

Pregnancy, Breastfeeding May Cut Bone Loss

BY DOUG BRUNK

SAN DIEGO — The combination of breastfeeding and delaying pregnancy until a woman has acquired the majority of her bone mass appears to have a protective effect on bones, a study of more than 600 women found.

“Several studies have shown that people who have had many pregnancies have less bone loss than women with no preg-

nancies,” lead author Dr. Peter F. Schnatz said in an interview.

“Our study is the first to our knowledge looking at the effect of pregnancy during the time of peak bone mineral acquisition and its eventual and ultimate effect on the development of postmenopausal osteoporosis. Most prior adolescent pregnancy studies, for instance, are limited to the immediate postpartum period,” he said at a poster

session at the annual meeting of the North American Menopause Society.

Dr. Schnatz, residency program director in the department of obstetrics and gynecology at Reading (Pa.) Hospital and Medical Center, and his associates analyzed data from 619 women over 49 years old who presented for bone density scanning at one of four radiology groups in the Hartford, Conn., area. They assessed risk factors for osteo-

porosis, including a previous atraumatic fracture of the hip or spine, pregnancy information, and dual-energy x-ray absorptiometry results. They defined osteoporosis as a T score of -2.5 or lower at the lumbar spine, the femoral neck, or the total femur.

The mean age of the study participants was 62 years, and 50% were either current or past smokers. Slightly more than one-quarter (27%) were using or had used a bisphosphonate, 64% were using or had used hormonal therapy, and 5% had used steroids.

Women with any breastfeeding had a significantly lower prevalence of osteoporosis (8%) than women who did not breastfeed (19%), a finding that surprised

Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed

Adacel®

Brief Summary: Please see package insert for full prescribing information.

INDICATIONS AND USAGE Adacel vaccine is indicated for active booster immunization for the prevention of tetanus, diphtheria and pertussis as a single dose in persons 11 through 64 years of age. The use of Adacel vaccine as a primary series, or to complete the primary series, has not been studied. Vaccination with Adacel vaccine may not protect all of vaccinated individuals.

CONTRAINDICATIONS A severe allergic reaction (e.g., anaphylaxis) after a previous dose of Adacel vaccine or any other tetanus toxoid, diphtheria toxoid or pertussis containing vaccine or any other component of this vaccine is a contraindication to vaccination with Adacel vaccine. Because of uncertainty as to which component of the vaccine may be responsible, none of the components should be administered. Alternatively, such individuals may be referred to an allergist for evaluation if further immunizations are to be considered. (1,2) Encephalopathy within 7 days of a previous dose of a pertussis containing vaccine not attributable to another identifiable cause is a contraindication to vaccination with Adacel vaccine. (1-3)

WARNINGS Persons who experienced Arthus-type hypersensitivity reactions (e.g., severe local reactions associated with systemic symptoms) (4) following a prior dose of tetanus toxoid usually have high serum tetanus antitoxin levels and should not be given emergency doses of tetanus toxoid containing vaccines more frequently than every 10 years, even if the wound is neither clean nor minor. (1,2,5,6) If Guillain-Barré syndrome occurred within 6 weeks of receipt of prior vaccine containing tetanus toxoid, the decision to give Adacel vaccine or any vaccine containing tetanus toxoid should be based on careful consideration of the potential benefits and possible risks. (1-3) In the following situations, Adacel vaccine should generally be deferred:

- Moderate or severe acute illness with or without fever, until the acute illness resolves. (1,2)
- In adolescents, progressive neurologic disorder, including progressive encephalopathy, or uncontrolled epilepsy, until the condition has stabilized. (2)
- In adults, unstable neurologic condition (e.g., cerebrovascular events and acute encephalopathic conditions), until the condition has resolved or is stabilized. (1)

PRECAUTIONS General Before administration of Adacel vaccine, the patient's current health status and medical history should be reviewed in order to determine whether any contraindications exist and to assess the benefits and risks of vaccination. (See **CONTRAINDICATIONS** and **WARNINGS**.) Epinephrine Hydrochloride Solution (1:1,000) and other appropriate agents and equipment should be available for immediate use in case of anaphylactic or acute hypersensitivity reaction occurs. If Adacel vaccine is administered to immunocompromised persons, including persons receiving immunosuppressive therapy, the expected immune response may not be obtained.

Information for Vaccine Recipients and/or Parent or Guardian Before administration of Adacel vaccine, health-care providers should inform the vaccine recipient and/or parent or guardian of the benefits and risks. The health-care provider should inform the vaccine recipient and/or parent or guardian about the potential for adverse reactions that have been temporally associated with Adacel vaccine or other vaccines containing similar components. The health-care provider should provide the Vaccine Information Statements (VIS) that are required by the National Childhood Vaccine Injury Act of 1986 to be given with each immunization. The vaccine recipient and/or parent or guardian should be instructed to report any serious adverse reactions to their health-care provider. Females of child-bearing potential should be informed that Sanofi Pasteur Inc. maintains a pregnancy surveillance system to collect data on pregnancy outcomes and newborn health status outcomes following vaccination with Adacel vaccine during pregnancy. If they are pregnant or become aware they were pregnant at the time of Adacel vaccine immunization, they are encouraged to contact directly or have their health-care professional contact Sanofi Pasteur Inc. at 1-800-822-2463 (1-800-VACCINE). Reporting adverse events after vaccination to VAERS (Vaccine Adverse Event Reporting System) by recipients and/or parents or guardian should be encouraged. The toll-free number for VAERS forms and information is 1-800-822-7967. Reporting forms may also be obtained at the VAERS website at www.vaers.hhs.gov.

Drug Interactions Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs and corticosteroids (used in greater than physiologic doses), may reduce the immune response to vaccines. (See **PRECAUTIONS**, **General**.) For information regarding simultaneous administration with other vaccines refer to the **ADVERSE REACTIONS** and **DOSAGE AND ADMINISTRATION** sections.

Carcinogenesis, Mutagenesis, Impairment of Fertility No studies have been performed with Adacel vaccine to evaluate carcinogenicity, mutagenic potential, or impairment of fertility.

Pregnancy Category C Animal reproduction studies have not been conducted with Adacel vaccine. It is also not known whether Adacel vaccine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Adacel vaccine should be given to a pregnant woman only if clearly needed. Animal fertility studies have not been conducted with Adacel vaccine. The effect of Adacel vaccine on embryo-fetal and pre-weaning development was evaluated in two developmental toxicity studies using pregnant rabbits. Animals were administered Adacel vaccine twice prior to gestation, during the period of organogenesis (gestation day 6) and later during pregnancy on gestation day 29, 0.5 mL/rabbit/occasion (a 17-fold increase compared to the human dose of Adacel vaccine on a body weight basis), by intramuscular injection. No adverse effects on pregnancy, parturition, lactation, embryo-fetal or pre-weaning development were observed. There were no vaccine related fetal malformations or other evidence of teratogenesis noted in this study. (7)

Nursing Mothers It is not known whether Adacel vaccine is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Adacel vaccine is given to a nursing woman.

Pediatric Use Adacel vaccine is not indicated for individuals less than 11 years of age. (See **INDICATIONS AND USAGE**.) For immunization of persons 6 weeks through 6 years of age against diphtheria, tetanus and pertussis refer to manufacturers' package inserts for DTap vaccines.

Geriatric Use Adacel vaccine is not indicated for individuals 65 years of age and older. No data are available regarding the safety and effectiveness of Adacel vaccine in individuals 65 years of age and older as clinical studies of Adacel vaccine did not include participants in the geriatric population.

ADVERSE REACTIONS The safety of Adacel vaccine was evaluated in 4 clinical studies. A total of 5,841 individuals 11-64 years of age inclusive (3,393 adolescents 11-17 years of age and 2,448 adults 18-64 years) received a single dose of Adacel vaccine. The principal safety study was a randomized, observer-blind, active controlled trial that enrolled participants 11-17 years of age (Adacel vaccine N = 1,184; Td vaccine N = 792) and 18-64 years of age (Adacel vaccine N = 1,752; Td vaccine N = 573). Study participants had not received tetanus or diphtheria containing vaccines within the previous 5 years. Solicited local and systemic reactions and unsolicited adverse events were monitored daily for 14 days post-vaccination using a diary card. From days 14-28 post-vaccination, information on adverse events necessitating a medical contact, such as a telephone call, visit to an emergency room, physician's office or hospitalization, was obtained via telephone interview or an interim clinic visit. From days 28 to 6 months post-vaccination, participants were monitored for unexpected visits to a physician's office or to an emergency room, onset of serious illness and hospitalizations. Information regarding adverse events that occurred in the 6 month post-vaccination time period was obtained from the participant via telephone. Approximately 96% of participants completed the 6-month follow-up evaluation. In the concomitant vaccination study with Adacel and Hepatitis B vaccines, local and systemic adverse events were monitored daily for 14 days post-vaccination using a diary card. Local adverse events were only monitored at site/arm of Adacel vaccine administration. Unsolicited reactions (including immediate reactions, serious adverse events and events that elicited seeking medical attention) were collected at a clinic visit or via telephone interview for the duration of the trial, i.e., up to six months post-vaccination. In the concomitant vaccination study with Adacel vaccine and trivalent inactivated influenza vaccine, local and systemic adverse events were monitored for 14 days post-vaccination using a diary card. All unsolicited reactions occurring through day 14 were collected. From day 14 to the end of the trial, i.e., up to 84 days, only events that elicited seeking medical attention were collected. In all the studies, participants were monitored for serious adverse events throughout the duration of the study. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a vaccine cannot be directly compared to rates in the clinical trials of another vaccine and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to vaccine use and for approximating rates of those events.

Serious Adverse Events in All Safety Studies Throughout the 6-month follow-up period in the principal safety study, serious adverse events were reported in 1.5% of Adacel vaccine recipients and 1.4% in Td vaccine recipients. Two serious adverse events in adults were neuropathic events that occurred within 28 days of Adacel vaccine administration; one severe migraine with unilateral facial paralysis and one diagnosis of nerve compression in neck and left arm. Similar or lower rates of serious adverse events were reported in the other trials and there were no additional neuropathic events reported.

Solicited Adverse Events in the Principal Safety Study Most selected solicited adverse events (erythema, swelling, pain and fever) that occurred during Days 0-14 following one dose of Adacel vaccine or Td vaccine were reported at a similar frequency. Few participants

($<1\%$) sought medical attention for these reactions. Pain at the injection site was the most common adverse reaction occurring in 63 to 78% of all vaccinees. In addition, overall rates of pain were higher in adolescent recipients of Adacel vaccine compared to Td vaccine recipients. Rates of moderate and severe pain in adolescents did not significantly differ between the Adacel vaccine and Td vaccine groups. Among adults the rates of pain, after receipt of Adacel vaccine or Td vaccine, did not significantly differ. Fever of 38°C and higher was uncommon, although in the adolescent age group, it occurred significantly more frequently in Adacel vaccine recipients than Td vaccine recipients. (7) Among other solicited adverse events headache was the most frequent systemic reaction and was usually of mild to moderate intensity. In general, the rates of the events following Adacel vaccine were comparable with those observed with Td vaccine. Local and systemic solicited reactions occurred at similar rates in Adacel vaccine and Td vaccine recipients in the 3 day post-vaccination period. Most local reactions occurred within the first 3 days after vaccination (with a mean duration of less than 3 days). The rates of unsolicited adverse events reported from days 14-28 post-vaccination were comparable between the two groups, as were the rates of unsolicited adverse events from day 28 through 6 months. There were no spontaneous reports of whole-arm swelling of the injected limb in this study, nor in the other three studies which contributed to the safety database for Adacel vaccine.

Adverse Events in the Concomitant Vaccine Studies

Local and Systemic Reactions when Given with Hepatitis B Vaccine The rates reported for fever and injection site pain (at the Adacel vaccine administration site) were similar when Adacel and Hep B vaccines were given concurrently or separately. However, the rates of injection site erythema (23.4% for concomitant vaccination and 21.4% for separate administration) and swelling (23.9% for concomitant vaccination and 17.9% for separate administration) at the Adacel vaccine administration site were increased when co-administered. Swollen and/or sore joints were reported by 22.5% for separate administration and 17.9% for separate administration. The rates of generalized body aches in the individuals who reported swollen and/or sore joints were 86.7% for concomitant vaccination and 72.2% for separate administration. Most joint complaints were mild in intensity with a mean duration of 1.8 days. The incidence of other solicited and unsolicited adverse events were not different between the 2 study groups. (7)

Local and Systemic Reactions when Given with Trivalent Inactivated Influenza Vaccine The rates of fever and injection site erythema and swelling were similar for recipients of concurrent and separate administration of Adacel vaccine and TIV. However, pain at the Adacel vaccine injection site occurred at statistically higher rates following concurrent administration (66.6%) versus separate administration (60.8%). The rates of sore and/or swollen joints were 13% for concurrent administration and 9% for separate administration. Most joint complaints were mild in intensity with a mean duration of 2.0 days. The incidence of other solicited and unsolicited adverse events were similar between the 2 study groups. (7)

Additional Studies An additional 1,806 adolescents received Adacel vaccine as part of the lot consistency study used to support Adacel vaccine licensure. This study was a randomized, double-blind, multi-center trial designed to assess lot consistency as measured by the safety and immunogenicity of 3 lots of Adacel vaccine when given as a booster dose to adolescents 11-17 years of age inclusive. Local and systemic adverse events were monitored for 14 days post-vaccination using a diary card. Unsolicited adverse events and serious adverse events were collected for 28 days post-vaccination. Pain was the most frequently reported local adverse event occurring in approximately 80% of all participants. Headache was the most frequently reported systemic event occurring in approximately 44% of all participants. Sore and/or swollen joints were reported by approximately 14% of participants. Most joint complaints were mild in intensity with a mean duration of 2.0 days. (7) An additional 962 adolescents and adults received Adacel vaccine in three supportive Canadian studies used as the basis for licensure in other countries. Within these clinical trials, the rates of local and systemic reactions following Adacel vaccine were similar to those reported in the four principal trials in the US with the exception of a higher rate (86%) of adults experiencing any local injection site pain. The rate of severe pain (0.8%), however, was comparable to the rates reported in four principal trials conducted in the US. (7) There was one spontaneous report of whole-arm swelling of the injected limb among the 277 Td vaccine recipients, and two spontaneous reports among the 962 Adacel vaccine recipients in the supportive Canadian studies.

Postmarketing Reports The following adverse events have been spontaneously reported during the post-marketing use of Adacel vaccine in the US and other countries. Because these events are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to vaccine exposure. The following adverse events were included based on severity, frequency of reporting or the strength of causal association to Adacel vaccine. *General disorders and administration site conditions:* Large injection site reactions (>50 mm), extensive limb swelling from the injection site beyond one or both joints. *Injection site bruising, sterile abscess. Nervous system disorders:* Paraesthesia, hypoesthesia, Guillain-Barré syndrome, facial palsy, convulsion, syncope, myelitis. *Immune system disorders:* Anaphylactic reaction, hypersensitivity reaction (angioedema, edema, rash, hypotension) *Skin and subcutaneous tissue disorders:* Pruritus, urticaria. *Musculoskeletal and connective tissue disorders:* Myositis, muscle spasm. *Cardiac disorders:* Myocarditis.

Additional Adverse Events Additional adverse events, included in this section, have been reported in conjunction with receipt of vaccines containing diphtheria, tetanus toxoids and/or pertussis antigens. Arthus-type hypersensitivity reactions, characterized by severe local reactions (generally starting 2-8 hours after an injection), may follow receipt of tetanus toxoid. Such reactions may be associated with high levels of circulating antitoxin in persons who have had overly frequent injections of tetanus toxoid. (8) (See **WARNINGS**.) Persistent nodules at the site of injection have been reported following the use of adsorbed products. (4) Certain neurological conditions have been reported in temporal association with some tetanus toxoid containing vaccines or tetanus and diphtheria toxoid containing vaccines. A review by the Institute of Medicine (IOM) concluded that the evidence favors acceptance of a causal relation between tetanus toxoid and both brachial neuritis and Guillain-Barré syndrome. Other neurological conditions that have been reported include: demyelinating diseases of the central nervous system, peripheral mononeuropathies, and cranial mononeuropathies. The IOM has concluded that the evidence is inadequate to accept or reject a causal relation between these conditions and vaccines containing tetanus and/or diphtheria toxoids.

Reporting of Adverse Events The National Vaccine Injury Compensation Program, established by the National Childhood Vaccine Injury Act of 1986, requires physicians and other health-care providers who administer vaccines to maintain permanent vaccination records of the manufacturer and lot number of the vaccine administered in the vaccine recipient's permanent medical record along with the date of administration of the vaccine and the name, address and title of the person administering the vaccine. The Act further requires the health-care professional to report to the US Department of Health and Human Services the occurrence following immunization of any event set forth in the Vaccine Injury Table. These include: anaphylaxis or anaphylactic shock within 7 days; brachial neuritis within 28 days; an acute complication or sequelae (including death) of an illness, disability, injury, or condition referred to above, or any events that would contraindicate further doses of vaccine, according to this Adacel vaccine package insert. (9-11) The US Department of Health and Human Services has established the Vaccine Adverse Event Reporting System (VAERS) to accept all reports of suspected adverse events after the administration of any vaccine. Reporting of all adverse events occurring after vaccine administration is encouraged from vaccine recipients, parents/guardians and the health-care provider. Adverse events following immunization should be reported to VAERS. Reporting forms and information about reporting requirements or completion of the form can be obtained from VAERS through a toll-free number 1-800-822-7967 or visit the VAERS website at www.vaers.hhs.gov. (9-11) Health-care providers should also report these events to Sanofi Pasteur Inc., Discovery Drive, Swiftwater, PA 18370 or call 1-800-822-2463 (1-800-VACCINE).

DOSAGE AND ADMINISTRATION Adacel vaccine should be administered as a single injection of one dose (0.5 mL) by the intramuscular route. Adacel vaccine should not be combined through reconstitution or mixed with any other vaccine. Just before use, shake the vial well until a uniform, white, cloudy suspension results. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If these conditions exist, the vaccine should not be administered. When administering a dose from a rubber-stoppered vial, do not remove either the stopper or the metal seal holding it in place. The preferred site is into the deltoid muscle. The vaccine should not be injected into the gluteal area or areas where there is a major nerve trunk. Do NOT administer this product intravenously or subcutaneously. Five years should have elapsed since the recipient's last dose of tetanus toxoid, diphtheria toxoid and/or pertussis containing vaccine. There are no data to support repeat administration of Adacel vaccine. The use of Adacel vaccine as a primary series or to complete the primary series for tetanus, diphtheria, or pertussis has not been studied.

STORAGE Store at 2° to 8°C (35° to 46°F). DO NOT FREEZE. Product which has been exposed to freezing should not be used. Do not use after expiration date.

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Women with any breastfeeding had a lower prevalence of osteoporosis than women who did not breastfeed.

DR. SCHNATZ

the researchers. “It would seem that breastfeeding, which requires acquisition of calcium from the mother to nourish the baby, would cause bone loss,” Dr. Schnatz said. “We wonder if there may be a rebound anabolic phenomenon, hence resulting in overall benefit.”

Within the group of women who breastfed, those who were younger than age 27 years at their first pregnancy had a significantly higher prevalence of osteoporosis, compared with those who were 27 years of age and older at their first pregnancy (11% vs. 5%), he reported.

Of the women who were at least 27 years old at first pregnancy, there was a significantly increased prevalence of osteoporosis in those who did not breastfeed, compared with those who did (25% vs. 5%).

Women who were at least 27 years old at their first pregnancy and who breastfed had a statistically lower prevalence of osteoporosis, compared with their counterparts who had their first pregnancy when they were younger than age 27 and who had no history of breastfeeding (5% vs. 16%).

Among women who did not breastfeed, there was little difference in the risk of postmenopausal osteoporosis if the first pregnancy occurred at or after age 22 or 27 years, Dr. Schnatz wrote.

“Based on the current evidence, along with these results, women should be encouraged to wait until the postadolescent years for childbearing and should be encouraged to breastfeed,” he concluded.

Dr. Schnatz acknowledged certain limitations of the study, including its retrospective design.

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