Genetics and Development (including Gene Regulation)

ENDOCRINE DISRUPTING CHEMICALS

3-Generation Study of Metabolic Disruption by Pregnancy Serum PFASs: Associations With Abdominal and Whole-Body Obesity in Granddaughters in a 60-Year Follow-Up of the Child Health and Development Studies Cohort

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SAT-LB132

Introduction. We previously found a 3.6-fold increased risk of breast cancer in daughters associated with high maternal (F0) early postpartum serum EtFOSAA combined with high F0 cholesterol (https://doi.org/10.1016/j.reprotox.2019.06.012). Here we test the hypothesis that F0 early postpartum EtFOSAA, in combination with F0 serum cholesterol predicts abdominal obesity (waist circumference > 88cm) and/or whole-body overweight or obesity (body mass index > 25 kg/m^2) in daughters (F1) at age 30 and granddaughters (F2) at age 20. Methods. We measured F1 and F2 weight, height, waist circumference and blood pressure when F1 were an average age of 50 years and adult F2 were an average age of 20 years (N=213 triads). F1 also reported their weight at age 30, near the mean age of their pregnancies with their daughters (F2) to allow control for obesity during F2 gestation. EtFOSAA, PFOS, and cholesterol were assayed in archived early postpartum F0 serum samples collected within 3 days of delivery. Results. F0 cholesterol significantly ($p<0.05$) modified the association of F0 EtFOSAA with self-reported obesity at age 30 in F1 and measured abdominal and whole-body obesity, and blood pressure at age 20 in F2. Association patterns were similar for all outcomes: F0 EtFOSAA was associated with high metabolic risk when F0 serum cholesterol was low (Quartile 1): e.g. 20-year-old F2 had an estimated 2.3 fold increase in the joint risk of abdominal and whole-body obesity over the inter-quartile range of F0 ETFOSAA, 95% Confidence Interval= 1.1, 4.8. F0 EtFOSAA associations with F2 metabolic risk were independent of F0 race, early pregnancy overweight (BMI >25 kg/m^2), and serum PFOS. F1 obesity at age 30 did not mediate F0 EtFOSAA associations with F2 outcomes, but additionally predicted high metabolic F2 risk. Conclusions. Findings support the hypothesis that *in utero* exposure to EtFOSAA impacts metabolic risk factors in female F2 exposed as germline and also independently via promotion of overweight in F1 (their mothers) during F2 gestation.

Reproductive Endocrinology

TRANSGENDER MEDICINE AND RESEARCH

Pharmacokinetics of Sublingual Versus Oral Estradiol in Transgender Women

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SUN-LB9

Sublingual administration of estradiol (E2) may be a safer and more effective hormone replacement therapy (HRT) route than oral estradiol, the most commonly used formulation, but it has yet to be investigated in transgender women. Unlike oral E2, sublingual E2 is thought to bypass the first pass effect by the liver, making it less likely to impact hepatic clotting factor synthesis, and thus decreasing the risk of thromboembolic events posed by oral administration, such as VTE and ischemic stroke (1). Additionally, studies in cisgender women have demonstrated a 13-fold higher peak serum concentration and a decreased estrone (E1) to estradiol ratio with sublingual administration, suggesting that sublingual E2 is more a physiologically potent route (2). To advance the understanding of sublingual E2 as an alternative method of administration in transgender HRT, we investigated the pharmacokinetics of estradiol when administered orally versus sublingually in transgender women. Ten transgender women naïve to estrogen were provided 1.0 mg of oral estradiol. Blood samples were collected via percutaneous intravenous catheter at baseline and at T=1,2,3,4,6, and 8 hours post-dosing. After a 7-day washout period, 1.0 mg of sublingual estradiol was dosed with identical sampling over time. Analysis of serum samples was performed using LC-MS/MS and estradiol immunoassay. Initial results demonstrate a higher peak serum concentration within 8 hours with sublingual dosing in both LC-MS/MS and immunoassay quantification (178±47 and 150±31 pg/mL, respectively) compared to oral administration (36±5 and 35±4 pg/mL, respectively; N=5). Peak concentration was reached at T=1 hour for sublingual E2 in both LC-MS/MS and immunoassay analysis, whereas oral E2 reached peak serum concentration at T=8 hours in LC-MS/MS analysis and T=6 hours in immunoassay analysis. Sublingual E2 still maintained higher overall mean concentrations of estradiol across the 8 hours compared to oral E2. Importantly, subjects reported high satisfaction with sublingual administration due to rapid dissolution (<2 minutes) and minimal taste; as a result, subjects predicted high ease of adherence in future HRT, which indicates the feasibility of sublingual E2 as an alternative to oral E2. Additional analysis of half-life and oral clearance will be performed at the completion of the study, in order to further establish pharmacokinetic differences and potency between the two routes. This pharmacokinetic data will allow future studies on optimal dosing, safety, and efficacy compared to oral estradiol in hormone replacement therapy. (1) Hembree et al. *J Clin Endocrinol Metab*. 2017;102(11):3869-3903. (2) Price et al., *Obstet Gynecol*. 1997.

Diabetes Mellitus and Glucose Metabolism

DIABETES DIAGNOSIS, TREATMENT AND COMPLICATIONS

Remission of Type 2 Diabetes (DMT2) in Hypogonadal Men Under Long-Term Testosterone Therapy

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