NAAT Outperforms Antepartum GBS Culture

BY SUSAN LONDON

FROM THE ANNUAL MEETING OF THE SOCIETY FOR MATERNAL-FETAL MEDICINE

SAN FRANCISCO - A rapid intrapartum test for group B streptococcus may improve identification of colonized pregnant women, according to study results reported at the meeting.

When the rapid test - a nucleic acid

amplification test (NAAT) that yields results within an hour - was compared with a conventional antepartum bacterial culture, the rapid test was superior in identifying which of the 559 laboring women in the study had group B streptococcus (GBS) colonization (sensitivity, 91% vs. 69%). The rapid test also had a significantly better negative predictive value, and its specificity and positive predictive value were similarly high.

"In our population, intrapartum NAAT appeared to have superior test characteristics to antepartum culture for predicting intrapartum GBS culture status," said Dr. Munish Gupta, an associate director of the neonatal intensive care unit at the Beth Israel Deaconess Medical Center in Boston.

"NAAT may be able to help identify women who are positive for GBS by intrapartum culture but negative by antepartum culture, a group of women that would be at particularly high risk for GBS transmission to their newborns by current standard management," he commented.

In fact, about 60% of cases of neonatal early-onset GBS disease occur in infants born to mothers who screened negative by conventional means during their pregnancy, according to Dr. Gupta. "In addition, it has been well documented that results of antepartum GBS screening cultures do not always accurately predict

PREMARIN® (CONJUGATED ESTROGENS) VAGINAL CREAM BRIEF SUMMARY: See Package Insert for Full Prescribing Information. For further product information and current package insert, please visit www.premarinvaginalcreamhcp.com or call our medical communication department toll-free at 1-800-934-5556.

WARNING: CARDIOVASCULAR DISORDERS, ENDOMETRIAL CANCER, BREAST CANCER and PROBABLE DEMENTIA ESTROGEN-ALONE THERAPY

ENDOMETRIAL CANCER

ENDUMETRIAL CANCER There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens. Adding a progestin to estrogen therapy has been shown to reduce the risk of endome hyperplasia, which may be a precursor to endometrial cancer. Adequate diagnostic measures, in directed or random endometrial sampling when indicated, should be undertaken to rule out mali in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding [see Warnings and Precautions (5.3)]. CARDIOVASCULAR DISORDERS AND PROBABLE DEMENTIA Estrogen-alone therapy should not be used for the prevention of cardiovascular disease or doman ures, inclu

Estrogen-alone therapy should not be used for the prevention of cardiovascular disease or dementia [see Warnings and Precautions (5.2, 5.4), and Clinical Studies (14.2, 14.3) in full prescribing information

[see Warnings and Precautions (5.2, 5.4), and Clinical Studies (14.2, 14.3) in full prescribing information]. The Women's Health Initiative (WHI) estrogen-alone substudy reported increased risks of stroke and deep vein thrombosis (DVT) in postmenopausal women (50 to 79 years of age) during 7.1 years of treatment with daily oral conjugated estrogens (CE) (0.625 mg), relative to placebo [see Warnings and Precautions (5.2), and Clinical Studies (14.2) in full prescribing information]. The WHI Memory Study (WHIMS) estrogen alone ancillary study of WHI reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 5.2 years of treatment with daily CE (0.625 mg) alone, relative to placebo. It is unknown whether this finding applies to younger postmenopausal women [see Warnings and Precautions (5.4), Use in Specific Populations (6.5), and Clinical Studies (14.3) in full prescribing information]. In the absence of comparable data, these risks should be assumed to be similar for other doses of CE and other dosage forms of estrogens.

is with or without progestions should be prescribed at the lowest effective doses and for the t duration consistent with treatment goals and risks for the individual woman.

shortest duration consistent with treatment goals and risks for the individual woman. <u>ESTROGEN PLUS PROGESTIN THERAPY</u> CARDIOVASCULAR DISORDERS AND PROBABLE DEMENTIA Estrogen plus progestin therapy should not be used for the prevention of cardiovascular disease or dem *[see Warnings and Precautions (5.2, 5.4), and Clinical Studies (14.2, 14.3) in full prescribing information*. The WHI estrogen plus progestin substudy reported increased risks of DVT, pulmonary embolism, strof and myocardial infarction in postmenopausal women (50 to 79 years of age) during 5.6 years of treatm with daily oral EC (0.625 mg) combined with medroxyprogesterone acetate (MPA) [2.5 mg], relative to placebo *[see Warnings and Precautions (5.2), and Clinical Studies (14.2) in full prescribing information*. placebo (see Warnings and Precautions (5.2), and Clinical Studies (14.2) in tuit prescribing information). The WHIMS service in progestin ancillary study of the WHI, reported an increased risk of develop probable dementia in postmenopausal women 65 years of age or older during 4 years of treatment with daily CE (0.625 mg) combined with MPA (2.5 mg), relative to placebo, It is unknown whother this finding applies to younger postmenopausal women [see Warnings and Precautions (5.4), Use in Specific Populations (8.5), and Clinical Studies (14.3) in full prescribing information]. ons (5.4). Use in

BREAST CANCER

BHEAST CANCEH The WHI estrogen plus progestin substudy also demonstrated an increased risk of invasive breast cancer [see Warnings and Precautions (5.3), and Clinical Studies (14.2) in full prescribing informatic In the absence of comparable data, these risks should be assumed to be similar for other doses of CE and MPA, and other combinations and dosage forms of estrogens and progestins. 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.

INDICATIONS AND USAGE

Treatment of Atrophic Vaginitis and Kraurosis Vulvae

Treatment of Moderate to Severe Dyspareunia, a Symptom of Vulvar and Vaginal Atrophy, due to Menopause CONTRAINDICATIONS CONTRAINDICATIONS PREMARIN Vaginal Cream therapy should not be used in women with any of the following conditions: • Undiagnosed abnormal genital bleeding • Known, suspected, or history of breast cancer • Known or suspected estrogen-dependent neoplasia • Active deep vein thrombosis, pulmonary embolism or a history of these conditions

 Active deep vein thrombosis, pulmonary embolism or a history of these conditions
Active arterial thromboembolic disease (for example, stroke, and myocardial infarction), or a history of Active arteriat informboembolic dise these conditions
Known liver dysfunction or disease
Known itver dysfunction or disease
Known or suspected pregnancy
WARNINGS AND PRECAUTIONS
Picke Error Sustemic Absorption

Risks From Systemic Absorption

Systemic absorption occurs with the use of PREMARIN Vaginal Cream. The warnings, precautions, and adverse reactions associated with oral PREMARIN treatment should be taken into account. Cardiovascular Disorders

An increased risk of stroke and deep vein thrombosis (DVT) has been reported with estrogen-alone therapy. An increased risk of pulmonary embolism, DVT, stroke and myocardial infarction has been reported with estrogen plus progestin therapy. Should any of these occur or be suspected, estrogens with or without progestins should be discontinued immediately.

Risk factors for arterial vascular disease (for example, hypertension, diabetes mellitus, tobacco use, hypercholesterolemia, and obesity) and/or venous thromboembolism (for example, personal history of venous thromboembolism [VTE], obesity, and systemic lupus erythematosus) should be managed appropriately.

Stroke In the Women's Health Initiative (WHI) estrogen-alone substudy, a statistically significant increased risk of stroke was reported in women 50 to 79 years of age receiving daily CE (0.625 mg) compared to women in the same age group receiving placebo (45 versus 33 per 10,000 women-years). The increase in risk was demonstrated in year one and persisted [*see Clinical Studies* (14.2) in full prescribing information]. Should a stroke occur or be suspected, estrogens should be discontinued immediately.

stroke occur or be suspected, estrogens should be discontinued immediately. Subgroup analyses of women 50 to 59 years of age suggest no increased risk of stroke for those women receiving CE (0.625 mg) versus those receiving placebo (18 versus 21 per 10,000 women-years).¹ In the WHI estrogen plus progestin substudy, a statistically significant increased risk of stroke was reported in all women receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to placebo (33 versus 25 per 10,000 women-years) [see *Clinical Studies* (14.2) in *full prescribing information*]. The increase in risk was demonstrated after the first year and persisted.¹

Coronary Heart Disease In the WHI estrogen-alone substudy, no overall effect on coronary heart disease (CHD) events (defined as nonfatal myocardial infarction [MI], silent M, or CHD death) was reported in women receiving estrogen-alone compared to placebo [see Clinical Studies (14.2) in full prescribing information].¹

Subgroup analyses of women 50 to 59 years of age suggest a statistically non-significant reduction in CHD events (20.625 mg compared to placebo) in women with less than 10 years since menopause (8 versus 16 per 10,000 women-years).

In the WHI estrogen plus progestin substudy, there was a statistically non-significant increased risk of CHD events in women receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to women receiving placebo (41 versus 34 per 10,000 women-years).¹ An increase in relative risk was demonstrated in year 1, and a trend toward decreasing relative risk was reported in years 2 through 5 (see *Clinical Studies* (14.2) in full prescribing information]. In postmenopausal women with documented heart disease (n = 2,763), average age 66.7 years, in a controlled clinical trial of secondary prevention of cardiovascular disease (Heart and Estrogen/Progestin Replacement

Study [HERS]), treatment with daily CE (0.625 mg) plus MPA (2.5 mg) demonstrated no cardiovascular benefit. During an average follow-up of 4.1 years, treatment with CE plus MPA did not reduce the overall rate of CHD events in postmenopausal women with established coronary heart disease. There were more CHD events in the CE plus MPA-treated group than in the placebo group in year 1, but not during subsequent users. Two thousand, three hundred and twenty-one (2,321) women from the original HERS trial agreed to participate in an open label extension of HERS, HERS II. Average follow-up in HERS II was an additional 2.7 years, for a total of 6.8 years overall. Rates of CHD events were comparable among women in the CE (0.625 mg) plus MPA (2.5 mg) group and the placebo group in HERS, HERS II, and overalI.

We group and up to be group of the set of th intormation, Should a VIE occur of be suspected, estrogens should be discontinued immediately. In the WHI estrogen plus progestin substudy, a statistically significant 2-fold greater rate of VTE was reported in women receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to women receiving placebo (35 versus 17 per 10,000 women-years). Statistically significant increases in risk for both DVT (26 versus 13 per 10,000 women-years) and PE (18 versus 8 per 10,000 women-years) were also demonstrated. The increase in VTE risk was observed during the first year and persisted' (see Clinical Studies (14.2) in full prescribing information). Should a VTE occur or be suspected, estrogens should be discontinued immediately. If feasible, estrogens should be discontinued at least 4 to 6 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization. Malignant Neoplasms

Endometrial Cancer

Endometrial Cancer An increased risk of endometrial cancer has been reported with the use of unopposed estrogen therapy in a woman with a uterus. The reported endometrial cancer risk among unopposed estrogen users is about 2- to 12-fold greater than in non-users, and appears dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with use of estrogens for less than 1 year. The greatest risk appears to be associated with prolonged use, with increased risks of 15- to 24-fold for 5 to 10 years or more, and this risk has been shown to persist for at least 8 to 15 years after estrogen therapy is discontinued. Clinical surveillance of all women using estrogen-alone or estrogen plus progestin therapy is montant. Adequate diagnostic measures, including directed or random endometrial asmpling when indicated, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding. There is no evidence that the use of natural estrogens results in a different endometrial risk profile than synthetic estrogens of equivalent estrogen dose. Adding a progestin to postmenopausal estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer. In a 52-week clinical trial using PREMARIN Vaginal Cream alone (0.5 g inserted twice weekly or daily for 21 days, then off for 7 days), there was no evidence of endometrial hyperplasia or endometrial carcinoma. *Breast Cancer*

Breast Cancer The most important randomized clinical trial providing information about breast cancer in estrogen-alone users is the Women's Health Initiative (WHI) substudy of daily CE (0.625 mg). In the WHI estrogen-alone substudy, after an average follow-up of 7.1 years, daily CE (0.625 mg) was not associated with an increased risk of invasive breast cancer [relative risk (RR) 0.80]¹⁵ [see Clinical Studies (14.2) in full prescribing information].

The most important randomized clinical trial providing information about breast cancer in estrogen plus progest users is the WHI substudy of daily CE (0.625 mg) plus MPA (2.5 mg). After a mean follow-up of 5.6 years, the estrogen plus progestin substudy reported an increased risk of breast cancer in women who took daily CE plus The incomposition relation incomposition of the provided and provided in the provided provided in the provided in the provided in the provided provided provided provided provided in the provided in the provided provid

The use of estrogen-alone and estrogen plus progestin therapy has been reported to result in an increase in abnormal mammograms, requiring further evaluation.

All women should receive yearly breast examinations by a healthcare provider and perform monthly breast self-examinations. In addition, mammography examinations should be scheduled based on patient age, risk factors, and prior mammogram results. Ovarian Cancer

Ovarian Cancer The WHI estrogen plus progestin substudy reported a statistically non-significant increased risk of ovarian cancer. After an average follow-up of 5.6 years, the relative risk for ovarian cancer for CE plus MPA versus placebo, was 1.58 (95 percent nCl 0.77-3.24). The absolute risk for CE plus MPA versus placebo was 4 versus 3 cases per 10,000 women-years.⁷ In some epidemiologic studies, the use of estrogen-only products, in particular for 5 or more years, has been associated with an increased risk of ovarian cancer. However, the duration of exposure associated with increased risk is not consistent across all epidemiologic studies, and some report no association.

Associated min not access to the probable Dementia In the estrogen-alone Women's Health Initiative Memory Study (WHIMS), an ancillary study of WHI, a population of 2,947 hysterectomized women 65 to 79 years of age was randomized to daily CE (0.625 mg) or placebo. In the WHIM's estrogen-alone ancillary study, after an average follow-up of 5.2 years, 28 women in the estrogen-alone group and 19 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for CE-alone versus placebo was 1.49 (95 percent nCl 0.83-2.66). Th absolute risk of probable dementia for CE-alone versus placebo was 1.79 years 25 cases per 10,000 women-years⁶ (see Use in Specific Populations (8.3), and Clinical Studies (14.3) in full prescribing inform

women-years⁶ [see Use in Specific Populations (8.3), and Clinical Studies (14.3) **in full prescribing information**, In the WHIMS estrogen plus progestin ancillary study, a population of 4,532 postmenopausal women 65 to 79 years of age was randomized to daily CE (0.625 mg) plus MPA (2.5 mg) or placebo. After an average follow-up of 4 years, 40 women in the CE plus MPA group and 21 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for CE plus MPA versus placebo was 45 versus 22 cases per 10,000 women-years⁶ [see Use in Specific Populations (8.3), and Clinical Studies (14.3) **in full prescribing information**].

When data from the two populations were pooled as planned in the WHIMS protocol, the reported overall relative risk for probable dementia was 1.76 (95 percent not 1.19-2.60). Since both substudies were conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women⁸ [see Use in Specific Populations (8.5), and Clinical Studies (14.3) **in full prescribing information**].

Gallbladder Disease A 2 to 4-fold increase in the risk of gallbladder disease requiring surgery in postmenopausal women receiving estrogens has been reported.

Hypercalcemia Estrogen administration may lead to severe hypercalcemia in women with breast cancer and bone metastases. If hypercalcemia occurs, use of the drug should be stopped and appropriate measures taken to reduce the serum calcium level.

(continued on next page)

Major Finding: The rapid intrapartum GBS test, compared with antepartum culture, A

had a significantly better sensitivity (91% vs. 69%) and negative predictive value (97% vs. 91%). The specificity and positive

predictive value were similarly high. Data Source: A prospective study of 559 women in labor who had documented antepartum culture results and had not received intrapartum antibiotics.

Disclosures: Dr. Gupta did not report any relevant financial disclosures. Cepheid loaned the investigators the system used for rapid testing.

Retinal vascular thrombosis has been reported in patients receiving estrogens. Discontinue medication pending examination if there is sudden partial or complete loss of vision, or a sudden onset of proptosis, diplopia, or migraine. If examination reveals papilledema or retinal vascular lesions, estrogens should be permanently discontinued.

Fund Actention Estrogens may cause some degree of fluid retention. Patients with conditions that might be influenced by this factor, such as cardiac or renal dysfunction, warrant careful observation when estrogens are prescribed.

A few cases of malignant transformation of residual endometrial implants have been reported in women treated post-hysterectomy with estrogen-alone therapy. For women known to have residual endometriosis post-hysterectomy, the addition of progestin should be considered.

nypocancernia Estrogens should be used with caution in individuals with hypoparathyroidism as estrogen-induced hypocalcernia may occur.

Exogenous estrogens may induce or exacerbate symptoms of angioedema, particularly in women with

Visual Abnormalities

Fluid Retention

Hypocalcemia

Angioedema

Exacerbation of Endometriosis

intrapartum GBS status."

The investigators prospectively studied pregnant women who were admitted to the labor and delivery department, had documented results of an antepartum GBS culture performed at 35-37 weeks' gestation, and had not received intrapartum antibiotics.

Two intrapartum rectovaginal samples were obtained according to Centers for Disease Control and Prevention guidelines.

One sample was sent for GBS culture by the hospital laboratory, and

the result of this intrapartum culture served as the reference standard for the study, Dr. Gupta explained.

The other sample was used for rapid testing with the Xpert GBS test, performed in the department 24/7 on a system loaned to the investigators by the manufacturer, Cepheid.

"Of note, the intrapartum culture and NAAT results were not used for clinical management," he pointed out

Study results were based on 559 women who were 32 years old, on average. About 61% were white, 14%

5 (3.5) 4 (5.6) 7 (5.0) 1 (1.5) Vasodilatation Table 1: Number (%) of Patients Reporting Treatment Emergent Adverse Events \ge 5 Percent Only **Digestive System** Diarrhea 4 (2.8) 2 (2.8) 10 (7.1) 1(1.5)Nausea 5 (3.5) 4 (5.6) 3 (4.4) 3 (2.1) Musculoskeletal System Arthralgia 5 (3.5) 5 (6.9) 6 (4.3) 4 (5.9) Nervous Systen 3 (4.2) 4 (2.9) 4 (5.9) nsomnia 6 (4.2) **Respiratory System** Cough Increased 0 1 (1.4) 7 (5.0) 3 (4.4) Pharyngitis 3 (2.1) 2 (2.8) 7 (5.0) 3 (4.4) 1 (0.7) 3 (4.2) 2 (1.4) 4 (5.9) Sinusitis Skin And Appendages 12 (8.4) 7 (9.7) 16 (11.4) 3 (4.4) Urogenital System 1 (1.4) 4 (2.9) Breast Pain 8 (5.6) 0 Leukorrh 3 (2.1) 2 (2.8) 4 (2.9) 6 (8.8) 8 (5.6) 3 (4.2) 7 (5.0) 3 (4.4) Vaginitis adverse events, since a patient may

Postmarketing Experience The following adverse reactions have been reported with PREMARIN Vaginal Cream. Because these reactions 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 drug exposure.

Genitourinary System Abnormal uterine bleeding/spotting, dysmenorrhea/pelvic pain, increase in size of uterine leiomyomata, vaginitis (including vaginal candidiasis), change in cervical secretion, cystitis-like syndrome, application site reactions of vulvovaginal discomfort, (including burning, irritation, and genital pruritus), endometrial hyperplasia, endometrial cancer, precocious puberly, leukorrhea.

Breasts Tenderness, enlargement, pain, discharge, fibrocystic breast changes, breast cancer, gynecomastia in males.

r*diovascuiar* ep venous thrombosis, pulmonary embolism, myocardial infarction, stroke, increase in blood pressure. Gastrointestinal Nausea, vomiting, abdominal cramps, bloating, increased incidence of gallbladder disease.

Skin Chloasma that may persist when drug is discontinued, loss of scalp hair, hirsutism, rash

Eyes Retinal vascular thrombosis, intolerance to contact lenses.

Exogenous estrogens may induce or exacerbation of asthma, diabetes mellitus, epilepsy, migraine, porphyria, systemic bacerbation of Other Conditions Estrogen therapy may cause an exacerbation of asthma, diabetes mellitus, epilepsy, migraine, porphyria, systemic lupus erythematosus, and hepatic hemangiomas and should be used with caution in women with these conditions. Effects on Barrier Contraception PREMARIN Vaginal Cream exposure has been reported to weaken latex condoms. The potential for PREMARIN Vaginal Cream to weaken and contribute to the failure of condoms, diaphragms, or cervical caps made of latex or rubber should be considered. Central Nervous System Headache, migraine, dizziness, mental depression, nervousness, mood disturbances, irritability, dementia Miscellaneous

Inscrease or decrease in weight, glucose intolerance, edema, arthralgias, leg cramps, changes in libido, urticaria, anaphylactic reactions, exacerbation of asthma, increased triglycerides, hypersensitivity. Additional postmarketing adverse reactions have been reported in patients receiving other forms of hormone therapy.

DRUG INTERACTIONS

No formal drug interaction studies have been conducted for PREMARIN Vaginal Cream

Metabolic Interactions

nbin III activity:

Metabolic Interactions In vitro and in vivo studies have shown that estrogens are metabolized partially by cytochrome P450 3A4 (CYP3A4). Therefore, inducers or inhibitors of CYP3A4 may affect estrogen drug metabolism. Inducers of CYP3A4, such as St. John's Wort (*Hypericum perforatum*) preparations, phenobarbital, carbamazepine, and rifampin, may reduce plasma concentrations of estrogens, possibly resulting in a decrease in therapeutic effects and/or changes in the uterine bleeding profile. Inhibitors of CYP3A4, such as erythromycin, clarithromycin, ketoconazole, itraconazole, i USE IN SPECIFIC POPULATIONS

Pregnancy PREMARIN Vaginal Cream should not be used during pregnancy *[see Contraindications (4)]*. There appears to be little or no increased risk of birth defects in children born to women who have used estrogens and progestins as an oral contraceptive inadvertently during early pregnancy.

Autoring domacepute inauverleing doming early pregnancy. Nursing Mothers PREMARIN Vaginal Cream should not be used during lactation. Estrogen administration to nursing mothers has been ishown to decrease the quantity and quality of the breast milk. Detectable amounts of estrogens have been identified in the breast milk of mothers receiving estrogens. Caution should be exercised when PREMARIN Vaginal Cream is administered to a nursing woman. Pediatric Use

PREMARIN Vaginal Cream is not indicated in children. Clinical studies have not been conducted in the pediatric

Geriatric Use

There have not been sufficient numbers of geriatric women involved in clinical studies utilizing PREMARIN Vaginal Cream to determine whether those over 65 years of age differ from younger subjects in their respo to PREMARIN Vaginal Cream.

The Women's Health Initiative Study In the Women's Health Initiative (WH) estrogen-alone substudy (daily conjugated estrogens 0.625 mg versus placebo), there was a higher relative risk of stroke in women greater than 65 years of age [see Clinical Studies (14.2) in full prescribing information].

In the prescripting information. In the WHI estrogen plus progestin substudy, there was a higher relative risk of nonfatal stroke and invasive breast cancer in women greater than 65 years of age [see Clinical Studies (14.2) in full prescripting information]. The Women's Health Initiative Memory Study In the Women's Health Initiative Memory Study (WHIMS) of postmenopausal women 65 to 79 years of age, there was an increased risk of developing probable dementia in women receiving estrogen-alone or estrogen plus progestin when compared to placebo [see Clinical Studies (14.3) in full prescribing information].

Since both ancillary studies were conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women[®] [see Clinical Studies (14.3) in full prescribing information] Renal Impairment The effect of renal impairment on the pharmacokinetics of PREMARIN Vaginal Cream has not been studied.

Hepatic Impairment The effect of hepatic impairment on the pharmacokinetics of PREMARIN Vaginal Cream has not been studied.

OVERDOSAGE Overdosage of estrogen may cause nausea and vomiting, breast tenderness, dizziness, abdominal pain, drowsiness/fatigue, and withdrawal bleeding in women. Treatment of overdose consists of discontinuation of PREMARIN therapy with institution of appropriate symptomatic care. This brief summary is based on PREMARIN Vaginal Cream Prescribing Information W10413C022 ET01, Rev 05/10.



were Asian or Pacific Islander, 13% were black, 10% were Hispanic, and the rest were of other races or ethnicities.

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The women had a mean gestational age of 39.4 weeks, and 99% had singleton pregnancies. Nearly three-fourths delivered vaginally.

Overall, 24% of the women had a positive result on the intrapartum GBS culture, according to Dr. Gupta.

The rapid test, compared with antepartum culture, had a significantly better sensitivity (91% vs. 69%) and negative predictive value (97% vs. 91%), and a similarly high specificity (98% vs. 96%) and positive predictive value (92% vs. 84%).

The results of antepartum and intrapartum culture were discordant in 10% of women overall. But the rate of discordance varied by race/ethnicity (P = .006), ranging from 4% in Asian women to 18% and 19% in their black and Hispanic counterparts, respectively.

Among women with a negative antepartum culture, 9% had a positive intrapartum culture, Dr. Gupta reported. Most of this subset did not receive intrapartum antibiotics (98%) and had infants who did not receive a sepsis evaluation (78%). Fully 81% of the subset had a positive rapid test result.

Previous studies of NAAT testing have raised concerns about the frequency of indeterminate test results in clinical practice, he noted. The results of the rapid test were indeterminate on first testing in 13% of the women studied, but they were indeterminate on repeated testing in merely 2%. The sample preparation time for the rapid test was 5 minutes, and the median processing time was 48 minutes, with 99.6% of samples processed in 50 minutes or less.

"Future work is needed to continue to explore the role of intrapartum GBS NAAT in clinical practice," Dr. Gupta asserted. "It may be that the NAAT will prove to be a useful adjunct in certain populations in which the antepartum culture may not be a sufficient determinant of intrapartum GBS risk, such as [women who] are GBS negative on antepartum culture, black and Hispanic women, and preterm deliveries."

The study did not have adequate power to assess the potential impact of the rapid test on neonatal outcomes, but they should be a focus in future studies, he recommended.

When asked by an attendee if he would argue with new guidelines that recommend prophylaxis in women with risk factors even if they have a negative NAAT test result, Dr. Gupta emphatically said he would not argue with them.

"I don't think any of us ... involved in this study would look at the NAAT as a replacement for antepartum screening. Antepartum screening clearly has been incredibly effective and very important for reducing the burden of GBS disease, so I think the idea would be that NAAT might be a supplement in certain populations who are currently being missed by the antepartum culture," he commented. "So I agree with current treatment for either antepartum culture-positive moms or moms with other risk factors. This [test] doesn't really seem to replace that."

of moderate to severe symptoms of vulvar and vaginal atrophy. **Drug-Laboratory Test Interactions** Accelerated prothrombin time, partial thromboplastin time, and platelet aggregation time; increased platincreased factors II, VII antigen, VIII antigen, VIII caqualant activity, IX, X, XII, VII-X complex, II-VII-X completa-thromboplobulin; decreased levels of antifactor X and antifitrombin III decreased antifitrombin III increased levels of fibrinogen and fibrinogen activity; increased plasminogen antigen and activity. Increased thyroid-binding globulin (TBG) leading to increased circulating total thyroid-binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured b protein-bound iodine (PB), T, levels (by column or by radioimmunoassar, T, resin uptake is decreased, reflecting the elevated TBG, Free T, and free T, concentrations are unaltered. Wome on thyroid replacement therapy may require higher doses of thyroid hormone. Other binding proteins may be elevated in serum, for example, corticosteroid binding globulin (CBG), sex hormone-binding globulin (SHBG), leading to increased total circulating corticosteroids and sex steroids, respectively. Free hormone concentrations, such as testosterone and estratiol, may be decreased. Other plasm proteins may be increased (angiotensinogen/renin substrate, alpha-1-antitrypsin, ceruloplasmin).

Laboratory Tests Serum follicle stimulating hormone and estradiol levels have not been shown to be useful in the management of moderate to severe symptoms of vulvar and vaginal atrophy.

Increased plasma HDL and HDL₂ cholesterol subfraction concentrations, reduced LDL cholesterol concentrations, increased triglyceride levels. e tolerance. Impaired glucose tolera ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the labeling: Cardiovascular Disorders [see Boxed Warning, Warnings and Precautions (5.2)]
Endometrial Cancer [see Boxed Warning, Warnings and Precautions (5.3)]

Clinical Study Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trial of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

reflect the rates observed in practice. In a 12-week, randomized, double-blind, placebo-controlled trial of PREMARIN Vaginal Cream (PVC), a total of 423 postmenopausal women received at least 1 dose of study medication and were included in all safety analyses: 143 women in the PVC-21/7 treatment group (0.5 g PVC daily for 21 days, then 7 days off), 72 wor in the matching placebo treatment group; 140 women in the PVC-2x/wk treatment group (0.5 g PVC twice weekly), 68 women in the matching placebo treatment group. A 40-week, open-label extension followed, in which a total of 394 women received treatment with PVC, including those subjects randomized at baseline to placebo. In this study, the most common adverse reactions > 5 percent are shown below (Table 1) *[see Clinical Studies (14.1) in full prescribing information].*

Table 1: Number (%) of Patients Reporting Treatment Emergent Adverse Events \ge 5 Percent Only				
Treatment				
Body System ^a Adverse Event	PVC 21/7 (n=143)	Placebo 21/7 (n=72)	PVC 2x/wk (n=140)	Placebo 2x/wk (n=68)
	Number (%) of Patients with Adverse Event			
Any Adverse Event	95 (66.4)	45 (62.5)	97 (69.3)	46 (67.6)
Body As A Whole				
Abdominal Pain	11 (7.7)	2 (2.8)	9 (6.4)	6 (8.8)
Accidental Injury	4 (2.8)	5 (6.9)	9 (6.4)	3 (4.4)
Asthenia	8 (5.6)	0	2 (1.4)	1 (1.5)
Back Pain	7 (4.9)	3 (4.2)	13 (9.3)	5 (7.4)
Headache	16 (11.2)	9 (12.5)	25 (17.9)	12 (17.6)
Infection	7 (4.9)	5 (6.9)	16 (11.4)	5 (7.4)
Pain	10 (7.0)	3 (4.2)	4 (2.9)	4 (5.9)
Cardiovascular System				

Addition of a Progestin When a Woman Has Not Had a Hysterectomy Studies of the addition of a progestin for 10 or more days of a cycle of estrogen administration or daily with estrogen in a continuous regimen have reported a lowered incidence of endometrial hyperplasia than would be induced by estrogen treatment alone. Endometrial hyperplasia may be a precursor to endometrial cancer. There are, however, possible risks that may be associated with the use of progestins with estrogens compared to estrogen-alone regimens. These include an increased risk of breast cancer. In a small number of case reports, substantial increases in blood pressure have been attributed to idiosyncratic reactions to estrogens. In a large, randomized, placebo-controlled clinical trial, a generalized effect of estrogen therapy on blood pressure was not seen. Hypertriglyceridemia In patients with pre-existing hypertriglyceridemia, estrogen therapy may be associated with elevations of plasma triglycerides leading to pancreatitis. Consider discontinuation of treatment if pancreatitis occurs. Hepatic Impairment and/or Past History of Cholestatic Jaundice Estrogens may be poorly metabolized in women with impaired liver function. For women with a history of cholestatic jaundice associated with past estrogen use or with pregnancy, caution should be exercised, and in the case of recurrence, medication should be discontinued. Hypothyroidism Estrogen administration leads to increased thyroid-binding globulin (TBG) levels. Women with normal thyroid function can compensate for the increased TBG by making more thyroid hormone, thus maintaining free T₁ and T₃ serum concentrations in the normal range. Women dependent on thyroid hormone replacement therapy who are also receiving estrogens may require increased doses of their thyroid hormone levels in an acceptable range. Body system totals are not necessarily the sum of the report two or more different adverse events in the same