T_2* and DCE measurements. D-US was used to measure uterine artery (Uta) and umbilical vein velocimetry and diameter to calculate Uta volume blood flow (cQuta) and placental volume blood flow (cQuv). After non-invasive imaging, animals underwent C-section delivery for placenta collection and fetal necropsy at G110 (n=6) or G135 (n=6).

RESULTS: By D-US, cQuta and cQuv were reduced at G110 and G135 in EE vs. CON (Fig 1). Reductions in placental blood flow were evident by DCE-MRI (Fig 1). As we demonstrated recently, T_2* values vary throughout the placenta, and reveal regions of high oxyhemoglobin concentration (long T_2*) and high deoxyhemoglobin concentration (short T_2*). Distributions of T_2* throughout the placenta (Fig 2) shows global reduction in T_2* (and hence blood oxyhemoglobin) in EE vs. CON at G110 and G135. Fetal brain measurements were decreased at G110, but similar at G135 in EE vs. CON (Fig 1).

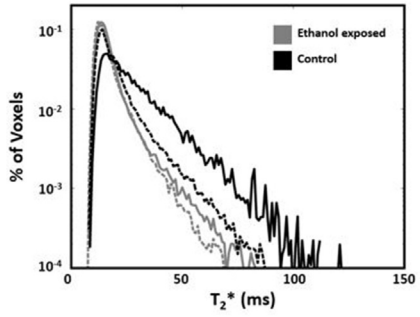
CONCLUSION: Chronic first trimester EE reduces placental perfusion and impairs fetal growth and development apparent at mid-gestation. However, both placental function and fetal brain development improved by late-gestation suggesting that placental adaptation to early perturbations allows for compensated placental function and maintenance of fetal growth.

Figure 1. D-US and MRI-based measurements of fetal biometry and placental function and oxygenation in control and ethanol exposed animals

Parameter	Gestational day 110		Gestational day 135	
	Control (n=3)	Ethanol (n=3)	Control (n=3)	Ethanol (n=3)
cQuta (ml/min/kg)	48	19	34	27
cQuv	22	15*	29	26
Placental blood flow (ml/min)	681	284*	558	501
BPD (mm)	39	35*	45	44
Fetal weight (g)	217	175*	333	318
Placental weight (g)	75	65	78	83
Brain weight (g)	13	11	20	19
Brain volume (mm^3)	20097	17066	31003	29173
Brain surface area (mm^2)	6133	5372	11530	10838

Definition of abbreviations:
VTI = velocity time integral, CSA (cross section of uterine artery) = π(diameter/2)^2
Vmean (mean velocity) = 0.5 x maximum umbilical vein velocity
cQuta (uterine artery blood flow) = VTI x CSA x HR adjusted for maternal weight
cQuv (placental volume blood flow) = Vmean x CSA x 60
BPD = biparietal diameter
*p<0.05

Figure 2. Histogram plot of T_2* versus percent of placental voxels displayed for ethanol exposed vs. control animals at G110 (solid line) and G135 (dashed line). Ethanol exposed animals had a smaller fraction of large T_2* values compared to controls, demonstrating decreased fetal oxygen availability in the former.



29 The effect of maternal heparins and/or aspirin on the amount of cell-free fetal DNA in the maternal circulation

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OBJECTIVE: Inflammation results in apoptosis in the placenta which causes cell-free fetal DNA to be shed into the maternal circulation. As cell-free fetal DNA testing is extensively used for genetic screening and a sufficient amount of fetal DNA within the maternal circulation is required for test accuracy, it is important to understand if anti-inflammatory agents alter the amount of fetal DNA within the maternal circulation. A retrospective cohort study was performed to determine if unfractionated and low-molecular weight heparins and/or low-dose aspirin, which are thought to decrease placental hypoxia and inflammation in early pregnancy, affect the amount of fetal DNA in the maternal circulation.

STUDY DESIGN: A multi-institutional retrospective cohort study was performed using women receiving cell-free fetal DNA testing at the Wake Forest and Indiana University Departments of OB/GYN from January 1, 2014 - June 30, 2016. Data on patient demographics, medical comorbidities, medication use, and fetal fraction of cell-free DNA were gathered. Regression analyses were performed to determine if there were differences in maternal demographics, medical comorbidities, or fetal fraction of cell-free DNA in the maternal circulation in those women that received heparins and/or low-dose aspirin compared to controls.

RESULTS: Data from 924 women was gathered. Women on heparins or aspirin (n=65) had higher gravidity, and rates of hypertension and diabetes compared to controls (n=860). Women using heparins and/or aspirin had significantly less fetal fraction (8.4%) compared to controls (12.7%) after adjustment for gestational age at collection, gravidity, and medical comorbidities ($p<0.0001$).

CONCLUSION: Maternal use of heparins and aspirin was associated with a decrease in cell-free fetal DNA in the maternal circulation. Although the mechanism of this change is unclear, it is possible that the decreased placental thrombosis thought to occur with the use of anticoagulants and anti-platelet agents leads to a decrease in hypoxia and inflammation related apoptosis in the placenta, the primary source of fetal DNA within the maternal circulation.

30 The impact of cytochrome p450 3a and progesterone receptor polymorphisms on 17-ohpc concentrations and efficacy

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OBJECTIVE: 1) To correlate 17-Hydroxyprogesterone caproate (17-OHPC) plasma concentrations with SNPs in CYP3A4/5, the main enzymes involved in 17-OHPC metabolism; 2) To test the association between spontaneous preterm birth (SPTB) rates and plasma concentrations of 17-OHPC with progesterone receptor (PR) SNPs.

STUDY DESIGN: We performed a genetic polymorphism analysis from 268 pregnant women treated with 17-OHPC, who participated in an omega-3 supplementation placebo-controlled trial. 17-OHPC trough plasma concentrations were measured between 25-28 weeks

gestation after a minimum of 5 injections of 17-OHPC. We extracted DNA from maternal blood samples and genotyped the samples using TaqMan® SNP Genotyping Assays for the following SNPs: *CYP3A4*1B*, *CYP3A4 *1G*, *CYP3A4*22*, *CYP3A5*3* and rs578029, rs471767, rs666553, rs503362 and rs500760 for *PR*. To correct for potential confounders pre-pregnancy body mass index, race and treatment group were adjusted for in multivariable models. Differences in the plasma concentrations of 17-OHPC by genotype were evaluated for each CYP SNP using general linear models. The association between PR SNPs and SPTB rates was tested using logistic regression. A logistic model also tested the association between SPTB and 17-OHPC concentrations, with each PR SNP used as a covariate.

RESULTS: The association between any CYP SNP and trough plasma concentrations of 17-OHPC was not statistically significant (Table). In an adjusted logistic regression model low trough plasma concentrations of 17-OHPC were statistically associated with an increased risk of SPTB. The association between PR SNPs and SPTB rates was not statistically significant. In an interaction model, there was no significant association between SPTB rates and trough concentrations of 17-OHPC with any of the PR SNPs.

CONCLUSION: SPTB appears to be influenced by trough 17-OHPC plasma concentrations. However, trough 17-OHPC plasma concentrations are not associated with SNPs in CYP3A4 and CYP3A5 genes, and SPTB rates are not associated with PR SNPs.

Table. The median and percentiles of trough plasma concentrations of 17-OHPC by genotype of CYP SNPs

SNP	Genotype	N	Genotypic frequencies	Allele frequencies	17-OHPC (25th-75th) ng/ml
*CYP3A4 *22* rs35599367	GG	243	0.931	G=0.964	9.8 (8.0-12.4)
	GA	17	0.065		10.2 (7.1-16.5)
	AA	1	0.004	A=0.036	10.9 (10.9-10.9)
*CYP3A4 *1G* rs2242480	CC	128	0.559	C=0.699	9.9 (8.2-12.3)
	CT	64	0.279		10.0 (7.2-12.5)
	TT	37	0.162	T=0.301	10.0 (8.2-13.5)
*CYP3A4 *1B* rs2740574	TT	184	0.689	T=0.798	9.9 (8.4-12.4)
	CT	58	0.217		11.0 (8.3-13.6)
	CC	25	0.094	C=0.202	9.8 (7.9-12.1)
*CYP3A5 *3* rs776746	CC	154	0.592	C=0.733	9.9 (8.3-12.4)
	CT	73	0.281		10.0 (7.2-12.1)
	TT	33	0.127	T=0.267	9.9 (8.4-13.3)