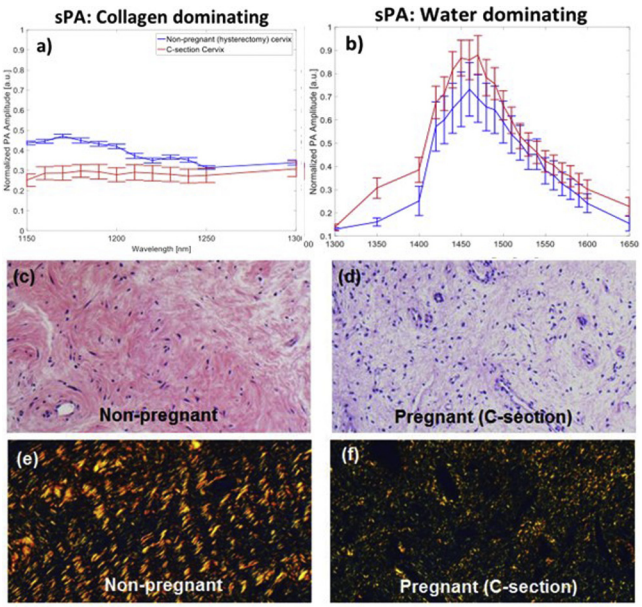

Figure: (a,b) PA signals of human cervix samples at collagen peak absorption and water peak absorption bandwidths; (c,d) H&E staining and (e,f) Sirius Red-stained images of non-pregnant and pregnant cervical tissue samples.

Abbreviations: C-section, cesarean section; H&E, hematoxylin and eosin; PA, photoacoustic

18 Influence of maternal body size on pharmacokinetics of weekly 17 alpha Hydroxyprogesterone Caproate (17OHPC)

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OBJECTIVE: Goal of the study is to estimate the pharmacokinetics (PK) of weekly 17OHPC in an obstetrical population and evaluate the effect of maternal body size on the PK parameters.

STUDY DESIGN: Prospective population PK study. Plasma samples and clinical variables were collected in pregnant women between 16 and 36 weeks gestational age (GA), carrying singleton pregnancy and receiving 17OHPC, 250 mg IM weekly for the prevention of recurrent spontaneous preterm birth. Liquid chromatography mass spectrometry was used to measure 17OHPC plasma concentrations. PK parameters and significant clinical covariates were estimated using mixed effect modeling. Population PK parameters were determined by nonlinear mixed effects modeling. Influence of demographic and clinical variables was evaluated by stepwise addition of covariates into the final population model. Four body size indicators were used in the model to predict PK parameters: Lean Body Weight (LBW), Total Body Weight (TBW), Body Mass Index (BMI) and Body Surface Area (BSA). The influence of maternal body size indicators on individual Bayesian PK estimates of 17OHPC were evaluated by ANOVA.

RESULTS: Fifty-four pregnant women, ages 18 to 44 years and BMIs 14.5 to 54.6 kg/m2, provided 114 17OHPC plasma samples concentration for analysis. A 1-compartment model with first order absorption satisfactorily described 17OHPC PKs. Compared to other body size indicators, lean body weight (LBW) best explained inter-subject variability, with coefficient of variation for apparent clearance (CL/F) decreasing 24.8% to 17.9% following addition of LBW into the population PK model. Age, race and GA did not influence 17OHPC PK. Mean (relative SE) population PK parameters were CL/F 151 (1.3%) L/h/50 kg LBW, apparent volume of distribution 59874 (1.8%) L and absorption rate constant 0.111 (41.5%) h-1. Mean + SD 17OHPC CL/F was significantly ($p<0.001$) higher in subjects with BMI > 35 kg/m2 (182+/-31 L/h/50 kg LBW) compared to subjects with BMIs <26 kg/m2 (133+/- 30 L/h/50 kg LBW), > 26 to 30 kg/m2 (137+/- 30 L/h/50 kg LBW), and >30 to 35 kg/m2 (144+/- 26 L/h/50 kg LBW).

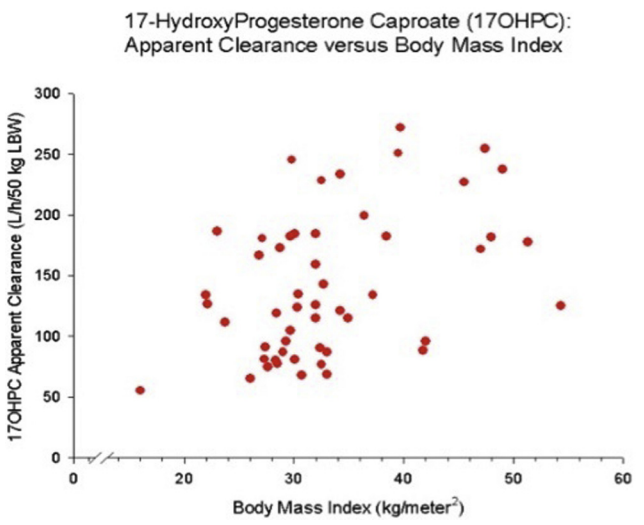
CONCLUSION: Population PK analysis indicates 17OHPC apparent clearance significantly increases at BMI>35 kg/m2. Higher 17OHPC doses are required in subjects with BMI > 35 to achieve similar plasma concentrations compared to BMI < 35.

Table 1: Maternal and Obstetrical Characteristics

Variables N = 54	Median (25th - 75th percentile)
Maternal Age (years)	31.5 (27 – 32.3)
GA at delivery (weeks)	38.4 (37.1 – 39.2)
	n (%)
Ethnicity/Race, n (%)	
African America	*34 (63.0)*
Hispanic	*5 (9.2)*
White	*3 (5.6)*
Others	*12 (22.2)*
BMI Category (kg/m2), n (%)	
BMI greater than 35	15 (27.8)
BMI less than 35	39 (72.2)
BMI 30 – 35	11 (20.4)
BMI 26 – 30	18 (31.5)
BMI less than 26	10 (18.5)
Number of prior sPTB, n (%)	
One prior sPTB	39 (72.2)
More than one prior sPTB	15 (27.8)

BMI: Body mass index, GA: Gestational age, SAB: Spontaneous abortion, ETOP: Elective termination of pregnancy, sPTB: Spontaneous preterm birth.

Figure 1: Relationship of 17-OHPC Apparent Clearance and Body Mass Index.



19 Increased concentration of 17-alpha hydroxyprogesterone caproate correlates with IL-10 to reduce spontaneous preterm birth

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OBJECTIVE: 17-alpha hydroxyprogesterone caproate (17-OHPC) 250 mg reduces recurrent spontaneous preterm birth in women by 33%. We have previously demonstrated that women with the lowest quartile of plasma concentrations of 17- OHPC have elevated rates of preterm birth compared with women in the 2-4th quartiles. The mechanism of action of 17-OHPC is unknown but immune modulation is a possibility. We have previously reported elevated cytokines in the cervical fluid of women with a prior preterm birth. Additionally, circulating cytokines of immunoinhibitory IL-10 and pro-inflammatory TNF alpha have correlated with spontaneous preterm birth. This study sought to determine the relationship between the concentration of 17-OHPC and serum cytokines to determine if efficacy of 17-OHPC correlates with altered immunity.

STUDY DESIGN: This was an ancillary study analyzing laboratory results from the placebo controlled, randomized trial of omega-3 supplementation and reduction of recurrent preterm birth. Peripheral blood mononuclear cells were isolated from paired blood samples drawn at 16-22 weeks gestation (baseline) and 25-28 weeks gestation (post treatment). IL-10 and TNF-alpha levels were measured with and without stimulation by lipopolysaccharide by ELISA. All women received 17-OHPC in this trial. 17-OHPC concentrations were determined from a single blood sample obtained between 25-28 weeks. Baseline and post-treatment cytokine levels were compared with 17-OHPC serum concentrations in women with and without preterm birth.

RESULTS: We compared serum cytokines in women with 17OHPC levels in the first quartile to women in quartiles 2-4. There was a statistically significant increase in LPS stimulated concentrations of IL-10 in women with quartiles 2-4 compared the first quartile ($p<0.0001$). No differences were seen prior to treatment. There was no statistically significant differences in post treatment TNF-alpha levels.

CONCLUSION: After 17-OHPC administration, there appears to be a concentration relationship between 17-OHPC and LPS stimulated IL-10, an immunoinhibitory cytokine. As has been demonstrated by Harper *et al* 2013, IL-10 levels correlate with preterm birth. This finding supports an immunomodulatory mechanism of 17-OHPC to prevent recurrent preterm birth.