

- 13 RISK OF BIRTH DEFECTS ASSOCIATED WITH ANTIRETROVIRAL EXPOSURE DURING PREGNANCY** KAREN BECKERMAN¹, DEBORAH COVINGTON², HEATHER WATTS³, HUGH TILSON⁴, SCOTT CHAVERS⁵, SUSAN SACKS⁶, ¹New York University School of Medicine, Department of Ob-Gyn, New York, NY ²PharmaResearch Corp, A member of the Inveresk Group, Wilmington, NC ³National Institute of Child Health and Human Development, Pediatric, Adolescent, Maternal AIDS Branch, Rockville, MD ⁴University of North Carolina at Chapel Hill, School of Public Health, Chapel Hill, NC ⁵GlaxoSmithKline, Epidemiology, Research Triangle Park, NC ⁶F. Hoffmann-La Roche, Ltd, Epidemiology, Nutley, NJ
- OBJECTIVE:** To examine the teratogenic risk of antiretroviral drugs.
- STUDY DESIGN:** The Antiretroviral Pregnancy Registry (APR) monitors prenatal exposures to antiretroviral (ARV) drugs to detect a potential increase in the risk of birth defects through a prospective exposure-registration cohort. Clinicians register pregnant women with prenatal exposures to any ARV, report data on exposure throughout pregnancy, and provide birth outcome data. Birth defect prevalence is compared to the CDC's population-based surveillance system. Statistical inference is based on exact methods for binomial proportions. For all defects combined, a cohort of 200 is required to detect a doubling of risk compared to CDC's expected prevalence, with 80% power and a type I error rate of 5%. For specific defects, the power varies with the population's frequency of the defect and the size of the exposed group.
- RESULTS:** From 1989 through January 2003, the APR has monitored 3160 live births exposed to ARV. Among 1242 first-trimester exposures, there were 35 birth defects, prevalence of 2.8% (95% CI = 2.0, 3.9). This rate is not significantly different from the CDC's system with a prevalence of 3.1 per 100 live births (95% CI = 3.1, 3.2). For lamivudine, nelfinavir, nevirapine, stavudine, and zidovudine, sufficient numbers of first-trimester exposures have been monitored to allow detection of at least a twofold increase in risk of overall birth defects and defects in the more common classes, cardiovascular and genitourinary systems. No such increases have been detected.
- CONCLUSION:** APR data demonstrate no increase in the prevalence of birth defects overall or among women exposed to lamivudine, nelfinavir, nevirapine, stavudine, and zidovudine. First-trimester exposures to other antiretroviral therapies are of insufficient size to support a separate analysis. Prospective reports of antiretroviral exposures are critically important to determine their teratogenic potential and can be made by calling (800) 258-4263.
- 14 FIRST-TRIMESTER PLACENTAL GROWTH FACTOR, sFlt-1, AND RISK FOR PREECLAMPSIA** JEFFREY ECKER¹, ANANTH KARUMANCHI², JAMES ROBERTS³, ROBERT TAYLOR⁴, RICHARD LEVINE⁵, RAVI THADHANI⁶, ¹Harvard University, Obstetrics, Gynecology & Reproductive Biology, Boston, MA ²Beth Israel Deaconess Medical Center, Medicine, Boston, MA ³University of Pittsburgh, Obstetrics, Gynecology and Reproductive Sciences, Pittsburgh, PA ⁴University of California, San Francisco, Obstetrics, Gynecology and Repro. Sciences, San Francisco, CA ⁵National Institutes of Health, Epidemiology, Bethesda, MD ⁶Massachusetts General Hospital, Boston, MA
- OBJECTIVE:** Angiogenesis is a critical component of normal placental development, and an imbalance of angiogenic growth factors and their inhibitors may lead to an increased risk for preeclampsia. We investigated whether serum levels of placental growth factor, a potent angiogenic factor, and its inhibitor, soluble fms-like tyrosine kinase 1 (sFlt1), identified women at risk for preeclampsia, isolated gestational hypertension, or delivering a small for gestational age newborn.
- STUDY DESIGN:** We performed a prospective nested case-control study of 40 women who developed preeclampsia (PE), 40 who developed gestational hypertension (GH), 40 who delivered a small for gestational age newborn (SGA), and 80 contemporaneous randomly selected controls. Blood samples were collected on or before 12 weeks of gestation, stored at -80°C until testing, and tested for PlGF and sFlt1 within 18 months of collection.
- RESULTS:** Compared with controls, first-trimester serum levels of PlGF were lower among women who subsequently developed PE (23 ± 24 pg/mL vs 63 ± 145 pg/mL, $P < 0.01$), developed GH (27 ± 19 pg/mL, $P = 0.03$), or delivered SGA newborns (21 ± 16 pg/mL, $P < 0.01$). First-trimester serum levels of sFlt-1 were slightly but not significantly elevated in women who developed PE (1048 ± 657 pg/mL) or who delivered SGA newborns (1011 ± 479 pg/mL), compared to women who developed GH (942 ± 437 pg/mL) or to normal controls (973 ± 490 pg/mL). Multivariable analysis demonstrated that compared to normotensive controls, there was a 3.7-fold (95% CI 1.2-12.5) increase in risk for PE for every one log unit decrease in serum levels of PlGF. Similar analyses for risk for GH or SGA were not significant.
- CONCLUSION:** Our data suggest the combination of first-trimester serum levels of PlGF and sFlt-1 strongly identifies women at high risk for subsequent preeclampsia, and distinguishes these women from those at risk for developing gestational hypertension, delivery of a small for gestational age infant, or having a normal pregnancy outcome.
- 15 A RANDOMIZED TRIAL OF TEMPORIZING MANAGEMENT WITH OR WITHOUT PLASMA VOLUME EXPANSION IN SEVERE AND EARLY PREECLAMPSIA: MATERNAL MORBIDITY** ANNELIES REP¹, WESSEL GANZEVOORT², HANS WOLF², HANNEKE DE VRIES¹, ¹VU University Medical Center, Amsterdam, The Netherlands ²Academisch Medisch Centrum, Amsterdam, The Netherlands
- OBJECTIVE:** Preeclampsia, HELLP syndrome, and associated fetal growth restriction (FGR) are important causes of perinatal and maternal morbidity and mortality. TempORIZING management until fetal or maternal condition necessitates delivery improves neonatal outcome, without increasing (irreversible) maternal morbidity. The value of plasma volume expansion (PVE) is still debated. We performed an RCT on PVE in severe and early preeclampsia. Here we report on maternal morbidity.
- STUDY DESIGN:** 216 patients with severe preeclampsia, HELLP syndrome, eclampsia, or pregnancy-induced hypertension with FGR and a gestational age between 24 and 34 weeks and acceptable fetal condition were randomized for tempORIZING management with (n = 111) or without (n = 105) PVE (Hydroxy Ethyl Starch 6%, 500 mL daily). Primary outcome was neonatal neurological development at term age and one year post term. An independent monitoring committee used well-defined criteria to determine safety endpoints (maternal and neonatal morbidity and mortality) after case review.
- RESULTS:** Baseline characteristics (age, race, clinical characteristics, and gestational age on inclusion) were distributed equally. Gestational age at inclusion was 29.5 weeks. Mean prolongation of pregnancy (live births) was 11.4 days.
- 52 transient maternal complications occurred in 39/216 (18%) patients: maternal death (n = 0), eclampsia (n = 6), liver hematoma (n = 1), renal insufficiency (n = 0), cerebral hemorrhage (n = 0), pulmonary edema (n = 8), thromboembolism (n = 3), infection (n = 12), abruptio placentae (n = 5), encephalopathy (n = 4), post-op hemorrhage (n = 3), others (n = 10).
- In the group with PVE there were 25 complications in 19/111 patients and in the group without PVE there were 27 complications in 20/105 patients.
- CONCLUSION:** There were no statistically significant differences in maternal morbidity between treatment groups.
- 16 TRANSCRIPTION LEVELS OF VEGFR-1 IN PRETERM PREECLAMPSIA** RAMEN CHMAIT¹, ANDREW HULL¹, THOMAS MOORE¹, LUBI BOGIC², ¹University of California, San Diego, Reproductive Medicine, San Diego, CA ²University of California, San Diego, Reproductive Medicine, La Jolla, CA
- OBJECTIVE:** The regulation of alternative splicing of vascular endothelial growth factor receptor-1 (VEGFR-1) pre-mRNA to generate Flt-1 and/or sFlt-1 is unknown. It has been suggested that excess circulating sFlt-1 leads to endothelial dysfunction, hypertension, and proteinuria by antagonizing the circulating VEGF and placental growth factor in the preeclampsia disorder. The objective was to characterize the ratio of the mature VEGFR-1 mRNAs in patients with preterm preeclampsia.
- STUDY DESIGN:** Primers specific for the two receptor forms (Flt-1 & sFlt-1) were used to perform RT-PCR on placenta delivered at 23-26 weeks of gestation in patients with and without preeclampsia. In the preeclampsia group (n = 5) the preterm labor was induced due to the severity of the disease. The reasons for the delivery in the control group (n = 7) were the premature rupture of membranes and the non-reassuring fetal status. The ratio of sFlt-1:Flt-1 was determined as copies/cell = 1550/2 cycle number of gene of interest-cycle number of EIF-1a.
- RESULTS:** The expression of both receptor forms sFlt-1 and Flt-1 was upregulated from 5-15 times in different regions of preeclamptic placenta. The ratio of sFlt-1/Flt-1 mRNAs was not significantly different between patient groups. However, the expression of sFlt was significantly higher in comparison to Flt-1. In fetal membranes both receptor forms were upregulated in preeclampsia patients (20x) and the average ratio of sFlt-1 to Flt-1 was 70:1 copies/cell. The same ratio was 20:1 in controls.
- CONCLUSION:** These results suggest that transcription and pre-mRNA processing of VEGFR-1 in the human placenta are not independent events. As it may be, the alternative splicing of VEGFR-1 is under transcriptional control. In fetal membranes VEGFR-1 pre-mRNA processing is under the control of independent membrane-specific splicing factors. The excess of circulating sFlt-1 in preeclampsia patients might be partially generated by the action of matrix proteases.