

Early Data Suggest Adalimumab Safe in Pregnancy

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BERLIN — Treatment of pregnant women with the biologic immunomodulator adalimumab did not appear to adversely affect the fetuses or pregnancies in preliminary data from a prospective study that currently includes 23 exposed pregnancies.

"The findings do not suggest an increased risk for adverse pregnancy out-

comes with exposure to adalimumab early in pregnancy," although additional data from more pregnancies exposed to the drug are needed, Diana L. Johnson said at the 14th United European Gastroenterology Week.

Adalimumab (Humira) is a fully human antibody to tumor necrosis factor (TNF)- α , which gives it a mechanism of action that's similar to other biologic TNF- α inhibitors including etanercept (Enbrel), infliximab (Remicade), and cer-

tolizumab (Cimzia). To date, there is no evidence that the use of these drugs during pregnancy leads to malformations, spontaneous abortions, or prematurity, said Ms. Johnson, a toxicologist and study manager at the University of California, San Diego.

However, only limited data are available so far for all of these exposures.

The analysis of data from women who were treated with adalimumab during pregnancy comes from a larger study of

autoimmune diseases in pregnancy that has been developed by the Organization of Teratology Information Specialists (OTIS).

The OTIS group is a network of university-based pregnancy-risk counseling services in North America.

The centerpiece of the autoimmune disease study is a prospective cohort study of women with rheumatoid arthritis who are being treated with an anti-TNF drug.

In addition, pregnant women who have similar drug exposures for other autoimmune diseases, such as psoriatic arthritis, ankylosing spondylitis, psoriasis, or Crohn's disease, are enrolled in a registry.

The OTIS study so far has data on the birth outcomes of 23 women who were treated with adalimumab early in pregnancy. Twelve of the women are in the prospective cohort, and 11 are in the registry.

These women have had a total of 21 live births and two spontaneous abortions, reported Ms. Johnson at the meeting, which was sponsored by the United European Gastroenterology Federation.

Twenty of the deliveries were term, and the single premature birth involved an infant with congenital hip dysplasia.

Women who are diagnosed with severe Crohn's disease and are on a successful anti-TNF regimen are usually advised to continue their medication if they become pregnant, although the pros and cons of ongoing treatment are discussed with them, commented Dr. Pia Munkholm, a gastroenterologist at Herlev Hospital in Copenhagen.

"There is an incentive to keep these patients in remission," she said.

OTIS receives funding from eight pharmaceutical companies, as well as from other organizations.

VAGIFEM[®]
25µg
estradiol vaginal tablets

Brief summary of prescribing information.

ESTROGENS HAVE BEEN REPORTED TO INCREASE THE RISK OF ENDOMETRIAL CARCINOMA. Three independent, case controlled studies have reported an increased risk of endometrial cancer in postmenopausal women exposed to exogenous estrogens for more than one year. This risk was independent of the other known risk factors for endometrial cancer. These studies are further supported by the finding that incident rates of endometrial cancer have increased sharply since 1969 in eight different areas of the United States with population-based cancer-reporting systems, an increase which may be related to the rapidly expanding use of estrogens during the last decade.

The three case-controlled studies reported that the risk of endometrial cancer in estrogen users was about 4.5 to 13.9 times greater than in nonusers. The risk appears to depend on both duration of treatment and on estrogen dose. In view of these findings, when estrogens are used for the treatment of menopausal symptoms, the lowest dose that will control symptoms should be utilized and medication should be discontinued as soon as possible. When prolonged treatment is medically indicated, the patient should be reassessed, on at least a semi-annual basis, to determine the need for continued therapy.

Close clinical surveillance of all women taking estrogens is important. In all cases of undiagnosed persistent or recurring abnormal vaginal bleeding, adequate diagnostic measures should be undertaken to rule out malignancy. There is no evidence at present that "natural" estrogens are more or less hazardous than "synthetic" estrogens at equi-estrogenic doses.

INDICATIONS AND USAGE VAGIFEM is indicated for the treatment of atrophic vaginitis.

CONTRAINDICATIONS

The use of VAGIFEM is contraindicated in women who exhibit one or more of the following:

1. Known or suspected breast carcinoma.
2. Known or suspected estrogen-dependent neoplasia; e.g., endometrial carcinoma.
3. Abnormal genital bleeding of unknown etiology.
4. Known or suspected pregnancy (see PRECAUTIONS).
5. Porphyria.
6. Hypersensitivity to any VAGIFEM constituents.
7. Active thrombophlebitis or thromboembolic disorders.
8. A past history of thrombophlebitis, thrombosis, or thromboembolic disorders associated with previous estrogen use (except when used in treatment of breast malignancy).

WARNINGS

1. Induction of malignant neoplasms.

Long-term, continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, cervix, vagina, and liver. There are now reports that estrogens increase risk of carcinoma of the endometrium in humans (see Boxed Warning). At the present time there is no satisfactory evidence that estrogens given to postmenopausal women increase the risk of cancer of the breast, although a recent long-term follow-up of a single physician's practice has raised this possibility. Because of the animal data, there is a need for caution in prescribing estrogens for women with a strong family history of breast cancer or who have breast nodules, fibrocystic disease, or abnormal mammograms.

2. Gallbladder disease.

A recent study has reported a 2- to 3-fold increase in the risk of surgically confirmed gallbladder disease in women receiving postmenopausal estrogens, similar to the 2-fold increase previously noted in users of oral contraceptives.

3. Effects similar to those caused by estrogen-progestogen oral contraceptives.

There are several serious adverse effects of oral contraceptives, most of which have not, up to now, been documented as consequences of postmenopausal estrogen therapy. This may reflect the comparatively low doses of estrogens used in postmenopausal women. It would be expected that the larger doses of estrogen used to treat prostatic or breast cancer are more likely to result in these adverse effects, and, in fact, it has been shown that there is an increased risk of thrombosis in men receiving estrogens for prostatic cancer.

a. **Thromboembolic disease.** It is now well established that users of oral contraceptives have an increased risk of various thromboembolic and thrombotic vascular diseases, such as thrombophlebitis, pulmonary embolism, stroke, and myocardial infarction. Cases of retinal thrombosis, mesenteric thrombosis, and optic neuritis have been reported in oral contraceptive users. There is evidence that the risk of several of these adverse reactions is related to the dose of the drug. An increased risk of post-surgery thromboembolic complications has also been reported in users of oral contraceptives. If feasible, estrogen should be discontinued at least 4 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization. While an increased rate of thromboembolism and thrombotic disease in postmenopausal users of estrogens has not been found, this does not rule out the possibility that such an increase may be present, or that subgroups of women who have underlying risk factors, or who are receiving large doses of estrogens, may have increased risk. Therefore, estrogens should not be used (except in treatment of malignancy) in a person with a history of such disorders in association with estrogen use. They should be used with caution in patients with cerebral vascular or coronary artery disease and only for those in whom estrogens are clearly needed.

Large doses of estrogens (5 mg conjugated estrogens per day), comparable to those used to treat cancer of the prostate and breast, have been shown in a large prospective clinical trial in men, to increase the risk of nonfatal myocardial infarction, pulmonary embolism, and thrombophlebitis. When estrogen doses of this size are used, any of the thromboembolic and thrombotic adverse effects associated with oral contraceptive use should be considered a clear risk.

b. **Hepatic adenoma.** Benign hepatic adenomas appear to be associated with the oral contraceptives. Although benign, and rare, these may rupture and may cause death through intra-abdominal hemorrhage. Such lesions have not yet been reported in association with other estrogen or progestogen preparations but should be considered in estrogen users having abdominal pain and tenderness, abdominal mass, or hypovolemic shock. Hepatocellular carcinoma has also been reported in women taking estrogen-containing oral contraceptives. The relationship of this malignancy to these drugs is not known at this time.

c. **Elevated blood pressure.** Women using oral contraceptives sometimes experience increased blood pressure which, in most cases, returns to normal on discontinuing the drug. There is now a report that this may occur with the use of estrogens in the menopause and blood pressure should be monitored with estrogen use, especially if high doses are used.

d. **Glucose tolerance.** A worsening of glucose tolerance has been observed in a significant percentage of patients on estrogen-containing oral contraceptives. For this reason, diabetic patients should be carefully observed while using estrogens.

4. Hypercalcemia.

Administration of estrogens may lead to severe hypercalcemia in patients with breast cancer and bone metastases. If this occurs, the drug should be stopped and appropriate measures taken to reduce the serum calcium level.

5. **Rare Event:** Trauma induced by the VAGIFEM applicator may occur, especially in patients with severely atrophic vaginal mucosa.

PRECAUTIONS

A. General Precautions

1. A complete medical and family history should be taken prior to the initiation of any estrogen therapy. The pretreatment and periodic physical examinations should include special references to blood pressure, breast, abdomen, and pelvic organs, and should include a Papanicolaou smear. As a general rule, estrogens should not be prescribed for longer than one year without another physical exam being performed.
2. **Fluid retention**—Because estrogens may cause some degree of fluid retention, conditions which might be influenced by this factor, such as asthma, epilepsy, migraine, and cardiac and renal dysfunction, require careful observation.
3. **Familial Hyperlipoproteinemia**—Estrogen therapy may be associated with massive elevations of plasma triglycerides leading to pancreatitis and other complications in patients with familial defects of lipoprotein metabolism.
4. Certain patients may develop undesirable manifestations of excessive estrogenic stimulation, such as abnormal or excessive uterine bleeding, mastodynia, etc.
5. Prolonged administration of unopposed estrogen therapy has been reported to increase the risk of endometrial hyperplasia in some patients.
6. Preexisting uterine leiomyomata may increase in size during estrogen use.
7. The pathologist should be advised of estrogen therapy when relevant specimens are submitted.

8. Patients with a history of jaundice during pregnancy have an increased risk of recurrence of jaundice while receiving estrogen-containing oral contraceptive therapy. If jaundice develops in any patient receiving estrogen, the medication should be discontinued while the cause is investigated.
9. Estrogens may be poorly metabolized in patients with impaired liver function and should be administered with caution in such patients.
10. Because estrogens influence the metabolism of calcium and phosphorus, they should be used with caution in patients with metabolic bone diseases that are associated with hypercalcemia or in patients with renal insufficiency.
11. Because of the effects of estrogens on epiphyseal closure, they should be used judiciously in young patients in whom bone growth is not yet complete.
12. Insertion of the VAGIFEM applicator—Patients with severely atrophic vaginal mucosa should be instructed to exercise care during insertion of the applicator. After gynecological surgery, any vaginal applicator should be used with caution and only if clearly indicated.
13. **Vaginal infection**—Vaginal infection is generally more common in postmenopausal women due to the lack of normal flora seen in fertile women, especially lactobacilla; hence the subsequent higher pH. Vaginal infections should be treated with appropriate antimicrobial therapy before initiation of VAGIFEM therapy.

B. Information for the Patient

See full prescribing information, INFORMATION FOR PATIENTS.

C. Drug/Laboratory Test Interactions

Certain endocrine and liver function tests may be affected by estrogen-containing oral contraceptives. The following similar changes may be expected with larger doses of estrogens:

- a. Increased prothrombin and factors VII, VIII, IX, and X, decreased antithrombin III, increased norepinephrine induced platelet aggregability.
- b. Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by T₄ by column, or T₄ by radioimmunoassay. Free T₄ resin uptake is decreased, reflecting the elevated TBG, free T₄ concentration is unaltered.
- c. Impaired glucose tolerance.
- d. Reduced response to metyrapone test.
- e. Reduced serum folate concentration.
- f. Increased serum triglyceride and phospholipid concentration.

D. Carcinogenesis, Mutagenesis and Impairment of Fertility

Long term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, uterus, vagina and liver (see CONTRAINDICATIONS AND WARNINGS).

E. Pregnancy Category X

Estrogens are not indicated for use during pregnancy or the immediate postpartum period. Estrogens are ineffective for the prevention or treatment of threatened or habitual abortion. Treatment with diethylstilbestrol (DES) during pregnancy has been associated with an increased risk of congenital defects and cancer in the reproductive organs of the fetus, and possibly other birth defects. The use of DES during pregnancy has also been associated with a subsequent increased risk of breast cancer in the mothers.

F. Nursing Mothers

As a general principle, administration of any drug to nursing mothers should be done only when clearly necessary since many drugs are excreted in human milk. In addition, estrogen administration to nursing mothers has been shown to decrease the quantity and quality of the milk. Estrogens are not indicated for the prevention of postpartum breast engorgement.

G. Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

H. Geriatric Use

Clinical studies of VAGIFEM did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE EVENTS

Adverse events generally have been mild: vaginal spotting, vaginal discharge, allergic reaction and skin rash. Adverse events with an incidence of 5% or greater are reported for two comparative trials. Data for patients receiving either VAGIFEM or placebo in the double blind study and VAGIFEM in the open label comparator study are listed in the following 2 tables, respectively.

ADVERSE EVENT	ADVERSE EVENTS REPORTED IN 5% OR GREATER NUMBER OF PATIENTS RECEIVING VAGIFEM IN THE PLACEBO CONTROLLED TRIAL	
	VAGIFEM % (n=91)	Placebo % (n=47)
Headache	9	6
Abdominal Pain	7	4
Upper Respiratory Tract Infection	5	4
Genital Molluscias	5	2
Back Pain	7	6

ADVERSE EVENTS REPORTED IN 5% OR GREATER NUMBER OF PATIENTS RECEIVING VAGIFEM IN THE OPEN LABEL STUDY

ADVERSE EVENT	VAGIFEM % (n=80)
Genital Pruritus	6
Headache	10
Upper Respiratory Tract Infection	11

Other adverse events that occurred in 3-5% of VAGIFEM subjects included: allergy, bronchitis, dyspepsia, haematuria, hot flashes, insomnia, pain, sinusitis, vaginal discomfort, vaginitis. A causal relationship to VAGIFEM has not been established.

OVERDOSAGE

Numerous reports of ingestion of large doses of estrogen containing oral contraceptives by young children indicate that acute serious ill effects do not occur. Overdosage with estrogens may cause nausea, and withdrawal bleeding may occur in females.

DOSE AND ADMINISTRATION

VAGIFEM is gently inserted into the vagina as far as it can comfortably go without force, using the supplied applicator.

- Initial dose: One (1) VAGIFEM tablet, inserted vaginally, once daily for two (2) weeks. It is advisable to have the patient administer treatment at the same time each day.
- Maintenance dose: One (1) VAGIFEM tablet, inserted vaginally, twice weekly.

The need to continue therapy should be assessed by the physician with the patient. Attempts to discontinue or taper medication should be made at three to six month intervals.

HOW SUPPLIED

Each VAGIFEM[®] (estradiol vaginal tablets), 25 µg is contained in a disposable, single-use applicator, packaged in a blister pack. Cartons contain 8 or 18 applicators with inset tablets.

8 Applicators NDC 0169-5173-03

18 Applicators NDC 0169-5173-04

Store at 25°C (77°F); excursions permitted to 15°C-30°C (59°F-86°F) [see USP Controlled Room Temperature].

Rx only

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Reference: 1. Riox JE, Devlin MC, Gelfand MM, Steinberg WM, Hepburn DS. 17β-Estradiol vaginal tablet versus conjugated equine estrogen vaginal cream to relieve menopausal atrophic vaginitis. *Menopause*. 2000;7:156-161.

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