

# Lifestyle Change First-Line Tx in PCOS Infertility

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TORONTO — Lifestyle treatment should be the first-line therapy for the management of fertility in obese women with polycystic ovary syndrome, according to a consensus panel of the American Society for Reproductive Medicine and the European Society for Human Reproduction.

The consensus finding is based on a review of the evidence conducted in March.

This effort was part of a comprehensive review of all infertility treatment in PCOS, the results of which will be forthcoming in the near future, Dr. Kathy Hoeger said at the annual meeting of the Androgen Excess Society.

The available studies suggest that lifestyle interventions that lead to modest weight loss can improve ovulatory function in overweight women with polycystic ovary syndrome, said Dr. Hoeger, of the department of obstetrics and gynecology at the University of Rochester (N.Y.) and a participant in the March consensus meeting.

However, further study is needed on the effect of weight reduction and exercise on live-birth rates, she said. More research is also needed on the appropriate time frame for weight reduction prior to conception.

The general literature shows that lifestyle change is effective for metabolic improvement, but there are no large randomized trials for effect on ovulation in-

duction or restoration of menstrual function. All studies published to date, however, support an improvement in reproductive function with lifestyle change in women with PCOS, she said.

Among the smaller studies that have focused on reproductive outcomes, the findings suggest that modest weight loss—about 5%-10%—can improve reproductive status. "This degree of weight loss does not generally put people into a normal [body mass index] range," Dr. Hoeger said.

For example, in a nonrandomized study of 67 obese and anovulatory women who were offered an intensive lifestyle intervention over 6 months, there was an overall 9% reduction in starting weight, and 60 of the women resumed spontaneous ovulation. Also, 52 of the women achieved pregnancy, 18 of those spontaneously. Of the 67 women in the study, 45 achieved a live birth (Hum. Reprod. 1998;13:1502-5). In another small study, 9 of 18 women became regular ovulators following a 6-month individualized diet and exercise program. The study included infertile, anovulatory obese women with PCOS. The mean weight loss was less than in the earlier study, about 2%-5%. Resuming ovulation was closely linked with improved insulin sensitivity and reduced percentage of central body fat (J. Clin. Endocrinol. Metab. 1999;84:1470-4).

Some studies have also compared the use of diet and exercise interventions with metformin in stimulating the return of ovulation. For example, Dr. Hoeger conducted a small pilot study of 38 overweight and obese women with PCOS. The women were randomized to receive metformin, or lifestyle change plus metformin, or lifestyle change plus placebo, or placebo alone (Fertil. Steril. 2004;82:421-9).

All groups achieved at least some weight reduction, with the most weight loss occurring among the women who received both metformin and the lifestyle intervention. Ovulation rates were not significantly different among the four groups. However, an analysis of the data suggests that weight reduction likely plays a more significant role than does metformin in the resumption of ovulation, Dr. Hoeger said.

Larger studies are still needed to fill in some of the blanks surrounding fertility treatment in obese women with PCOS, Dr. Hoeger said. In the meantime, clinicians must face the pitfalls of implementing a successful lifestyle intervention. These programs can be hard to maintain because of high dropout rates, and they are expensive to perform in a clinical setting. It's also unclear whether modest weight changes can be maintained over time, as the longest trial examining lifestyle change in PCOS followed patients for 48 weeks, she said.

## 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). 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.

**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	Dose 2	Dose 3	Dose 1	Dose 2	Dose 3	Dose 1	Dose 2
<b>Local</b>	(N=385)	(N=382)	(N=374)	(N=382)	(N=376)	(N=369)	(N=382)	(N=369)
	%	%	%	%	%	%	%	%
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
<b>General</b>	TWINRIX			ENGERIX-B and HAVRIX				
	Dose 1	Dose 2	Dose 3	Dose 1	Dose 2	Dose 3		
	(N=385)	(N=382)	(N=374)	(N=382)	(N=376)	(N=369)		
	%	%	%	%	%	%		
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.<sup>b</sup> **Cardiovascular System:** Hypotension.<sup>b</sup> **Gastrointestinal:** Constipation,<sup>b</sup> dysgeusia.<sup>a</sup> **Hematologic/lymphatic:** Lymphadenopathy.<sup>\*\*b</sup> **Musculoskeletal System:** Elevation of creatine phosphokinase.<sup>a</sup> **Nervous System:** Hypertonic episode,<sup>a</sup> photophobia.<sup>a</sup>

**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.<sup>b</sup> **Special Senses:** Keratitis.<sup>b</sup> **Other:** Congenital abnormality.<sup>a</sup>

<sup>a</sup>Following HAVRIX; <sup>b</sup>Following ENGERIX-B; <sup>\*\*b</sup>Following either HAVRIX or ENGERIX-B.

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Reference: 1. Connor BA, Blatter MM, Beran J, Zou B, Trofa 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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