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Janssen Study Examines Impact of Environmental Exposure to Phthalates on Infant Genital Development

Specialists in pediatric environmental medicine are increasingly concerned about the effects that compounds called phthalates may have on the developing fetus. These chemicals, which are widespread in our environment, may disrupt the function of androgen and other sex hormones and have been linked to urogenital abnormalities in animal studies.

UCSF is one of four sites participating in a National Institutes of Healthfunded study that will attempt to correlate maternal phthalate levels with the development of reproductive organs in infant boys and girls. The Infant Development and Environmental Study (TIDES) will follow participating women through three trimesters of pregnancy and will record information about the urogenital development of their newborns shortly after birth, says Sarah Janssen, MD, PhD, MPH, director of TIDES at UCSF. Janssen holds academic appointments in Urology and Occupational and Environmental Medicine at UCSF and serves as a senior scientist in the Health and Environment Program of the Natural Resources Defense Council.

Ubiquitous chemicals in today's environment

Phthalates are chemical compounds, often called "plasticizers," that soften hard plastics, making them flexible and resilient. TIDES will measure levels of two common phthalates: bis(2-ethylhexyl) phthalate (DEHP) and dibutyl phthalate (DBP). DEHP is commonly used in medical devices such as tubing and IV bags. Both DEHP and DBP are used in food packaging, and food is thought to be the biggest source of exposure to these chemicals. Both DEHP and DBP have also been used in personal care products and air fresheners.

Phthalates enter the body by ingestion, inhalation and through skin contact. They are metabolized quickly and do not accumulate in tissue, but they are so common in the environment and exposure is so regular that they can be found in most people's urine, said Janssen. A National Health and Nutrition Examination Survey, conducted by the Centers for Disease Control and Prevention (CDC), found that most of the general population, including women of reproductive age and pregnant women, had measurable exposure to phthalates.



Evidence of adverse health effects

There is growing concern about the potential effect of phthalates on endocrine function and reproductive health. Studies suggest that sperm quality in adult men drops with increased exposure to phthalates. Some nonreproductive associations have also been observed, said Janssen, such as an increase in obesity and abnormal glucose metabolism. Animal studies support the idea that phthalates have anti-androgen effects. In male rats, for



Letter from the Chief

Laurence Baskin, MD

Dear Friends and Colleagues

Pediatric Urology continues to thrive at UCSF. My partners Mike DiSandro and Hillary Copp. our nurse practitioners Angie Champeau and Ann Arnhym and myself appreciate your support as our practice continues to grow at UCSF and Children's Hospital Oaklan along with our outreach clinics at CPMC, Salinas, Pleasanton and Walnut Creek. We know that experience demonstrated by high surgical volumes with minimal complications is critical to maintaining the highest level of competency. In the side bar, I have listed "our numbers" for just some of the common surgical procedures that we perform.

Herein, I am pleased to highlight the research efforts of our junior faculty. Shweta Choudhry, is part of our young scholar (KURe) training program and brings to our division specific expertise in medical genetics. I hope you enjoy her article on DNA methylation as a possible etiology of hypospadias. We are also pleased to welcome Sarah Janssen an expert in environmental health who is leading our TIDES study. Sarah can often be found in Sacramento testifying before our esteemed legislatures to keep our children safe from toxic environmental exposures. Finally, we are all worried about the over use of antibiotics. Hillary Copp has received national press for her work on over prescribing antibiotics in the treatment of urinary tract infection. I hope that these three short summaries give you an overview of the impressive research that these talented young investigators are performing in the pediatric urology division at UCSF.

Our pediatric urology training fellowship continues to graduate outstanding young pediatric urologists. Dr. Jenny Yiee just completed her two years at UCSF and is now an AUA scholar at UCLA. Dr. Zeke Rodriguez graduated from our research lab to the clinical year and Dr. Bruce Schlomer from Southwestern Medical Center in Dallas, Texas just joined us to begin his research year.

Our basic science and clinical research continues to thrive. We recently received a competitive renewal to continue our NIH funded project on the Hypospadias and Endocrine Disruptors. We are quite proud that our division of pediatric urology holds title to 2 NIH RO1 basic research grants (Hypospadias and Bladder Smooth Muscle Development), 3 NIH sponsored clinical grants (TIDES, MOMs (Bladder outcomes in the prenatal treatment of myelomeningocele and DSD outcomes (Dr. DiSandro)), 1 departmental training grant (KURe) and 1 grant from the National Science Foundation (Hyenas and the role of estrogen in sexual differentiation). (http://urology. ucsf.edu/baskinlab/index.html)

I would specifically like to acknowledge the help of our staff in the clinics, operating room, and academic offices; they are a critical part of our pediatric urology team. It remains a great honor to serve the children of Northern California and to help facilitate care for your pediatric urology patients. I hope you enjoy our newsletter. Please do not hesitate to contact us with specific questions or suggestions.

Sincerely

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Laurence S. Baskin, MD Chief, Pediatric Urology, Department of Urology Professor of Urology and Pediatrics, University of California, San Francisco

Study Examines Impact of Phthalates on Infant Genital Development ... continued

example, prenatal exposure to phthalates is associated with abnormalities of the penis (hypospadias), testes (cryptorchidism) and poor sperm quality.

Recruitment at UCSF

The UCSF arm of TIDES began recruiting pregnant women in the fall of 2010 and hopes to complete enrollment of approximately 220 women by early 2012.

Subjects are recruited through the UCSF Prenatal Diagnostic Clinic, where women are typically seen late in their first trimester. Those who agree to participate are asked to complete a questionnaire in each trimester of pregnancy to help determine possible sources of exposures to phthalates. Women also provide a urine sample each trimester and a blood sample in the first trimester. Once their babies are born, UCSF researchers, including Janssen and UCSF Pediatric Urology Chief Laurence Baskin, MD, document urogenital development of both male and female infants by taking a set of measurements within two weeks of birth. Boys will be examined again at one year of age.

Study goals

Approximately 1,200 infants will be included in TIDES, once data are gathered from UCSF and the other study sites (the University of Rochester, New York; Seattle Children's Hospital and University of Washington School of Medicine; and the University of Minnesota). Specific goals of the study are to:

- determine whether phthalate levels fluctuate during pregnancy.
- · establish a simple, reliable method of measuring anogenital distance (AGD) in both males and females and determine standard distributions for this measurement in newborns. The distance between the anus and genitalia is a standard toxicology measure of anti-androgen activity in animal studies, said Janssen, but the average length for human males and females has never been established. Rat models show that AGD is shorter in the male offspring of pregnant animals exposed to both DEHP and DBP, the two phthalates that will be measured in this study.
- · determine whether there is a correlation between maternal phthalate exposure and AGD in the newborn.
- determine whether AGD is a long-lasting marker of anti-androgen exposure, as appears to be the case in rats, or alters over time.

For more information about TIDES at UCSF, contact Sarah Janssen, MD, PhD, MPH, at sarah.janssen@ ucsf.edu or 415-875-6126.



Copp Antibiotics

Surveying Antibiotic Use in Pediatric Urinary Tract Infection

In a paper recently published in Pediatrics, UCSF urologist Hillary Copp, MD, MS, reported the results of a national survey of antibiotic prescribing patterns in the outpatient treatment of urinary tract



infections (UTIs) in children. Ambulatory visits for UTIs in children are common, with at least 1.5 million visits occurring each year in the United States.

Copp and her UCSF colleagues evaluated antibiotic prescribing patterns for pediatric UTI among US physicians using two ambulatory databases: the National Ambulatory Medical Care Survey (NAMCS) and the National Hospital Ambulatory Care Survey (NHACS). The

first-of-its-kind study retrospectively reviewed treatment records of children aged younger than 18 years from 1998 to 2007 who were seen in an outpatient setting.

The study showed that antibiotics were prescribed for 70% of pediatric UTI visits. Trimethoprin-sulfamethoxazole was prescribed most often (in approximately 50% of patients), but broad-sprectrum antibiotics were used in approximately one third of patients, a pattern that held steady over the course of the study. However, within this broadspectrum category, use of third-generation cephalosporins doubled during the study period, rising from 12% to 25%. Race, physician specialty, region and insurance status did not appear to be associated with antibiotic selection, but broad-spectrum antibiotics were more likely to be prescribed for female patients, children younger than 2 years old, and children running a fever.

Copp and her coauthors note that there may be specific reasons for using these broader spectrum drugs. Culture results are often not available when the child receives initial treatment, and broad spectrum antibiotics offer more assurance that treatment will cover the offending bacteria, an important consideration when follow-up is uncertain. However, the practice patterns identified by Copp and her colleagues do not necessarily match current recommendations. Most UTIs are caused by Escherichia coli (80-90% of cases), and resistance rates to first-generation cephalosporins are very low, yet these drugs were prescribed in only 5% of visits. Conversely, trimethoprin-sulfamethoxazole was prescribed about 50% of the time, despite studies that have shown resistance rates that range from 20-40%.

The authors note that many variables could not be tracked in the study, and it is not possible to say that broad-spectrum antibiotics are being overprescribed for UTIs in children, given the information available to physicians at the time of treatment. Still, given that most UTIs are likely to respond to narrower-spectrum antibiotics, broad-spectrum alternatives may not be necessary in many cases in which they are used.

Copp HL, Shapiro DJ, Hersh AL. National Ambulatory Antibiotic Prescribing Patterns for Pediatric Urinary Tract Infection, 1998-2007. Pediatrics. 2011 Jun;127(6):1027-33.

UCSF pediatric Urology Surgical Volumes

The pediatric urology program has successfully performed more than 3,300 surgeries since 2006. These include: hyopspadias and penile curvature repair - 1075; reflux procedures – 461; orchiopexies – 723; pyeloplasty – 134; Hydrocele/hernia repairs – 813; and bladder augmentation – 48.

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Web Links

UCSF Pediatric Urology urology.ucsf.edu/clinicalRes/CRpedUro.html

Patient handouts urology.ucsf.edu/patientGuides/pedUro.html

Baskin research laboratory ucsf.edu/baskinlab/

KURe training program http://urology.ucsf.edu/ facdevelop/facdevelop_kure.html

UCSF clinic: 415/353-2200 UCSF academic office: 415/476-1611 Children's Hospital Oakland clinic: 510/428-3402



Choudhry DNA methylation: Understanding Hypospadias

Genetic clues to hypospadias

Second-year KURe scholar Shweta Choudhry, PhD is studying the genetics of hypospadias, a



birth defect of the male urethra in which the urethral opening is abnormally placed. The condition is classified as mild to severe, depending on where the opening is located along

the penile shaft. Incidence figures for hypospadias range from as low as 1 in 4,000 in some countries to 1 in 250 boys born in the US, and there has been concern that the rate is rising.

The molecular events that lead to hypospadias remain largely unknown. There may be some genetic predisposition-seven percent of boys born with hypospadias have a father with the condition, and several genetic mutations are associated with a percentage of cases. Environmental exposures, including exposure to environmental estrogens, may also play a role in hypospadias. The condition can be induced in developing mice by in utero exposure to endocrine-disrupting chemicals with estrogenic or anti-androgenic activity. Prenatal exposure of mice to phthalates or estrogen also increases expression of genes that adversely affect male genitourinary development. In humans, some studies have suggested an increase in the incidence of hypospadias with exposure to farm chemicals, pesticides, phthalates and hair spray.

In an initial pilot study, Choudhry looked at the role of DNA methylation (the addition of a methyl group to a cytosine-pyrimidine ring in DNA) in hypospadias. Changes in methylation levels of various genes have been associated in other studies with diseases such as cancer, autoimmune disease, mental disorders and diabetes.

Using BeadChip[™] technology to probe DNA extracted from the foreskin tissue of 13 boys with severe hypospadias and 19 controls, Choudhry found a relationship between hypospadias and methylation of the CXorf6 gene, known to be important in the development of male genitalia. Choudhry hopes to confirm these findings in a larger sample and to add information on environmental exposures. Additional work in mouse models might provide clues to a possible cause-and-effect relationship.

Choudhry's second pilot study looked at genes that might be associated with hypospadias in 123 boys with the anomaly and 56 controls recruited from UCSF and Children's Hospital Oakland. Genotyping and analysis found association with genetic polymorphism in the 3' untranslated region of the ESR2 gene, an association she will attempt to confirm by expanding her sample size in future studies.

Dr. Choudhry's mentors include: John Witte, PhD (career mentor) Laurence Baskin, MD (lead research mentor), June Chan, ScD (co-mentor).

DNA Methylation Profile to Study Epigentic Factors in Hypospadias



Editor Laurence Baskin, MD

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