

Postpartum Thyroiditis Presents Dx Challenges

BY KERRI WACHTER

EXPERT OPINION FROM A MEETING SPONSORED BY THE AMERICAN THYROID ASSOCIATION

MINNEAPOLIS — In classic-course postpartum thyroiditis, the hyperthyroid phase is often missed, and it's much more common to identify women in the hypothyroid phase that follows, Dr. Erin Keely said.

"In my experience we miss the hyper-

thyroid phase clinically all the time because it's a little bit like the army—don't ask, don't tell," she said. The symptoms— anxiety, insomnia, fatigue, weight loss, and irritability—are normal for most new moms. The classic course of postpartum thyroiditis (PPT) is hyperthyroidism—which starts at about 6 weeks post partum and may last a few months—followed by hypothyroidism and then normalization.

More commonly, women present in the hypothyroid phase, which typically occurs 4-8 months after delivery and may last up to 9-12 months, said Dr. Keely, chief of endocrinology and metabolism at the Ottawa Hospital. Typical symptoms include fatigue, weight gain, constipation, dry skin, depression, and poor exercise tolerance. Women tested in the transition period might appear to have normal thyroid function,

however. About 30% of women remain hyperthyroid.

However, because PPT can cause both thyrotoxicosis (high thyroid hormone levels in the blood) and hypothyroidism (low thyroid hormone levels in the blood) in the first year post partum, "you can't make a diagnosis of permanent thyroid disease" at that time, said Dr. Keely.

The exception is for any woman with overt thyroid disease before pregnancy.

To complicate matters, Graves' disease can flare in the postpartum period, making it difficult to tell if a woman is having a flare or PPT. However, Graves' disease is much less common than postpartum thyroiditis, said Dr. Keely. "So, if you were a betting person, you would bet that it's postpartum thyroiditis."

If the diagnosis is really unclear, radioiodine uptake tests can be performed but most women will likely choose to wait and see, she said.

There are insufficient data currently to recommend screening all women for PPT, according to clinical guidelines from the Endocrine Society (J. Clin. Endocrinol. Metab. 2007;92:s1-s47 [doi:10.1210/jc.2007-0141]). Women who are known to be positive for autoantibodies to thyroid peroxidase (TPO-Ab) should have a thyroid-stimulating hormone (TSH) test performed at 3 and 6 months post partum.

Notably, the prevalence of PPT in women with type 1 diabetes is threefold greater than in the general population; postpartum screening (TSH test) is recommended for these women at 3 and 6 months post partum.

When it comes to treating PPT, "there is no one answer for all women," said Dr. Keely. However, in 2002, Dr. Alex S. Stagnaro-Green, now the senior associate dean for education at George Washington University, Washington, proposed a treatment algorithm for PPT (J. Clin. Endocrinol. Metab. 2002;87:4042-7).

In this algorithm, treatment is indicated for a TSH level of 4 mU/mL or greater in the first year post partum.

Dr. Keely added that "one of the most important aspects is to continue the treatment until [the woman] has completed her family."

If autoantibodies to thyroid peroxidase (TPO-Ab) are found in the first trimester, there is a 30%-55% risk of PPT. "It's interesting though, that 25% of women who are positive in the first trimester become negative by the third trimester," she said.

Women may become negative for TPO-Ab by term but will rebound in the postpartum period. If TPO-Ab is positive in the third trimester, the risk of PPT is greater than 80%—but if negative the risk is only 0%-5%.

Importantly, "postpartum thyroiditis is a very strong predictor of long-term Hashimoto's thyroiditis," said Dr. Keely. About 30% of these women develop Hashimoto's thyroiditis within 3 years.

Dr. Keely reported that she had no relevant financial relationships. ■

Fluzone® High-Dose Influenza Virus Vaccine 2010-2011 Formula

Rx only

BRIEF SUMMARY: Please consult package insert for full prescribing information.

INDICATIONS AND USAGE

Fluzone High-Dose is an inactivated influenza virus vaccine indicated for active immunization of persons 65 years of age and older against influenza disease caused by influenza virus subtypes A and type B contained in the vaccine. This indication is based on the immune response elicited by Fluzone High-Dose; there have been no controlled clinical studies demonstrating a decrease in influenza disease after vaccination with Fluzone High-Dose.

DOSE AND ADMINISTRATION

Dosage and Schedule

Basic dosing information for Fluzone High-Dose, and its respective age indication, is presented in Table 1.

Table 1: Fluzone High-Dose

Any vaccination status	Dose/Route	Schedule
65 years and older	0.5 mL/ Intramuscular	1 dose

Administration

Inspect Fluzone High-Dose syringes visually for particulate matter and/or discoloration prior to administration. If either of these conditions exist, the vaccine should not be administered. Shake the syringe before administering the vaccine. The vaccine should not be injected into the gluteal region or into areas where there may be a major nerve trunk. For needle length, refer to the Advisory Committee on Immunization Practices (ACIP) recommendations.* If Fluzone High-Dose is to be given at the same time as another injectable vaccine(s), the vaccine(s) should always be administered at separate injection sites.

Adults 65 years of age and older

Fluzone High-Dose should be administered as a single intramuscular dose preferably in the deltoid muscle.

DOSEAGE FORMS AND STRENGTHS

Fluzone High-Dose

Sterile suspension for intramuscular injection supplied in prefilled syringes, 0.5 mL, for adults 65 years of age and older, distinguished by a gray syringe plunger rod. Each 0.5 mL dose of Fluzone High-Dose contains influenza split virus antigens that are formulated to contain a total of 180 mcg of influenza virus hemagglutinin, 60 mcg each from the 3 influenza virus strains in the vaccine.

CONTRAINDICATIONS

Do not administer Fluzone High-Dose to anyone with a known hypersensitivity to egg proteins or any component of the vaccine, or life-threatening reactions after previous administration of any influenza vaccine.

WARNINGS AND PRECAUTIONS

Guillain-Barré Syndrome

If Guillain-Barré syndrome (GBS) has occurred within 6 weeks of previous influenza vaccination, the decision to give Fluzone High-Dose should be based on careful consideration of the potential benefits and risks.

Altered Immunocompetence

If Fluzone High-Dose is administered to immunocompromised persons, including those receiving immunosuppressive therapy, the immune response may be diminished.

Preventing and Managing Allergic Reactions

Appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following administration of the vaccine. The tip caps of the Fluzone High-Dose prefilled syringes may contain natural rubber latex which may cause allergic reactions in latex sensitive individuals.

Limitations of Vaccine Effectiveness

Vaccination with Fluzone High-Dose may not protect all recipients.

ADVERSE REACTIONS

Clinical Trial Experience

Fluzone High-Dose

A total of 3,876 individuals 65 years of age and older were randomized to receive either Fluzone High-Dose or Fluzone in a phase 3, multi-center, active-controlled, double-blind trial conducted in the US. The safety analysis set included 2,573 Fluzone High-Dose recipients and 1,260 Fluzone recipients.

Table 2 summarizes solicited injection site and systemic adverse events collected within 7 days post vaccination via diary cards. Onset was usually within the first 3 days after vaccination and majority of the reactions resolved within 3 days.

Table 2: Frequency of Solicited Injection Site and Systemic Adverse Events within 7 Days Post-Vaccination

	Fluzone High-Dose (N=2573) Percent	Fluzone (N=1260) Percent
Injection site reactions		
Pain	35.6	24.3
Erythema	14.9	10.8
Swelling	8.9	5.8
Systemic adverse events		
Myalgia	21.4	18.3
Malaise	18.0	14.0
Headache	16.8	14.4
Fever	3.6	2.3

*N is the number of subjects in the Safety Analysis Set.

Solicited injection site reactions and systemic adverse events were more frequent after vaccination with Fluzone High-Dose compared to standard Fluzone in adults 65 years of age and older.

Table 3 summarizes the severity of solicited adverse events that occurred during the first week after vaccination*:

Table 3: Frequency and Severity of Solicited Injection Site and Systemic Adverse Events within 7 Days Post-Vaccination

	Fluzone High-Dose (N=2573) Percent	Fluzone (N=1260) Percent
Injection Site Pain		
Mild	31.5	22.5
Moderate	3.7	1.7
Severe	0.3	0.2
Injection Site Erythema		
Mild	11.3	9.4
Moderate	1.9	0.8
Severe	1.8	0.6
Injection Site Swelling		
Mild	5.8	3.9
Moderate	1.6	1.3
Severe	1.5	0.6
Myalgia		
Mild	15.6	14.8
Moderate	4.2	3.2
Severe	1.6	0.2
Malaise		
Mild	11.7	9.8
Moderate	4.7	3.7
Severe	1.6	0.6
Headache		
Mild	12.6	11.7
Moderate	3.1	2.5
Severe	1.1	0.3

Table 3 (continued): Frequency and Severity of Solicited Injection Site and Systemic Adverse Events within 7 Days Post-Vaccination

	Fluzone High-Dose (N=2573) Percent	Fluzone (N=1260) Percent
Fever		
Mild	2.5	2.0
Moderate	1.1	0.2
Severe	0.0	0.1

*N is the number of subjects in the Safety Analysis Set.

The rates of Serious Adverse Events (SAEs) were comparable between the two groups; 156/2573 (6.1%) of Fluzone High-Dose recipients and 93/1260 (7.4%) of Fluzone recipients experienced SAEs.

No deaths were reported within 28 days post-vaccination. A total of 23 deaths were reported during the follow-up period of the study; 16/2573 (0.6%) among Fluzone High-Dose recipients and 7/1260 (0.6%) among Fluzone recipients. The majority of these participants had a medical history of cardiac, hepatic, neoplastic, renal, and/or respiratory diseases.

Post-Marketing Experience

The following events have been reported during the post-approval use of Fluzone. 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 vaccine exposure.

- **Blood and Lymphatic System Disorders:** Thrombocytopenia, lymphadenopathy
- **Immune System Disorders:** Anaphylaxis, other allergic/hypersensitivity reactions (including urticaria, angioedema)
- **Nervous System Disorders:** Guillain-Barré syndrome (GBS), convulsions, myelitis (including encephalomyelitis and transverse myelitis), facial palsy (Bell's palsy), optic neuritis/neuropathy, brachial neuritis, syncope (shortly after vaccination), dizziness, paresthesia
- **Vascular Disorders:** Vasculitis, vasodilation/flushing
- **Respiratory, Thoracic and Mediastinal Disorders:** Dyspnea, pharyngitis, rhinitis
- **Skin and Subcutaneous Tissue Disorders:** Stevens-Johnson syndrome
- **General Disorders and Administration Site Conditions:** Pruritus, asthenia/fatigue, pain in extremities, chest pain

Other Adverse Events Associated with Influenza Vaccines

Anaphylaxis has been reported after administration of Fluzone and other influenza vaccines. Although Fluzone and Fluzone High-Dose contain only a limited quantity of egg protein, this protein can induce immediate hypersensitivity reactions among persons who have egg allergy. Allergic reactions include anaphylaxis, angioedema, hives, and asthma.

The 1976 swine influenza vaccine was associated with an increased frequency of Guillain-Barré syndrome (GBS). Evidence for a causal relation of GBS with subsequent vaccines prepared from other influenza viruses is unclear. If influenza vaccine does pose a risk, it is probably slightly more than 1 additional case/1 million persons vaccinated.

USE IN SPECIFIC POPULATIONS

Fluzone High-Dose

Pediatric Use: Safety and effectiveness of Fluzone High-Dose in children have not been established.

Geriatric Use: Fluzone High-Dose is indicated for adults 65 years of age and older.

CLINICAL STUDIES

Immunogenicity of Fluzone High-Dose in Adults 65 Years of Age and Older

A total of 3,876 individuals 65 years of age and older were randomized to receive either Fluzone High-Dose or Fluzone in a phase 3, multi-center, randomized, active-controlled, double blind trial conducted in the US. Of those, 3,851 (2,576 randomized to Fluzone High-Dose and 1,275 randomized to Fluzone) were included in the immunogenicity analysis according to the vaccine they were randomized to receive.²

The primary endpoint of the study was HI titer 28 days after vaccination. Pre-specified statistical superiority criteria required that (1) the lower limit (LL) of the 2-sided 95% CI of the GMT ratio (Fluzone High-Dose/Fluzone) be greater than 1.50 for at least two of the strains, and if one strain failed, non-inferiority of that strain must be demonstrated (LL>0.67), and that (2) the lower limit of the 2-sided 95% CI of the seroconversion rate difference [Fluzone High-Dose - Fluzone] be greater than 10% for at least two of the strains, and if one strain failed, non-inferiority of that strain must be demonstrated (LL>10%). As shown in Table 4, statistically superior HI titers after vaccination with Fluzone High-Dose compared to standard dose Fluzone were demonstrated for two of the three influenza strains. There are no data demonstrating clinically relevant prevention of culture-confirmed influenza or its complications after vaccination with Fluzone High-Dose compared to standard dose Fluzone in individuals 65 years of age and older.

Table 4: GMT Ratios and Seroconversion Rates Following Vaccination with Fluzone High-Dose

Influenza Strain	GMT		GMT Ratio	Seroconversion % ^a		Difference	Met Both Pre-defined Endpoints? ^b
	Fluzone High-Dose N=2576	Fluzone N=1275		Fluzone High-Dose over Fluzone (95% CI)	Fluzone High-Dose N=2576		
A (H1N1)	115.8	67.3	1.7 (1.6; 1.8)	48.6	23.1	25.4 (22.4; 28.5)	Yes
A (H3N2)	608.9	332.5	1.8 (1.7; 2.0)	69.1	50.7	18.4 (15.1; 21.7)	Yes
B	69.1	52.3	1.3 (1.2; 1.4)	41.8	29.9	11.8 (8.6; 15.0)	No

Note: As defined in the study protocol:

^aSeroconversion: Paired samples with pre-vaccination HI titer <1:10 and post-vaccination (day 28) titer ≥1:40 or a 4-fold increase for those with pre-vaccination titer ≥1:10.

^bN is the number of subjects in the Immunogenicity Analysis Set.

^cPredefined superiority endpoint for seroconversion: the lower limit of the two-sided 95% CI of the difference of the seroconversion rates (Fluzone High-Dose minus Fluzone) is >10%. Predefined superiority endpoint for GMT ratio: the lower limit of the 95% CI for GMT ratio (Fluzone High-Dose divided by Fluzone) is >1.5.

REFERENCES

- Centers for Disease Control and Prevention. Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2009;58(RR-8):1-52.
- NCT00391053: www.clinicaltrials.gov.

HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

The tip caps of the Fluzone High-Dose prefilled syringes may contain natural rubber latex.

Fluzone High-Dose

Prefilled syringe, without needle, 0.5 mL, package of 10 prefilled syringes per carton - NDC 49281-385-65.

Storage and Handling

Store Fluzone High-Dose refrigerated at 2° to 8°C (35° to 46°F). DO NOT FREEZE. Discard if vaccine has been frozen. Do not use after the expiration date shown on the label.

PATIENT COUNSELING INFORMATION

Inform the patient or guardian that Fluzone High-Dose contains killed viruses and cannot cause influenza. Fluzone High-Dose does not prevent other respiratory infections.

- Vaccine recipients and guardians should be instructed to report any severe or unusual adverse reactions to their health care provider and/or to VAERS.

Fluzone is a registered trademark of Sanofi Pasteur Inc.

Manufactured by:
Sanofi Pasteur Inc.
Swiftwater PA 18370 USA

MKT20500-2

Product information
as of July 2010.

Printed in USA

5959-60-61