1 **FIRST TRIMESTER ANEUPLOID SCREENING: RESULTS OF THE NICHD MULTICENTER STUDY** RONALD J. WAPNER, MD, FOR THE BUN STUDY GROUP[1], [1]MCP Hahnemann University, Obstetrics and Gynecology, Philadelphia, PA

OBJECTIVE: To determine the performance of first trimester prenatal screening using maternal age (MA), biochemistry (BC) and nuchal translucency measurement (NT) when introduced into practice at multiple sites.

STUDY DESIGN: From June 1998-Dec 2000, 12 North American centers enrolled patients from 10-14 wks post LMP. Before starting, a sonographer from each center was certified by attending a didactic course and performing 50 NT measurements which were critically reviewed. Quality control consisted of quarterly review of NT and comparison with standards. PAPP-A and free β HCG were analyzed at NTD Labs. A standard algorithm with MA, BC, and NT was used. Trisomy (t) 21 risk of >1:270 or t18 risk of >1:150 were considered high risk. Results were used for management. Risk and outcome data were maintained at a data coordinating center.

RESULTS: 8514 patients were enrolled of which 7668 with EDC before 6/5/01 and with outcome on file (96% follow-up) were analyzed for this abstract. Data for the full sample will be available for presentation. For this analysis, 94 patients with t21 or t18 in a previous pregnancy were excluded. The mean MA was 33.6 yrs and the mean gestational age at screening was 86 days. Table shows test performance. The DR for t21 and/or t18 was 88.1% for an FPR of 10.6. For the 3484 women ≥35 yo the detection rate (DR) was 91.1% with a 16% false positive rate (FPR). Modeling the data on the US age distribution of livebirths the DR for t21 using BC, NT, and MA is 78.0% for a 5% FPR and 65.8% for 1% FPR.

CONCLUSION: First trimester aneuploidy screening with MA, BC, and NT is effective in screening for t21 and t18 when introduced into practice with appropriate quality control.

Table

Screening performance: t21 (57 cases) and t18 (10 cases)

	DR-T21	FPR-T21	DR 5% FPR	DR 1% FPR	DR-T18	FPR-T18
MA	80.7	48.6	31.6	10.5	20.0	7.3
MA/BC	84.2	23.4	66.7	33.3	80.0	3.3
MA/NT	84.2	12.0	71.9	49.1	80.0	2.9
MA/BC/NT	84.2	9.4	77.2	61.4	90.0	1.9

2 **A PAF ANTAGONIST PREVENTS PRETERM DELIVERY IN A MOUSE MODEL OF INFLAMMATORY PRETERM LABOR** MICHAL ELOVITZ[1], EDWARD CHIEN[1], DANIEL RYCHLIK[2], MARK PHILLIPPE[3]; [1]University of Chicago, Obstetrics and Gynecology, Chicago, IL; [2]University of Chicago, Obstetrics or Gynecology, Chicago, IL; [3]University of Chicago, Obstetrics & Gynecology, Chicago, IL

OBJECTIVE: Recent investigations have demonstrated that a proportion of preterm deliveries are associated with inflammation. Yet, the exact mechanisms and mediators responsible for the emptying of the uterus in the setting of inflammation have not been clarified. Platelet activating factor (PAF) is both a potent inflammatory and uterotonic agent. These studies were performed to investigate whether PAF is a crucial mediator of inflammatory preterm labor.

STUDY DESIGN: An animal model of localized intrauterine inflammation was created. Timed pregnant CD-1 mice (D 15) underwent a mini-laparotomy. The right uterine horn was identified and lipopolysaccharide (LPS) (n = 12) or vehicle (n = 8) was infused between two gestational sacs. Study animals received varying doses of CV-6209, a competitive PAF antagonist (n = 24). All animals were observed for preterm delivery and then were euthanized at 48 hours after surgery. Fisher's exact test was used to determine statistical significance.

RESULTS: No animals receiving only intrauterine saline delivered preterm. LPS induced a preterm delivery rate of 100%. Comparatively, animals receiving the highest dose of the PAF antagonist had a preterm delivery rate of only 50% ($P < .05$, Fisher's Exact). No remaining pups were observed at necroscopy in the LPS treated group, while 62.5% of animals treated with CV-6209 had pups in the uterine horns at 48 hours ($P < .01$). A few of the animals in the CV-6209 treated group appeared gravid after delivering one or two pups by 24 hours. These animals had live pups in utero at 48 hours. This phenomenon was not observed in any animal treated with LPS alone.

CONCLUSION: With these studies, we established an intrauterine model of inflammatory preterm labor resulting in a preterm delivery rate of 100%. Pretreatment with a PAF antagonist significantly decreased the preterm delivery rate. This study supports the hypothesis that PAF is a crucial mediator of inflammatory preterm labor. (SMFM Foundation Fellowship Award.)

3 **ON FETAL ORIGIN OF DISEASE: EFFECT OF IN UTERO ENVIRONMENT AND GENETIC IMPRINTING ON FUTURE VASCULAR REACTIVITY** MONICA LONGO[1], VENU JAIN[1], YURI VEDERNIKOV[2], GEORGE SAADE[1], ROBERT GARFIELD[1]; [1]University of Texas Medical Branch, Obstetrics and Gynecology, Galveston, TX; [2]University of Texas Medical Branch, Obstetrics & Gynecology, Galveston, TX

OBJECTIVE: To test the hypothesis regarding fetal origin of disease by examining maternal and paternal contributions to vascular reactivity in later life using transgenic mice lacking a functional endothelial nitric oxide synthase (NOS3).

STUDY DESIGN: Homozygous NOS3 knockout (C57BL/6J-NOS3 -/-) and wild type mice (NOS3 +/+) were cross-bred producing maternally-(NOS3+/-mat) and paternally-derived heterozygous NOS3 (NOS3+/-pat) and wild type (WT) litters. Two millimeter segments of carotid and mesenteric arteries from 7-8 wk females (n = 5-10/group) were mounted in a wire myograph for isometric force measurement and responses to contractile and relaxant agents were studied.

RESULTS: In the carotid artery, endothelium-dependent relaxant acetylcholine (ACh) caused relaxation in NOS3+/-pat and WT and produced contraction in NOS3+/-mat. In the mesenteric artery, relaxation by ACh was decreased in NOS3+/-mat compared to NOS3+/-pat and WT. Contractile responses to α-adrenergic agonist phenylephrine were significantly higher in NOS3+/-mat compared with NOS3+/-pat and WT in the carotid (maximal response: 202 ± 31.3 vs 115.9 ± 12.3 and 144.7 ± 9) and mesenteric (271.5 ± 47.8 vs 169.2 ± 6.4 and 208.9 ± 13.1) arteries. In both vessels, relaxation by β-adrenergic agonist isoproterenol was decreased in NOS3+/-mat compared to NOS3+/-pat and WT.

CONCLUSION: Despite both being heterozygous for the NOS3 gene, nitric oxide function does not appear to be different from normal in female mice from litters with paternally-derived mutation (normal female mated with KO males), but is deficient when the mutation is maternally-derived (KO females mated with normal males). These results support the role of genetic imprinting and uterine environment in determining cardiovascular risks in later life. In more general terms, phenotypic expression of various gene polymorphisms may depend on fetal programming and genetic imprinting.

4 **THE ROLE OF CYTOKINES IN THE REGULATION OF HEMOSTASIS IN HUMAN PREGNANCY** MICHAEL PAIDAS[1], GABRIELE URBAN[1], WAYNE KU[2], YALE ARKEL[2], EDWARD KUCZYNSKI[1], JEANINE MATURI[1], ANNE DILLEY[3], CHARLES LOCKWOOD[1]; [1]New York University, Obstetrics and Gynecology, New York, NY; [2]Maine Medical Center Research Institute, Portland, ME; [3]Centers for Disease Control and Prevention, Hematologic Diseases Branch, Atlanta, GA

OBJECTIVE: The state of immune tolerance in pregnancy has been characterized as a shift from a TH-1 (proinflammatory) to TH-2 (anti-inflammatory) response. We hypothesize that the prothrombotic state induced by thrombophilia is associated with persistence of the TH-1 response and that this response may, in turn, promote thrombosis.

STUDY DESIGN: We conducted a nested case control study among 16 patients with thrombophilia (mutations for Factor V Leiden and the prothrombin gene 20210, protein S deficiency) and prior adverse pregnancy outcomes (recurrent loss, growth restriction, abruption), and 29 controls with uncomplicated term pregnancies. We measured via immunoassay: soluble fibrin polymers (TpP), which reflect fibrin production due to thrombin interaction with fibrinogen; TH-1 cytokines, tumor necrosis factor-alpha (TNF), and Interleukin-1 (IL-1); and the TH-2 cytokine, Interleukin-8 (IL-8). We used an in vitro monocyte tissue culture assay to study the effect of thrombophilic and control plasma on induction of monocyte tissue factor (TF) activity. After incubating monocytes with 100ml of plasma added to 700ml of media (1:8 dilution), the supernatant was analyzed for cytokines while TF activity in the cell pellet was measured via a clotting assay.

RESULTS: Cases had elevated TpP levels (25.4 ± 15.1 vs. 12.2 ± 14.3 ug/ml; $P < .001$) and of TNF (11.4 ± 11.4 vs. 0.9 ± 2.2 pg/ml; $P < .001$) in the 1st trimester compared with controls. There was no significant difference in monocyte TF activity when the monocytes were exposed to plasma from thrombophilia and control patients. There were no differences in monocyte cytokine production following incubation with thrombophilic or control plasma.

CONCLUSION: We report a novel link between persistence of TH-1 immune response and the prothrombotic state in thrombophilic patients. The lack of stimulation of monocyte TF or TNF by thrombophilic plasma suggests that these cytokine-thrombin interactions are local not systemic.