

Should Women be Screened for Hypothyroidism?

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LOS ANGELES — The recent evidence suggests that many pregnant women who are hypothyroid are not picked up as such by their medical providers, to the detriment of the mother and child, Dr. Jorge H. Mestman said at a meeting of the Obstetrical and Gynecological Assembly of Southern California.

The experts cannot seem to reach a consensus on whether pregnant women should be screened routinely for thyroid disease, but even hypothyroidism that is subclinical prior to pregnancy appears to have quite a severe, negative impact on the

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pregnancy and the child, said Dr. Mestman, director of the Center for Diabetes and Metabolic Diseases at the University of Southern California, Los Angeles.

"There is no agreement," Dr. Mestman said. "This is going to be up to you. You have to decide in your office if you are going to check everybody for thyroid disease in the same way as for diabetes."

One important new study might not have been seen by many in the obstetrics community because it was published in an endocrinology journal, he noted.

The investigators in the study attempted to see if the strategy of identifying women at high risk of thyroid disease (those with a personal or family history) and performing thyroid testing only in those women would pick up most cases.

They enrolled 1,560 pregnant women on their first prenatal visit, and tested their thyroid function to determine whether they had thyroid antibodies. A total of 40 of the women were found to have elevated thyroid-stimulating hormone (TSH) levels, and 28 (70%) of those were in the high-risk group. That is, they had a personal history of thyroid disease or an autoimmune disease, or a family history of thyroid disease. But the other 12 women had no history and would not therefore have received testing according to the protocol being examined by the study. Thus, these 12 hypothyroid women (30%) would

have been missed, the investigators said (*J. Clin. Endocrinol. Metab.* 2007;92:203-7).

Chronic thyroiditis has an incidence in women of child-bearing age of between 5% and 20%, Dr. Mestman said. Subclinical hypothyroidism—a normal thyroxine (T4) level but an elevated TSH—may have an incidence of 2%.

Many studies have shown that hypothyroidism, even subclinical hypothyroidism, is associated with greater risk of miscarriage and premature delivery, any-

where from a two- to fivefold higher risk.

One study that looked at the children of mothers who were hypothyroid during pregnancy found that at age 7-9 years those children had a mean IQ that was 4 points lower than that of a group of control children. The mean IQ of children of women who were hypothyroid during pregnancy and not treated was 7 points lower (*N. Engl. J. Med.* 1999;341:549-55).

The detrimental effects of hypothyroidism presumably occur because the

mother produces all the thyroid hormone for her fetus during the first trimester at least, and fetal brains have been shown to have thyroid hormone receptors.

During the first trimester, T4 levels need to increase by 50%, which is why women who may be subclinical before conception can run into trouble. They cannot compensate for the increased demand.

By the second and third trimester, T4 levels return to normal; however, some women who become hypothyroid during

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the first trimester will become hypothyroid again after delivery. Those women will become hyperthyroid for the first 3 months after delivery, and then hypothyroid for approximately another 6 months. Of those, about 30% will become clinically hypothyroid within 5 years. All of these women should be followed for thyroid function after their pregnancy, Dr. Mestman said. The pattern can occur even after spontaneous abortion.

The good news is that treatment prevents pregnancy complications, Dr. Mestman said. In a series of 88 hypothyroid women seen at his institution, the pregnancy complication rate of those who never became

euthyroid during their pregnancy was 32% (6 of 19 patients), compared with a rate of 17% in those women who became euthyroid but only after 20 weeks' gestation (7 of 42), and 5% in those who became euthyroid before 20 weeks (1 of 21).

One of the tragedies they observed in that series of women concerned the 30% who were already on levothyroxine prior to their pregnancy, Dr. Mestman said. Some of them were told to stop all medications when they became pregnant and they stopped their thyroid medication.

Another, more recent study also looked at the pregnancy complication rate in women who were euthyroid but who had

thyroid peroxidase antibodies. They treated half of a group of 115 antibody-positive women with levothyroxine, and compared those women with 869 pregnant women who were antibody negative.

The treated antibody-positive women had a miscarriage rate of 3%, similar to the rate in the control group, 2%. But the untreated antibody-positive women had a rate of 14%. The treated women had a premature delivery rate of 7%, similar to the 8% for the control group. That compared with a rate of 22% for the untreated women.

Given those findings, Dr. Mestman recommended that antibody-positive euthyroid women who are pregnant should be

treated. The treatment should include a prenatal vitamin with 150 mcg of iodine, because there is some suggestion that many Americans may no longer get adequate iodine in their diet. And they should have their TSH and T4 levels monitored every 4-6 weeks during the first 20 weeks of pregnancy.

After 20 weeks, they should have their TSH and T4 measured once at 28 weeks. In addition, they should be treated with 50-75 mcg a day of levothyroxine. If the patient is already on levothyroxine at the time, the dose should be increased by 25 mcg.

"Early treatment prevents all the known complications," Dr. Mestman said. ■

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Estrogens with or without progestins should not be used for the prevention of cardiovascular disease or dementia. (See **CLINICAL STUDIES** and **WARNINGS**, Cardiovascular disorders and Dementia in prescribing information.)

The estrogen plus progestin substudy of the Women's Health Initiative (WHI) reported increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep vein thrombosis in postmenopausal women (50 to 79 years of age) during 5.6 years of treatment with oral conjugated estrogens (CE 0.625 mg) combined with medroxyprogesterone acetate (MPA 2.5 mg) per day, relative to placebo. (See **CLINICAL STUDIES** and **WARNINGS**, Cardiovascular disorders and Malignant neoplasms, *Breast cancer* in prescribing information.)

The estrogen-alone substudy of the WHI reported increased risks of stroke and deep vein thrombosis (DVT) in postmenopausal women (50 to 79 years of age) during 6.8 years and 7.1 years, respectively, of treatment with oral conjugated estrogens (CE 0.625 mg) per day, relative to placebo. (See **CLINICAL STUDIES** and **WARNINGS**, Cardiovascular disorders in prescribing information.)

The Women's Health Initiative Memory Study (WHIMS), a substudy of the WHI study, reported increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 4 years of treatment with CE 0.625 mg combined with MPA 2.5 mg and during 5.2 years of treatment with CE 0.625 mg alone, relative to placebo. It is unknown whether this finding applies to younger postmenopausal women. (See **CLINICAL STUDIES**, **WARNINGS**, Dementia and **PRECAUTIONS**, Geriatric Use in prescribing information.)

Other doses of oral conjugated estrogens with medroxyprogesterone acetate and other combinations and dosage forms of estrogens and progestins were not studied in the WHI clinical trials and, in the absence of comparable data, these risks should be assumed to be similar. Because of these trials, estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

Other warnings include: gallbladder disease, hypercalcemia, and visual abnormalities.

Activella should not be used in women with any of the following conditions: undiagnosed abnormal genital bleeding; known, suspected, or history of cancer of the breast; known or suspected estrogen-dependent neoplasia; active deep vein thrombosis, pulmonary embolism, or history of these conditions; active or recent (e.g., within the past year) arterial thromboembolic disease (e.g., stroke, myocardial infarction); liver dysfunction or disease; known hypersensitivity to the ingredients of Activella 0.5 mg/0.1 mg; known or suspected pregnancy.

In a clinical trial, the most commonly reported adverse events (reported at a frequency of $\geq 5\%$) were back pain, headache, pain in extremity, nausea, diarrhea, nasopharyngitis, endometrial thickening, and vaginal hemorrhage.

REFERENCES: 1. Activella [package insert]. Princeton, NJ: Novo Nordisk Inc; 2007. 2. Loose-Mitchell DS, Stancel GM. Estrogens and progestins. In: Hardman JG, Limbird LE, eds. *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. 10th ed. New York, NY: McGraw-Hill; 2001:1598. 3. Panay N, Ylikorkala O, Archer DF, Gut R, Lang E. Ultra-low-dose estradiol and norethisterone acetate: effective menopausal symptom relief. *Climacteric*. 2007;10:120-131. 4. Data on file. CTR. Novo Nordisk Inc, Princeton, NJ.

Please see brief summary of prescribing information on following page.