

# Repeat Down's Screening Can Cut False Positives

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SAN FRANCISCO — Repeating one of the assays used in serum-integrated screening for Down syndrome could halve the false-positive rate, Dr. Fergal D. Malone said at the annual meeting of the Society for Maternal-Fetal Medicine.

Adding another repeat assay could reduce the false-positive rate by a further 25%, said Dr. Malone, professor and chair-

man of ob.gyn. at the Royal College of Surgeons, Dublin.

Conventional serum-integrated screening entails collecting first- and second-trimester blood samples. The first-trimester sample is assayed for pregnancy-associated plasma protein A (PAPP-A) and assays are performed on the second-trimester sample for several other markers of Down syndrome risk: alpha-fetoprotein, total HCG, unconjugated estradiol, and inhibin A. The marker results are

combined in a single assessment of risk for trisomy 21.

Serum-integrated screening detects 90% of Down syndrome cases with a 4.9% false-positive rate. If the PAPP-A assay is simply repeated on the second-trimester serum sample, the false-positive rate would drop to 1.9%, according to a modeling study that Dr. Malone and associates conducted using data from the First and Second Trimester Evaluation of Risk trial.

Doing an HCG assay on the first-

trimester sample in addition to repeating the PAPP-A assay on the second-trimester sample should further reduce the false-positive rate to 1.4%, he added.

Repeating the PAPP-A assay would improve the Down syndrome detection rate to about 92%. Doing the PAPP-A and the HCG assays on first- and second-trimester samples would increase detection to nearly 100%, he calculated.

A similar benefit is seen when repeating PAPP-A measures in fully integrated screening for Down syndrome, which combines first-trimester imaging of nuchal translucency with serum-integrated screening. Fully integrated screening detects 90% of Down syndrome cases with a 1.3% false-positive rate. Repeating the PAPP-A assay on the second-trimester serum sample would decrease the false-positive rate to 0.5%, Dr. Malone said.

**The concept of repeat-measures screening takes screening strategies beyond conventional notions of evaluating each marker individually.**

Reducing false positives could reduce the use of invasive tests for Down syndrome and terminations of some pregnancies, and im-

prove the cost-effectiveness of screening.

These preliminary modeling results must be supported by prospective studies before repeat-measures screening is adopted in clinical practice, he cautioned.

The concept of repeat-measures screening expands screening strategies beyond conventional notions of evaluating each marker individually and measuring it at the one time point where it provides the best information. Measuring PAPP-A alone at 10 weeks' gestation, for example, detects 85% of Down syndrome cases with a 17% false-positive rate. Measuring PAPP-A alone only in the second trimester produces a massive 60% false-positive rate.

"Conventional wisdom says that PAPP-A in the first but not the second trimester is the way to proceed," Dr. Malone noted. "However, things are not that simple."

Measuring PAPP-A at 10 weeks and again between 14 and 22 weeks has not been recommended because the marker is highly correlated across gestation ages and is a poor marker for detection in the second trimester alone.

"It may surprise you, therefore, to see that PAPP-A in the first and second trimester has been estimated to provide a huge improvement in performance, for an 85% detection rate and only a 2% screen positive rate," he said.

A low PAPP-A at 10 weeks accurately identifies trisomy 21 but falsely identifies quite a few unaffected infants. PAPP-A levels tend to be higher in Down syndrome cases in the second trimester.

"Having the added knowledge of what the second-trimester PAPP-A value is allows us to almost completely discriminate Down syndrome from normal pregnancies," Dr. Malone said.

**VAGIFEM**<sup>25µg</sup>  
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 breast 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 PBI, T<sub>4</sub> by column, or T<sub>4</sub> by radioimmunoassay. Free T<sub>4</sub> resin uptake is decreased, reflecting the elevated TBG, free T<sub>4</sub> 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 EVENTS REPORTED IN 5% OR GREATER NUMBER OF PATIENTS RECEIVING VAGIFEM IN THE PLACEBO CONTROLLED TRIAL

ADVERSE EVENT	VAGIFEM % (n=91)	Placebo % (n=47)
Headache	9	6
Abdominal Pain	7	4
Upper Respiratory Tract Infection	5	5
Genital Moniliasis	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.

#### DOSAGE 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<sup>®</sup> (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

VAGIFEM<sup>®</sup> is a trademark owned by Novo Nordisk A/S.

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**Reference:** 1. Rioux 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.