DESIGN: In vivo treatments in a Primate Research Center.

MATERIALS AND METHODS: We performed hysterosalpingogram (HSG) examinations on anesthetized healthy female baboons to confirm tubal patency, and then infused normal saline (NS, negative control, 6mL), 5% polidocanol foam (PF, positive control, 20mL), or Sclerodine® (ISA, 3-6 mL) via the HSG balloon catheter. Females received an intramuscular injection of depomedroxyprogesterone acetate (DMPA, 2.0 mg/kg) immediately after the treatment. In experiment 1, Anubis females [NS (n=3), PF (n=3) ISA (n=3)] underwent laparotomy with cornual resection to remove one fallopian tube including the intramural segment on post-treatment day 3, followed by necropsy for collection of the remainder of the reproductive tract on day 30. In experiment 2, Hamadryas females (n=4) received ISA, followed by laparoscopy on day 3 and necropsy on day 60 -70. The primary endpoint was the histologic appearance [epithelium (intact/damaged), lumen (patent/dilated/collapsed), and subepithelial tissue (normal/inflammation/scaring)] of the intramural fallopian tube (IMT) at the various timepoints.

RESULTS: In experiment 1, the IMT of NS-treated (negative control) females showed intact epithelium, normal lumen, and healthy subepithelial tissue at 3, and 30 days while treatment with PF (positive control) resulted in epithelial disruption with a collapsed lumen at 3 days that progressed to complete occlusion with subepithelial scaring at 30 days. Treatment with the ISA led to epithelial cell death and lumen dilation at day 3 leading to collapse of the lumen with peritubular edema and mild chronic inflammation without scarring or occlusion at 30 days. In experiment 2, at day 60, the IMT from ISA-treated females revealed complete bilateral occlusion with scarring in one animal, and a variety of less severe damage patterns including subepithelial scarring, lumen narrowing and tortuosity, and chronic inflammation in the other three.

CONCLUSIONS: Compared to PF, transcervical treatment with an ISA resulted in inconsistent patterns of tubal damage. Additional studies are needed to fully evaluate the potential of ISAs as agents for nonsurgical permanent contraception.

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POLYCYSTIC OVARY SYNDROME AND ANDROGEN EXCESS

O-169 Tuesday, October 31, 2017 11:00 AM

PARADOXICAL INFLAMMATORY RESPONSES INVOLVING LIPOPOLYSACCHARIDE (LPS) IN MONONUCLEAR CELLS (MNC) OF LEAN VERSUS OBESE WOMEN WITH POLYCYSTIC OVARY SYNDROME (PCOS) ARE LINKED TO HYPERANDROGENISM.

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OBJECTIVE: LPS from gut-related bacteria plays a role in obesity-related metabolic inflammation. Circulating LPS is higher in obese women with PCOS compared with obese ovulatory women.[1] In pronounced inflammatory conditions, repetitive exposure to proinflammatory stimuli involving LPS suppresses cytokine secretion in a phenomenon known as LPS tolerance.[2] Androgens can also suppress LPS action.[3] We examined the effect of saturated fat ingestion followed in tandem by *in vitro* LPS exposure on cytokine secretion from MNC in women with PCOS compared with ovulatory controls; and its relationship with HCG-stimulated ovarian androgen secretion.

DESIGN: Cross-sectional study

MATERIALS AND METHODS: We studied 23 women with PCOS (13 lean; 10 obese) diagnosed on the basis of oligo- or amenorrhea and hyperandrogenemia, and 23 ovulatory controls (13 lean; 10 obese) all between ages 18-40. Subjects ingested 100 ml of dairy cream and received a 5,000 IU IM injection of HCG within 5-8 days of menses. MNC isolated from blood samples drawn while fasting and 2, 3 and 5 hours after cream ingestion were then exposed to LPS in culture. TNFα, IL-6 and IL-1β were measured by ELISA in MNC supernatants. Androgens were measured by RIA from blood samples drawn while fasting and 24, 48 and 96 hours after HCG administration. Insulin sensitivity was derived by IS_{OGTT}.

RESULTS: The absolute change in cytokine secretion (pg/ml) from a fasting baseline increased ($p<0.02$) in lean women with PCOS and obese controls, and was significantly different ($p<0.007$) compared with lean controls and obese women with PCOS which decreased ($p<0.05$) at 2 hours (TNFα: 187±48, 139±36 vs. -280±93, -221±125; IL-6: 257±89, 208±121 vs. -329±117, -317±145; IL-1β: 435±77, 338±63 vs. -795±203, -696±175) and 3 hours (TNFα: 264±52, 200±60 vs. -306±69, -210±176; IL-6: 238±57, 120±45 vs. -414±79, -362±153; IL-1β: 476±85, 325±63 vs. -664±97, -581±85), and returned to baseline at 5 hours (TNFα: 14±9, 12±6 vs. -8±10, -4±12; IL-6: -2±7, 5±3 vs. -6±3, -1±12; IL-1β: 9±9, 8±9 vs. -4±7, -4±9). Compared with weight-matched controls, women with PCOS exhibited a greater HCG-stimulated area under the curve (AUC) for testosterone (T) (lean: 6324±606 vs. 3430±399, $p<0.002$; obese: 7639±1135 vs. 3682±180, $p<0.0003$) and androstenedione (A) (lean: 507±25 vs. 303±22, $p<0.0001$; obese: 562±48 vs. 321±34, $p<0.0001$). In women with PCOS, the postprandial peak cytokine responses were inversely correlated with AUC for T (TNFα: r= -0.49, $p<0.03$; IL-6: r= -0.55; $p<0.008$) and A (TNFα: r= -0.50; $p<0.03$), and directly correlated with IS_{OGTT} (TNFα: r=0.47, $p<0.04$; IL-6: r=0.58; $p<0.005$; IL-1β: r=0.46, $p<0.05$).

CONCLUSIONS: In PCOS, lipid-induced cytokine hypersecretion from MNC is independent of obesity. However, the LPS tolerance observed when obesity accompanies PCOS is indicative of a more profound inflammatory state, and may be potentiated by hyperandrogenism to limit insulin resistance.

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VITAMIN D DEFICIENCY IS ASSOCIATED WITH POOR REPRODUCTIVE OUTCOMES IN PCOS BUT NOT UNEXPLAINED INFERTILITY.

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OBJECTIVE: The impact of vitamin D deficiency on the success of ovulation induction (OI) cycles and the risk pregnancy complications after OI has not been extensively investigated. The goal of this study was to evaluate the relationship between preconception vitamin D status and reproductive outcomes in women with a diagnosis of either PCOS or unexplained infertility treated with OI.

DESIGN: Secondary analysis of the Reproductive Medicine Network multicenter randomized clinical trials PPCOS II (comparing the efficacy of CC vs. letrozole in PCOS) and AMIGOS (comparing rate of multiple birth in following CC, letrozole, or gonadotropins in unexplained infertility).

MATERIALS AND METHODS: 25OHD was measured in banked sera collected at baseline prior to initiation of study medications. A 25OHD cut-off of <20 ng/mL categorized women as Vitamin D deficient. The main outcome measures were clinical pregnancy (CP), live birth (LB), risk of preeclampsia, gestational diabetes, and IUGR. Statistical analysis was performed using χ^2, Student's *t*-tests, Wilcoxon Rank Sum testing and multivariable logistic regression.

RESULTS: 595 PPCOSII and 597 AMIGOS subjects with available sera were studied. In the PPCOSII univariate analysis, D deficiency was associated with diminished odds of CP (OR, 0.52 95% CI 0.35-0.79, p=0.002) and LB (OR, 0.54, 95% CI 0.37-0.8, p=0.002); in AMIGOS, no significant association between D deficiency and treatment outcomes or pregnancy complications was noted. Adjusting the association between D deficiency and treatment outcomes in PPCOSII for BMI, race, treatment (CC vs. letrozole) and HOMA-IR (to measure insulin resistance) yielded significant estimates for diminished CP (AOR 0.63, 95% CI 0.41-0.99, p=0.047) and LB (AOR 0.64, 95% CI 0.42-0.98, p=0.04). Associations between D deficiency and risk of preeclampsia (p=0.003), IUGR (p=0.01) and gestational diabetes (p=0.01) were observed in PCOS subjects, however, these were not significant in adjusted analyses.

CONCLUSIONS: In women with PCOS, preconception vitamin D deficiency is associated with a nearly 40% reduction in odds of live birth independent of the effects of obesity, race, insulin resistance, or OI treatment.