

## Platform Session I

### Basic and Clinical Teratology

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CHRISTIAN MS<sup>1</sup>, BRENT RL<sup>2</sup>, CALDA P<sup>3</sup>. <sup>1</sup>Argus International, Inc., Horsham, PA, United States, <sup>2</sup>Jefferson Medical College and duPont Hospital for Children, Wilmington, DE, United States, <sup>3</sup>Charles University, First Medical School, Department of Obstetrics and Gynecology, Prague, Czech Republic. Developmental Toxicity Signals Observed for 17 $\alpha$ -Hydroxyprogesterone Caproate in High Risk Pregnancies in the Non-Clinical Literature for Developmental Toxicity of Progestins

A recent NIH trial<sup>1</sup> showed IM injections of 17-hydroxyprogesterone caproate (17-OHP-C) reduces preterm births at 37 weeks of gestation. Natural progesterone given vaginally also reduces preterm births at 34 weeks of gestation<sup>2</sup>. Some concerns have been raised regarding increases in miscarriages and fetal death/stillbirths seen in the NIH trial and another large trial<sup>3</sup> of 17-OHP-C. To identify whether there were signals in animals, an extensive literature search was performed for progesterone, 17-hydroxyprogesterone and 17-OHP-C. Relevant studies for mice, rats, rabbits, guinea pigs, horses and non-human primates were found, but these studies did not meet current standards for drug development, were generally focused on teratogenicity and used supra-pharmacologic and/or high multiples of human exposure. Overall, 17-OHP-C was less potent than progesterone, and neither progestin consistently affected maternal weight gain, embryo-fetal viability or caused malformations. In one study<sup>4</sup> resorption/abortion occurred at the 17-OHP-P human equivalent dose, 10 mg/kg; in rhesus monkeys but not in cynomolgus monkeys. Some studies in rats showed potential postnatal effects. The relationship between these non-clinical signals and those in clinical trials is unclear in the absence of state-of-the-art reproductive toxicology and human pharmacokinetic studies. Further testing of 17-OHP-C for both efficacy and safety appears appropriate before widespread use in human pregnancies. References: 1. Meis PJ, et al. 2003. Prevention of recurrent preterm delivery by 17 alpha-hydroxyprogesterone caproate. *New Eng J Med* 348(24):2379-2385. 2. da Fonseca EB, et al. 2003. Prophylactic administration of progesterone by vaginal suppository to reduce the incidence of spontaneous preterm birth in women at increased risk: A randomized placebo-controlled double-blind study. *Am J Obstet Gynecol* 2003; 188:419-424. 3. Yemini, M, et al. 1985. Prevention of premature labor by 17  $\alpha$ -hydroxyprogesterone caproate. *Am J Obstet Gynecol* 1985;574-577. 4. Hendrickx AG, et al. 1987. Embryotoxicity of sex steroidal hormones in nonhuman primates: II. Hydroxyprogesterone caproate, estradiol valerate. *Teratology* 35(1):129-136.

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HERNANDEZ-DIAZ S<sup>2</sup>, SMITH CR<sup>1</sup>, WYSZYNSKI DF<sup>3</sup>, HOLMES LB<sup>1</sup>. <sup>1</sup>MassGeneral Hospital for Children, Boston, MA, United States, <sup>2</sup>Harvard School of Public Health, Boston, MA, United States, <sup>3</sup>Boston University School of Medicine, Boston, MA, United States. Risk of Major Malformations Among Infants Exposed to Carbamazepine During Pregnancy

Background: Carbamazepine has been considered less teratogenic than other anticonvulsant drugs. The AED (antiepileptic drug) Pregnancy Registry was established to monitor the occurrence of major malformations (MM) in AED-exposed newborns. Objective: To determine the rate of all MM and specific MM in infants exposed to carbamazepine in the first trimester of pregnancy. Methods: 4,688 pregnant women enrolled 1997-2006 in U.S. and Canada. Dose, folic acid use, demographic data was obtained in 3 interviews: enrolment, 7 mos GA and postpartum. Medical records were requested to confirm diagnosis and doses. A major malformation was defined as a structural abnormality with surgical, medical or cosmetic importance. Exclusions were minor anomalies, birth marks, positional deformities, genetic disorders and prematurity-related outcomes. The comparison population of newborns was surveyed at birth at Brigham & Women's Hospital, Boston: 69,277 infants and elective ab. for anomalies. Results: 22 MM were identified in 873 infants: 4 "isolated" cleft palate (CP), 1 cleft lip, 4 heart defects, 3 neural tube defects and 4 GU abnormalities. Prevalence 2.5%; 95% CI 1.6 to 3.7%. 497 of the 873 mothers enrolled before prenatal screening, so "pure" prospective: prevalence rate MM: 2.6% (95% CI 1.5-4.3). In comparison to population, prevalence of MM: 1.6%; odds ratio for carbamazepine exposed: 1.6 (95% CI 0.9-2.8). The frequency of "isolated" CP in comparison pop. 0.19/1,000. The rate in carbamazepine-exposed showed 24-fold increase (95 CI: 7.9-74.4). Conclusion: This is a new finding of an increased frequency CP in carbamazepine-exposed. We confirm previous finding (Rosa F: *NEJM* 1991; 324:674) of increased frequency of NTD in carbamazepine-exposed infants. *AED Pregnancy Registry supported by Abbott, Eisai, GlaxoSmithKline, Novartis, Ortho-McNeil, Pfizer.*