DiHODE*	Diol	98
	12,13-DiHODE	Diol	31
	15,16-DiHODE	Diol	100

LOX	9-HOTrE	Alcohol	65
	13-HOTrE	Alcohol	26

CYP	8(9)-EpETE	Epoxide	0
	11(12)-EpETE	Epoxide	0
	14(15)-EpETE	Epoxide	0
	17(18)-EpETE	Epoxide	0

EPA 20:5(ω-3)	8,9-DiHETE	Diol	0
	11,12-DiHETE	Diol	4
	14,15-DiHETE	Diol	0
	17,18-DiHETE	Diol	100

LOX	5-HEPE	Alcohol	10
	12-HEPE	Alcohol	46
	15-HEPE	Alcohol	0

DHA
22:6(ω-3)

CYP	7(8)-EpDPE	Epoxide	0
	10(11)-EpDPE	Epoxide	0
	13(14)-EpDPE	Epoxide	0
	16(17)-EpDPE	Epoxide	0
	19(20)-EpDPE	Epoxide	0

7,8-DiHDPE	Diol	15
10,11-DiHDPE	Diol	20
13,14-DiHDPE	Diol	9
16,17-DiHDPE	Diol	0
19,20-DiHDPE	Diol	15

LOX	17-HDoHE	Alcohol	9
	ResolvinD1	Triol	0
	ResolvinD2	Triol	0

CYP	9(10)-EpOME	Epoxide	100
	12(13)-EpOME	Epoxide	100
	9,10-DiHOME	Diol	100
	12,13-DiHOME	Diol	100

LOX	9,10,13-TriHOME	Triol	10
	9,12,13-TriHOME	Triol	61
	9-HODE	Alcohol	100
	13-HODE	Alcohol	63

	9-oxo-ODE	Ketone	0
	13-oxo-ODE	Ketone	9

a-ox	EKODE	Epoxide/ketone	100
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DGLA 20:3(ω-6)	LOX	15-HETrE	Alcohol	3
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COX	TXB2	Triol	53
	PGF2a	Triol	6
	PGD2	Diol/Ketone	5
	PGE2	Diol/Ketone	0

CYP	20-HETE	Alcohol	24
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5(6)-EpETrE	Epoxide	0
8(9)-EpETrE	Epoxide	0
11(12)-EpETrE	Epoxide	0
14(15)-EpETrE	Epoxide	0

5,6-DiHETrE	Diol	16
8,9-DiHETrE	Diol	14
11,12-DiHETrE**	Diol	94
14,15-DiHETrE	Diol	93

AA
20:4(ω-6)

LOX	LTB4	Diol	0
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5-HETE	Alcohol	0
8-HETE***	Alcohol	49
9-HETE	Alcohol	0
11-HETE	Alcohol	100
12-HETE	Alcohol	28
15-HETE	Alcohol	9

5-oxo-ETE	Ketone	0
12-oxo-ETE	Ketone	0
15-oxo-ETE	Ketone	16

*Lower levels associated with delivery before 34 weeks and within 48 hours

**Higher levels associated with delivery before 34 weeks

***Higher levels associated with delivery within 48 hours

8-HETE

9-HOTrE

9,10-DiHOME

9,10-DiHODE

11,12-DiHETrE

8-HETE

9,12,13-TriHOME

9,10-DiHOME

9,10-DiHODE