

Physicians “should consider vaccination of women during pregnancy with DTaP,” she said at the meeting.

In the prospective cohort study, 16 (23%) of 70 pregnant women received DTaP vaccine; 54 (77%) pregnant women selected as controls did not and had not been vaccinated for at least 2 years.

Four of the women (25%) in the DTaP group were vaccinated in the first trimester, eight (50%) in the second, and four (25%) in the third. Vaccination did not cause any adverse pregnancy outcomes.

Maternal blood and cord blood were collected at delivery.

Blood was also collected from children before and after their primary DTaP series and toddler booster doses at 12-18 months.

Blood samples were measured for pertussis antigens, including pertussis toxoid, filamentous hemagglutinin, pertactin, and fimbriae, by enzyme-linked immunosorbent assay.

Newborns in the DTaP group had higher pertussis antibody concentrations than their mothers, “showing efficient placental transfer of antibodies

to the infant,” Dr. Hardy-Fairbanks said.

They also had substantially higher concentrations than infants in the control group prior to the start of the primary DTaP series, and the differences were statistically significant.

However, at month 7, following completion of the DTaP series, infants born to vaccinated mothers had slightly lower antibody levels than infants in the control group.

The differences were not statistically significant, but “may represent some blunting of the infant immune response

to the [vaccine],” Dr. Hardy-Fairbanks said.

By the time they got their toddler booster doses, however, antibody levels “were essentially equivalent” in the two groups, she said. ■

Possible Blunted Immune Response?

Dr. Sarah Long thanked the study authors for their work. “Your findings are so very helpful. We don’t have this kind of information.”

She was concerned, however, that infants born to vaccinated mothers mounted only a blunted immune response to their primary DTaP vaccine series, and wondered if responses would be blunted to other vaccines. The study’s presenter said the question is currently being investigated, but so far that does not appear to be the case.

DR. LONG is the chief of the section of infectious diseases at St. Christopher’s Hospital for Children in Philadelphia. She said she had no conflicts of interest.

VIEW ON THE NEWS

New Onset Autoimmune Diseases (NOADs): The pooled safety database, which included controlled and uncontrolled trials which enrolled females 10 through 25 years of age, was searched for new medical conditions indicative of potential new onset autoimmune diseases. Overall, the incidence of potential NOADs, as well as NOADs, in the group receiving CERVARIX was 0.8% (95/12,533) and comparable to the pooled control group (0.8%, 87/10,730) during the 4.3 years of follow-up (mean 3.0 years) (Table 4). In the largest randomized, controlled trial (Study 2) which enrolled females 15 through 25 years of age and which included active surveillance for potential NOADs, the incidence of potential NOADs and NOADs was 0.8% among subjects who received CERVARIX (78/9,319) and 0.8% among subjects who received Hepatitis A Vaccine [720 EL.U. of antigen and 500 mcg Al(OH)₃] control (77/9,325).

Table 4. Incidence of New Medical Conditions Indicative of Potential New Onset Autoimmune Disease and New Onset Autoimmune Disease Throughout the Follow-up Period Regardless of Causality in Females 10 Through 25 Years of Age (Total Vaccinated Cohort^a)

	CERVARIX (N = 12,533)	Pooled Control Group ^b (N = 10,730)
	n (%) ^c	n (%) ^c
Total Number of Subjects With at Least One Medical Condition	95 (0.8)	87 (0.8)
Arthritis ^d	9 (0.0)	4 (0.0)
Celiac disease	2 (0.0)	5 (0.0)
Dermatomyositis	0 (0.0)	1 (0.0)
Diabetes mellitus insulin-dependent (Type 1 or unspecified)	5 (0.0)	5 (0.0)
Erythema nodosum	3 (0.0)	0 (0.0)
Hyperthyroidism ^e	14 (0.1)	15 (0.1)
Hypothyroidism ^f	30 (0.2)	28 (0.3)
Inflammatory bowel disease ^g	8 (0.1)	4 (0.0)
Multiple sclerosis	4 (0.0)	1 (0.0)
Myelitis transverse	1 (0.0)	0 (0.0)
Optic neuritis/Optic neuritis retrobulbar	3 (0.0)	1 (0.0)
Psoriasis ^h	8 (0.1)	11 (0.1)
Raynaud’s phenomenon	0 (0.0)	1 (0.0)
Rheumatoid arthritis	4 (0.0)	3 (0.0)
Systemic lupus erythematosus ⁱ	2 (0.0)	3 (0.0)
Thrombocytopenia ^j	1 (0.0)	1 (0.0)
Vasculitis ^k	1 (0.0)	3 (0.0)
Vitiligo	2 (0.0)	2 (0.0)

^a Total vaccinated cohort included subjects with at least one documented dose (N).

^b Pooled Control Group = Hepatitis A Vaccine control group [720 EL.U. of antigen and 500 mcg Al(OH)₃], Hepatitis A Vaccine control group [360 EL.U. of antigen and 250 mcg of Al(OH)₃], and a control containing 500 mcg Al(OH)₃.

^c n (%): number and percentage of subjects with medical condition.

^d Term includes reactive arthritis and arthritis.

^e Term includes Basedow’s disease, goiter, and hyperthyroidism.

^f Term includes thyroiditis, autoimmune thyroiditis, and hypothyroidism.

^g Term includes colitis ulcerative, Crohn’s disease, proctitis ulcerative, and inflammatory bowel disease.

^h Term includes psoriatic arthropathy, nail psoriasis, guttate psoriasis, and psoriasis.

ⁱ Term includes systemic lupus erythematosus and cutaneous lupus erythematosus.

^j Term includes idiopathic thrombocytopenic purpura and thrombocytopenia.

^k Term includes leukocytoclastic vasculitis and vasculitis.

Serious Adverse Events: In the pooled safety database, inclusive of controlled and uncontrolled studies, which enrolled females 10 through 72 years of age, 5.3% (862/16,142) of subjects who received CERVARIX and 5.9% (814/13,811) of subjects who received control reported at least one serious adverse event, without regard to causality, during the entire follow-up period (up to 7.4 years). Among females 10 through 25 years of age enrolled in these clinical studies, 6.4% of subjects who received CERVARIX and 7.2% of subjects who received the control reported at least one serious adverse event during the entire follow-up period (up to 7.4 years).

Deaths: In completed and ongoing studies which enrolled 57,323 females 9 through 72 years of age, 37 deaths were reported during the 7.4 years of follow-up: 20 in subjects who received CERVARIX (0.06%, 20/33,623) and 17 in subjects who received control (0.07%, 17/23,700). Causes of death among subjects were consistent with those reported in adolescent and adult female populations. The most common causes of death in the vaccine and control groups were motor vehicle accident and suicide, followed by neoplasm, autoimmune disease, infectious disease, homicide, cardiovascular disorders, and death of unknown cause. Among females 10 through 25 years of age, 31 deaths were reported (0.05%, 16/29,467) of subjects who received CERVARIX and 0.07%, 15/20,192 of subjects who received control.

6.2 Postmarketing Experience: In addition to reports in clinical trials, worldwide voluntary reports of adverse events received for CERVARIX since market introduction (2007) are listed below. This list includes serious events or events which have suspected causal association to CERVARIX. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to vaccination. **Blood and Lymphatic System Disorders:** Lymphadenopathy. **Immune System Disorders:** Allergic reactions (including anaphylactic and anaphylactoid reactions), angioedema, erythema multiforme. **Nervous System Disorders:** Syncope or vasovagal responses to injection (sometimes accompanied by tonic-clonic movements).

7 DRUG INTERACTIONS

7.1 Concomitant Vaccine Administration: There are no data to assess the concomitant use of CERVARIX with other vaccines. Do not mix CERVARIX with any other vaccine in the same syringe or vial. **7.2 Hormonal Contraceptives:** Among 7,693 subjects 15 through 25 years of age in Study 2 (CERVARIX, N = 3,821 or Hepatitis A Vaccine 720 EL.U., N = 3,872) who used hormonal contraceptives for a mean of 2.8 years, the observed efficacy of CERVARIX was similar to that

observed among subjects who did not report use of hormonal contraceptives.

7.3 Immunosuppressive Therapies: Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs, and corticosteroids (used in greater than physiologic doses), may reduce the immune response to CERVARIX [see Use in Specific Populations (8.6)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy: Pregnancy Category B. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. **Clinical Studies:**

Overall Outcomes: In clinical studies, pregnancy testing was performed prior to each vaccine administration and vaccination was discontinued if a subject had a positive pregnancy test. In all clinical trials, subjects were instructed to take precautions to avoid pregnancy until 2 months after the last vaccination. During pre-licensure clinical development, a total of 7,276 pregnancies were reported among 3,696 females receiving CERVARIX and 3,580 females receiving a control (Hepatitis A Vaccine 360 EL.U., Hepatitis A Vaccine 720 EL.U., or 500 mcg Al(OH)₃). The overall proportions of pregnancy outcomes were similar between treatment groups.

The majority of women gave birth to normal infants (62.2% and 62.6% of recipients of CERVARIX and control, respectively). Other outcomes included spontaneous abortion (11.0% and 10.8% of recipients of CERVARIX and control, respectively), elective termination (5.8% and 6.1% of recipients of CERVARIX and control, respectively), abnormal infant other than congenital anomaly (2.8% and 3.2% of recipients of CERVARIX and control, respectively), and premature birth (2.0% and 1.7% of recipients of CERVARIX and control, respectively). Other outcomes (congenital anomaly, stillbirth, ectopic pregnancy, and therapeutic abortion) were reported less frequently in 0.1% to 0.8% of pregnancies in both groups. **Outcomes Around Time of Vaccination:** Sub-analyses were conducted to describe pregnancy outcomes in 761 women [N = 396 for CERVARIX and N = 365 pooled control, HAV 360 EL.U., HAV 720 EL.U., and 500 mcg Al(OH)₃] who had their last menstrual period within 30 days prior to, or 45 days after a vaccine dose and for whom pregnancy outcome was known. The majority of women gave birth to normal infants (65.2% and 69.3% of recipients of CERVARIX and control, respectively). Spontaneous abortion was reported in a total of 11.7% of subjects (13.6% of recipients of CERVARIX and 9.6% of control recipients) and elective termination was reported in a total of 9.7% of subjects (9.9% of recipients of CERVARIX and 9.6% of control recipients). Abnormal infant other than congenital anomaly was reported in a total of 4.9% of subjects (5.1% of recipients of CERVARIX and 4.7% of control recipients) and premature birth was reported in a total of 2.5% of subjects (2.5% of both groups). Other outcomes (congenital anomaly, stillbirth, ectopic pregnancy, and therapeutic abortion) were reported in 0.3% to 1.8% of pregnancies among recipients of CERVARIX and in 0.3% to 1.4% of pregnancies among control recipients. It is not known whether the observed numerical imbalance in spontaneous abortions in pregnancies which occurred around the time of vaccination is due to a vaccine-related effect. **Pregnancy Registry:** Healthcare providers are encouraged to register pregnant women who inadvertently receive CERVARIX in the GlaxoSmithKline vaccination pregnancy registry by calling 1-888-452-9622. **8.3 Nursing Mothers:** In non-clinical studies in rats, serological data suggest a transfer of anti-HPV-16 and anti-HPV-18 antibodies via milk during lactation in rats. Excretion of vaccine-induced antibodies in human milk has not been studied for CERVARIX. Because many drugs are excreted in human milk, caution should be exercised when CERVARIX is administered to a nursing woman. **8.4 Pediatric Use:** Safety and effectiveness in pediatric patients younger than 10 years of age have not been established. The safety and effectiveness of CERVARIX have been evaluated in 1,193 subjects 10 through 14 years of age and 6,316 subjects 15 through 17 years of age. [See Adverse Reactions (6.1) and Clinical Studies (14.5) of full prescribing information.] **8.5 Geriatric Use:** Clinical studies of CERVARIX did not include sufficient numbers of subjects 65 years of age and older to determine whether they respond differently from younger subjects. CERVARIX is not approved for use in subjects 65 years of age and older. **8.6 Immunocompromised Individuals:** The immune response to CERVARIX may be diminished in immunocompromised individuals [see Drug Interactions (7.3)].

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility: CERVARIX has not been evaluated for its carcinogenic or mutagenic potential.

17 PATIENT COUNSELING INFORMATION
Provide the Vaccine Information Statements prior to immunization. This is required by the National Childhood Vaccine Injury Act of 1986 and are available free of charge at the Centers for Disease Control and Prevention (CDC) website (www.cdc.gov/vaccines). Inform the patient, parent, or guardian: Vaccination does not substitute for routine cervical cancer screening. Women who receive CERVARIX should continue to undergo cervical cancer screening per standard of care. CERVARIX does not protect against disease from HPV types to which a woman has previously been exposed through sexual activity. Since syncope has been reported following vaccination in young females, sometimes resulting in falling with injury, observation for 15 minutes after administration is recommended. Information regarding potential benefits and risks associated with vaccination. Report any adverse events to their healthcare provider. Safety has not been established in pregnant women. CERVARIX is not recommended for use in pregnant women or women planning to become pregnant during the vaccination course. Register women who receive CERVARIX while pregnant in the pregnancy registry by calling 1-888-452-9622.

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Paternal Postpartum Depression High

FROM JAMA

A significant number of men experience prenatal and postpartum depression, and the rate is marginally higher in the United States than in other countries, according to a meta-analysis of 43 studies.

The overall rate of paternal depression was 10.4%, with a U.S. rate of 14.1% vs. 8.2% in other countries. The study also reported maternal depression at a rate of 23.8%, with a moderate positive correlation between maternal and paternal depression.

The findings suggest that “more efforts should be made to improve screening and referral, particularly in light of the mounting evidence that early paternal depression may have substantial emotional, behavioral, and developmental effects on children,” noted James F. Paulson, Ph.D., and his colleague Sharnail D. Bazemore of the department of pediatrics at Eastern Virginia Medical School in Norfolk (JAMA 2010;303:1961-9). The correlation between paternal and maternal depression “also suggests a screening rubric – depression in one patient should prompt clinical attention to the other,” the investigators wrote.

The meta-analysis included studies from 16 countries and involved 28,004 new and expectant fathers aged 18 years or older.

—Kate Johnson