

# Sleep Apnea Linked to Hypertension in Pregnancy

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SAN FRANCISCO — Pregnant women who have obstructive sleep apnea have a 2.3-fold increased risk of gestational diabetes and a 4.2-fold increased risk of pregnancy-induced hypertension, compared with women without the sleep disorder, according to a poster presentation at the International Conference of the American Thoracic Society.

Previous research has suggested that obstructive sleep apnea (OSA) may induce systemic hypertension and diabetes mellitus in the general population, but the connection was much less clear in pregnant women, investigator Dr. Michael S. Nolleto of the Robert Wood Johnson Medical School, Princeton, N.J., said in a press briefing.

“A lot of times for patients who are pregnant and for ob.gyns., sleep-disordered breathing is not on the radar

screen,” he said. When a woman who is pregnant goes to see her obstetrician, the physician asks a zillion things but almost never inquires about risk factors for sleep apnea.

Dr. Nolleto suggested that physicians dealing with women with gestational diabetes or pregnancy-induced hypertension (PIH) should inquire about sleep-disordered breathing, especially because OSA is so simple to treat with continuous positive airway pressure (CPAP).

“It may be a condition that you need treatment for just for the time you’re carrying your baby,” Dr. Nolleto commented. “Once you deliver, the sleep apnea may resolve.”

Dr. Nolleto acknowledged, however, that his study contains no direct evidence that treating sleep apnea will improve PIH or gestational diabetes.

The study relied on data from the 2003 National Inpatient Sample, sponsored by the Agency for Healthcare Research and Quality.

This large database includes all inpatient records from a sample of about 20% of U.S. community short-stay hospitals and provides weights to calculate national estimates.

Using this database, the investigators calculated that there were 3,979,840 deliveries in the United States in 2003, of which 167,227 were complicated by gestational diabetes and 300,902 were complicated by PIH.

The overall rate of sleep apnea for these women was 1.14/10,000—but that rate was 4.01/10,000 among women with gestational diabetes and 5.52/10,000 among women with PIH.

When controlled for age and race, women with sleep apnea were 3.5 times more likely to develop gestational diabetes; when controlled for obesity, the odds ratio was still 2.3.

Similarly, the odds ratio for PIH in women with sleep apnea was 6.6 when controlling for age and race, and 4.2 after also controlling for obesity.

In an interview, Dr. Nolleto acknowledged that the overall rate of OSA recorded in the database—just over 1/10,000, or 0.01%—is much lower than the 2%-4% rate of OSA estimated for the general population.

He attributed this in part to the fact that physicians often don’t think to ask their pregnant patients about sleep-disordered breathing.

An alternative explanation for the results is that physicians may ask about sleep-disordered breathing more frequently when faced with patients with gestational diabetes or PIH, he said, and that this alone can account for the apparent increases in risk.

## TWINRIX® [Hepatitis A Inactivated & Hepatitis B (Recombinant) Vaccine]

The following is a brief summary only; see full prescribing information for complete product information.

**INDICATIONS AND USAGE:** TWINRIX is indicated for active immunization of persons 18 years of age or older against disease caused by hepatitis A virus and infection by all known subtypes of hepatitis B virus.

**CONTRAINDICATIONS:** Hypersensitivity to any component of the vaccine, including yeast and neomycin, is a contraindication (see DESCRIPTION in full prescribing information). This vaccine is contraindicated in patients with previous hypersensitivity to TWINRIX or monovalent hepatitis A or hepatitis B vaccines.

**WARNINGS:** There have been rare reports of anaphylaxis/anaphylactoid reactions following routine clinical use of TWINRIX. (See ADVERSE REACTIONS, Postmarketing Reports.) The tip cap and the rubber plunger of the needleless prefilled syringes contain dry natural latex rubber that may cause allergic reactions in latex sensitive individuals. The vial stopper is latex free. Hepatitis A and hepatitis B have relatively long incubation periods. TWINRIX may not prevent hepatitis A or hepatitis B infection in individuals who have an unrecognized hepatitis A or hepatitis B infection at the time of vaccination. Additionally, it may not prevent infection in individuals who do not achieve protective antibody titers.

**PRECAUTIONS: General:** Prior to immunization with TWINRIX, the patient’s current health status and medical history should be reviewed. The physician should review the patient’s immunization history for possible vaccine sensitivity, previous vaccination-related adverse reactions and occurrence of any adverse-event-related symptoms and/or signs, in order to determine the existence of any contraindication to immunization with TWINRIX and to allow an assessment of benefits and risks. Appropriate medical treatment and supervision should be readily available for immediate use in case of a rare anaphylactic reaction following the administration of the vaccine. Epinephrine injection (1:1,000) and other appropriate agents used for the control of immediate allergic reactions must be immediately available. As with other vaccines, delay administration, if possible, in persons with a moderate or severe acute illness. Minor illnesses such as mild upper respiratory infections with or without low grade fever are not contraindications. TWINRIX should be given with caution in persons with bleeding disorders such as hemophilia or thrombocytopenia and in persons on anticoagulant therapy, with steps taken to avoid the risk of hematoma following the injection. A separate, sterile syringe and needle or a sterile disposable unit should be used for each patient to prevent the transmission of other infectious agents from person to person. Needles should be disposed of properly and should not be recapped. As with any vaccine, if administered to immunosuppressed persons, including individuals receiving immunosuppressive therapy, the expected immune response may not be obtained.

**Multiple Sclerosis:** Results from 2 clinical studies indicate that there is no association between hepatitis B vaccination and the development of multiple sclerosis, and that vaccination with hepatitis B vaccine does not appear to increase the short-term risk of relapse in multiple sclerosis.

**Information for Vaccine Recipients:** Vaccine recipients should be informed by their healthcare provider of the potential benefits and risks of immunization with TWINRIX. When educating vaccine recipients regarding potential side effects, clinicians should emphasize that components of TWINRIX cannot cause hepatitis A or hepatitis B infection. Vaccine recipients should be instructed to report any severe or unusual adverse reactions to their healthcare provider. The vaccine recipients should be given the Vaccine Information Statements, which are required by the National Childhood Vaccine Injury Act of 1986 to be given prior to immunization. These materials are available free of charge at the CDC website ([www.cdc.gov/nip](http://www.cdc.gov/nip)). The Vaccine Adverse Events Reporting System (VAERS) toll-free number is 1-800-822-7967. Reporting forms may also be obtained at the VAERS website at [www.vaers.hhs.gov](http://www.vaers.hhs.gov).

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** TWINRIX has not been evaluated for its carcinogenic potential, mutagenic potential, or potential for impairment of fertility. **Pregnancy:** Pregnancy Category C: Animal reproduction studies have not been conducted with TWINRIX. It is also not known whether TWINRIX can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. TWINRIX should be given to a pregnant woman only if clearly indicated (see INDICATIONS AND USAGE). **Pregnancy Exposure Registry:** Healthcare providers are encouraged to register pregnant women who receive TWINRIX in the GlaxoSmithKline vaccination pregnancy registry by calling 1-888-825-5249. **Nursing Mothers:** It is not known whether TWINRIX is excreted in human milk. Because many drugs are excreted in human milk, use caution when administering TWINRIX to a nursing woman. **Pediatric Use:** Safety and effectiveness in pediatric patients below the age of 18 years have not been established. **Geriatric Use:** Clinical studies of TWINRIX did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

Table 1. Rate of Adverse Events Reported After Administration of TWINRIX or ENGERIX-B and HAVRIX

Adverse Event	TWINRIX			ENGERIX-B			HAVRIX	
	Dose 1 (N=385) %	Dose 2 (N=382) %	Dose 3 (N=374) %	Dose 1 (N=382) %	Dose 2 (N=376) %	Dose 3 (N=369) %	Dose 1 (N=382) %	Dose 2 (N=369) %
Local								
Soreness	37	35	41	41	25	30	53	47
Redness	8	9	11	6	7	9	7	9
Swelling	4	4	6	3	5	5	5	5
General								
Headache	22	15	13	19	12	14		
Fatigue	14	13	11	14	9	10		
Diarrhea	5	4	6	5	3	3		
Nausea	4	3	2	7	3	5		
Fever	4	3	2	4	2	4		
Vomiting	1	1	0	1	1	1		

**ADVERSE REACTIONS:** Because clinical trials are conducted under widely varying conditions, adverse event 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. As with any vaccine, there is the possibility that broad use of TWINRIX could reveal adverse events not observed in clinical trials. The safety of TWINRIX has been evaluated in clinical trials involving the administration of approximately 7,500 doses to more than 2,500 individuals. Of 773 volunteers who participated in a US comparative trial, 389 subjects received at least 1 dose of TWINRIX (0-, 1-, and 6-month schedule) and 384 received at least 1 dose each of ENGERIX-B® [Hepatitis B Vaccine (Recombinant)] and HAVRIX® (Hepatitis A Vaccine, Inactivated) as separate injections. Solicited local adverse events reported after administration of TWINRIX, compared with adverse events reported after the administration of ENGERIX-B or HAVRIX, are shown in the table above.

Adverse reactions seen with TWINRIX were similar to those observed after vaccination with the monovalent components. The frequency of solicited adverse events did not increase with successive doses of TWINRIX. Most events reported were considered by the subjects as mild and self-limiting and did not last more than 48 hours. In a clinical trial in which TWINRIX was given on a 0-, 7-, and 21- to 30-day schedule followed by a booster dose at 12 months, solicited local or general adverse events were comparable to those seen in other clinical trials of TWINRIX given on a 0-, 1-, and 6-month schedule. Among 2,299 subjects in 14 clinical trials, the following adverse experiences were reported to occur within 30 days following vaccination with the frequency shown below. Adverse experiences within 30 days of vaccination in the US clinical trial of TWINRIX given on a 0-, 7-, and 21- to 30-day schedule followed by a booster dose at 12 months were similar to those reported in other clinical trials and post marketing surveillance.

**Incidence 1% to 10% of Injections: Local Reactions at Injection Site:** Induration. **Respiratory System:** Upper respiratory tract infections.

**Incidence <1% of Injections: Local Reactions at Injection Site:** Pruritus, ecchymoses. **Body as a Whole:** Sweating, weakness, flushing, influenza-like symptoms. **Cardiovascular System:** Syncope. **Gastrointestinal System:** Abdominal pain, anorexia, vomiting. **Musculoskeletal System:** Arthralgia, myalgia, back pain. **Nervous System:** Migraine, paresthesia, vertigo, somnolence, insomnia, irritability, agitation, dizziness. **Respiratory System:** Respiratory tract illnesses. **Skin and Appendages:** Rash, urticaria, petechiae, erythema.

**Incidence <1% of Injections, Seen in Clinical Trials With HAVRIX® and/or ENGERIX-B®: Body as a Whole:** Tingling. **Cardiovascular System:** Hypotension. **Gastrointestinal:** Constipation, dysgeusia. **Hematologic/Lymphatic:** Lymphadenopathy. **Musculoskeletal System:** Elevation of creatine phosphokinase. **Nervous System:** Hypertonic episode, photophobia.

**Postmarketing Reports:** Worldwide voluntary reports of adverse events received for TWINRIX, HAVRIX, and/or ENGERIX-B since market introduction of these vaccines are listed below. These lists include serious events or events which have suspected causal connections to components of these or other vaccines or drugs. 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.

**Postmarketing Reports With TWINRIX: Body as a Whole:** Anaphylaxis/anaphylactoid reactions and allergic reactions. **Hypersensitivity:** Arthritis, serum sickness-like syndrome days to weeks after vaccination including arthralgia/arthritis (usually transient), fever, urticaria, erythema multiforme, ecchymoses, and erythema nodosum. **Cardiovascular System:** Tachycardia/palpitations. **Skin and Appendages:** Erythema multiforme, hyperhidrosis, angioedema, eczema, herpes zoster, erythema nodosum, alopecia. **Gastrointestinal System:** Jaundice, hepatitis, abnormal liver function tests, dyspepsia. **Hematologic/Lymphatic:** Thrombocytopenia. **Nervous System:** Convulsions, paresis, encephalopathy, neuropathy, myelitis, Guillain-Barré syndrome, multiple sclerosis, Bell’s palsy, transverse myelitis, optic neuritis. **Respiratory System:** Dyspnea, bronchospasm including asthma like symptoms. **Special Senses:** Conjunctivitis, visual disturbances, tinnitus, earache.

**Postmarketing Reports With HAVRIX and/or ENGERIX-B:** Worldwide voluntary reports of adverse events received for HAVRIX and/or ENGERIX-B but not already reported for TWINRIX are listed below. **Hypersensitivity:** Stevens-Johnson syndrome. **Special Senses:** Keratitis. **Other:** Congenital abnormality.

\*Following HAVRIX; †Following ENGERIX-B; ‡Following either HAVRIX or ENGERIX-B.


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Reference: 1. Connor BA, Blatter MM, Beran J, Zou B, Traft AF. Rapid and sustained immune response against hepatitis A and B achieved with combined vaccine using an accelerated administration schedule. *J Travel Med.* 2007;14:9-15.

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# Ob.Gyn. News

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