

Fluconazole-Resistant *Candida* VVC Emerging

BY PATRICE WENDLING

EXPERT ANALYSIS FROM THE ANNUAL MEETING OF THE INFECTIOUS DISEASES SOCIETY FOR OBSTETRICS AND GYNECOLOGY

CHICAGO – Even though the numbers remain small, fluconazole-resistant *Candida albicans* vulvovaginitis appears to be emerging as a thorny clinical problem, one expert suggests.

Since its introduction in 1990 as a prophylactic antifungal agent after bone marrow transplantation, fluconazole (Diflucan) has become established as the dominant therapy for vulvovaginal candidiasis (VVC) worldwide. In North America alone, roughly 8 million cases of recurrent vulvovaginitis are reported annually, with more than 90% due to *C. albicans*.

“So the possibility of resistance is a

tremendous problem and concern,” asserted Dr. Jack D. Sobel, chief of the division of infectious diseases and professor of obstetrics and gynecology at Wayne State University in Detroit.

Women with recurrent vulvovaginitis are treated with induction and prolonged, low-dose maintenance fluconazole regimens to achieve an asymptomatic state. Successful control, not cure, is achieved in more than 90%. Suscepti-

bility testing for *C. albicans* is not standard of care, so there is very little published data on prolonged fluconazole use, Dr. Sobel said at the meeting.

He and his colleagues published the only study to address the issue of resistance, and it failed to identify any evidence of fluconazole resistance in isolates of *C. albicans* after just 1 year of follow-up (N. Engl. J. Med. 2004;351:876-83).



BRIEF SUMMARY OF PRESCRIBING INFORMATION

Please consult full prescribing information.

INDICATIONS AND USAGE

Makena is a progestin indicated to reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth. The effectiveness of Makena is based on improvement in the proportion of women who delivered <37 weeks of gestation. There are no controlled trials demonstrating a direct clinical benefit, such as improvement in neonatal mortality and morbidity.

Limitation of use: While there are many risk factors for preterm birth, safety and efficacy of Makena has been demonstrated only in women with a prior spontaneous singleton preterm birth. It is not intended for use in women with multiple gestations or other risk factors for preterm birth.

CONTRAINDICATIONS

Do not use Makena in women with any of the following conditions:

- Current or history of thrombosis or thromboembolic disorders
- Known or suspected breast cancer, other hormone-sensitive cancer, or history of these conditions
- Undiagnosed abnormal vaginal bleeding unrelated to pregnancy
- Cholestatic jaundice of pregnancy
- Liver tumors, benign or malignant, or active liver disease
- Uncontrolled hypertension

WARNINGS AND PRECAUTIONS

Thromboembolic Disorders

Discontinue Makena if an arterial or deep venous thrombotic or thromboembolic event occurs.

Allergic Reactions

Allergic reactions, including urticaria, pruritus and angioedema, have been reported with use of Makena or with other products containing castor oil. Consider discontinuing the drug if such reactions occur.

Decrease in Glucose Tolerance

A decrease in glucose tolerance has been observed in some patients on progestin treatment. The mechanism of this decrease is not known. Carefully monitor prediabetic and diabetic women while they are receiving Makena.

Fluid Retention

Because progestational drugs may cause some degree of fluid retention, carefully monitor women with conditions that might be influenced by this effect (e.g., preeclampsia, epilepsy, migraine, asthma, cardiac or renal dysfunction).

Depression

Monitor women who have a history of clinical depression and discontinue Makena if clinical depression recurs.

Jaundice

Carefully monitor women who develop jaundice while receiving Makena and consider whether the benefit of use warrants continuation.

Hypertension

Carefully monitor women who develop hypertension while receiving Makena and consider whether the benefit of use warrants continuation.

ADVERSE REACTIONS

For the most serious adverse reactions to the use of progestins, see *Warnings and Precautions*.

Clinical Trials Experience

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

In a vehicle (placebo)-controlled clinical trial of 463 pregnant women at risk for spontaneous preterm delivery based on obstetrical history, 310 received 250 mg of Makena and 153 received a vehicle formulation containing no drug by a weekly intramuscular injection beginning at 16 to 20 weeks of gestation and continuing until 37 weeks of gestation or delivery, whichever occurred first. [See *Clinical Studies*.]

Certain pregnancy-related fetal and maternal complications or events were numerically increased in the Makena-treated subjects as compared to control subjects, including miscarriage and stillbirth, admission for preterm labor, preeclampsia or gestational hypertension, gestational diabetes, and oligohydramnios (Tables 1 and 2).

Table 1 Selected Fetal Complications

Pregnancy Complication	Makena n/N	Control n/N
Miscarriage (<20 weeks) ¹	5/209	0/107
Stillbirth (≥20 weeks) ²	6/305	2/153

¹N = Total number of subjects enrolled prior to 20 weeks 0 days

²N = Total number of subjects at risk ≥20 weeks

Table 2 Selected Maternal Complications

Pregnancy Complication	Makena N=310 %	Control N=153 %
Admission for preterm labor ¹	16.0	13.8
Preeclampsia or gestational hypertension	8.8	4.6
Gestational diabetes	5.6	4.6
Oligohydramnios	3.6	1.3

¹Other than delivery admission.

Common Adverse Reactions:

The most common adverse reaction was injection site pain, which was reported after at least one injection by 34.8% of the Makena group and 32.7% of the control group. Table 3 lists adverse reactions that occurred in ≥2% of subjects and at a higher rate in the Makena group than in the control group.

Table 3 Adverse Reactions Occurring in ≥2% of Makena-Treated Subjects and at a Higher Rate than Control Subjects

Preferred Term	Makena N=310 %	Control N=153 %
Injection site pain	34.8	32.7
Injection site swelling	17.1	7.8
Urticaria	12.3	11.1
Pruritus	7.7	5.9
Injection site pruritus	5.8	3.3
Nausea	5.8	4.6
Injection site nodule	4.5	2.0
Diarrhea	2.3	0.7

In the clinical trial, 2.2% of subjects receiving Makena were reported as discontinuing therapy due to adverse reactions compared to 2.6% of control subjects. The most common adverse reactions that led to discontinuation in both groups were urticaria and injection site pain/swelling (1% each).

Pulmonary embolus in one subject and injection site cellulitis in another subject were reported as serious adverse reactions in Makena-treated subjects.

DRUG INTERACTIONS

No drug-drug interaction studies were conducted with Makena.

Drugs Metabolized by CYP1A2, CYP2A6 and CYP2B6

The metabolism of drugs metabolized by CYP1A2 (such as theophylline, tizadine, clozapine), CYP2A6 (such as acetaminophen, halothane, nicotine) and CYP2B6 (such as efavirenz, bupropion, methadone) may be increased during treatment with Makena [See *Clinical Pharmacology*].

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category B: There are no adequate and well-controlled studies of Makena use in women during the first trimester of pregnancy. Data from a vehicle (placebo)-controlled clinical trial of 310 pregnant women who received Makena at weekly doses of 250 mg by intramuscular injection in their second and third trimesters, as well as long-term (2-5 years) follow-up safety data on 194 of their infants, did not demonstrate any teratogenic risks to infants from in utero exposure to Makena.

Reproduction studies have been performed in mice and rats at doses up to 95 and 5, respectively, times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to Makena.

Makena administration produced embryolethality in rhesus monkeys but not in cynomolgus monkeys exposed to 1 and 10 times the human dose equivalent every 7 days between days 20 and 146 of gestation. There were no teratogenic effects in either species.

Labor and Delivery

Makena is not intended for use to stop active preterm labor. The effect of Makena in active labor is unknown.

Nursing Mothers

Discontinue Makena at 37 weeks of gestation or upon delivery. Detectable amounts of progestins have been identified in the milk of mothers receiving progestin treatment. Many studies have found no adverse effects of progestins on breastfeeding performance, or on the health, growth, or development of the infant.

Pediatric Use

Makena is not indicated for use in children. Safety and effectiveness in pediatric patients less than 16 years of age have not been established. A small number of women under age 18 years were studied; safety and efficacy are expected to be the same in women aged 16 years and above as for users 18 years and older. [See *Clinical Studies*.]

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Nystatin: Old is New Again

Although it was patented back in 1957 as the world's first antifungal, antibiotic nystatin upstaged newer antifungal agents when used to treat vulvovaginal candidiasis caused by *Candida glabrata* in sequential, prospective clinical trials.

On day 7 to day 14 of follow-up, mycological cure of *C. glabrata* vulvovaginitis was achieved by 15 of 16 women (94%) treated with a nystatin vaginal suppository, compared with 8 of 19 (42%) given a miconazole nitrate vaginal suppository, 5 of 9 (56%) given oral fluconazole (Diflucan) and 7 of 15 (47%) given oral itraconazole (Sporanox). At day 30 to day 35 of follow-up, mycological cure rates, based on a positive or negative *Candida* culture, were 94%, 33%, 56%, and 40%, respectively.

“Nystatin vaginal suppository could be a therapy choice for vulvovaginal candidiasis caused by *Candida glabrata*,” Dr. Shangrong Fan said at the meeting.

While *C. albicans* is the most commonly isolated species, various studies have reported a shift towards infections caused by non-*albicans* *Candida* species such as *C. glabrata*.

The women were enrolled prospectively in separate, sequential, nonrandomized clinical trials and treated with nystatin vaginal suppository at 20 MU per day for 7 days or two 1,200-mg doses of miconazole vaginal suppositories 72 hours apart or oral fluconazole two 150-mg doses 72 hours apart or oral itraconazole 200 mg two times for 1 day.

Dr. Fan, an obstetrician/gynecologist and his colleagues at Peking University Shenzhen Hospital in Shenzhen, China, also conducted an in vitro susceptibility study. The in vitro susceptible rate of *C. glabrata* on nystatin was 100% (57/57), compared with 90% (51/57) for miconazole, 58% (40/69) for fluconazole, and 87% (58/67) for itraconazole. Resistance to nystatin or miconazole was not observed, and occurred in 3% of strains exposed to fluconazole and 1.5% exposed to itraconazole.

Dr. Fan and his associates reported no relevant financial disclosures.

Clinicians at Wayne State's Vaginitis Clinic, however, have observed an uptick in the frequency of refractory *Candida* vulvovaginitis cases in the last 10 years among the more than 500 women with recurrent vulvovaginitis that they follow. The women present either on a maintenance fluconazole regimen with a breakthrough of symptoms accompanied by positive cultures or fail to resolve acute symptomatic vulvovaginitis with multidose fluconazole and have increased minimum inhibitory concentration (MIC) in vitro, Dr. Sobel explained.

A retrospective review of patients referred to the Vaginitis Clinic between 2000 and 2010 revealed 25 patients with clinically refractory fluconazole-resistant vulvovaginitis with confirmed in vitro resistance, with an MIC at least 2 mcg/mL (median 8 mcg/mL).

"Two-thirds of these patients were seen in the last 5 years, so the incidence is increasing," he said.

Eight patients had an MIC of 2 mcg/mL and 17 had MICs ranging from 4 to 128 mcg/mL.

Cross resistance to itraconazole (Sporanox) was present in five women and to ketoconazole (Nizoral) in four.

The cohort consists of married, insured Caucasian women with an average or above average socioeconomic status. Their mean age was 43 years (range 32-56 years). All patients had significant consumption of and recent exposure to fluconazole, with 64% on low-dose, weekly maintenance fluconazole.

Significant risk factors for refractory *Candida* VVC included more than 10 lifetime sexual partners, recent use of antibiotics, and for mycological failure included increased fluconazole exposure and older age of VVC onset.

Management

Management of refractory VVC is possible, but can be extremely difficult, Dr. Sobel acknowledged.

"When you can't use fluconazole, the closet is pretty empty," he said.

Dr. Sobel recommends initially using boric acid 600 mg per day for 14 days until an MIC is available. For those with low-level resistance, defined by an MIC of 2-4 mcg/mL, clinicians should increase the fluconazole dose to 150-200 mg twice weekly. Eleven of the 25 patients in the study cohort were controlled on this regimen, with five eventually discontinuing fluconazole.

"In patients with high level resistance, treatment depends on the presence of azole cross-resistance," he said.

Among eight such patients, three were successfully controlled on 200 mg per day of itraconazole, and four of five were controlled on ketoconazole 100 mg per day, both typically for several months.

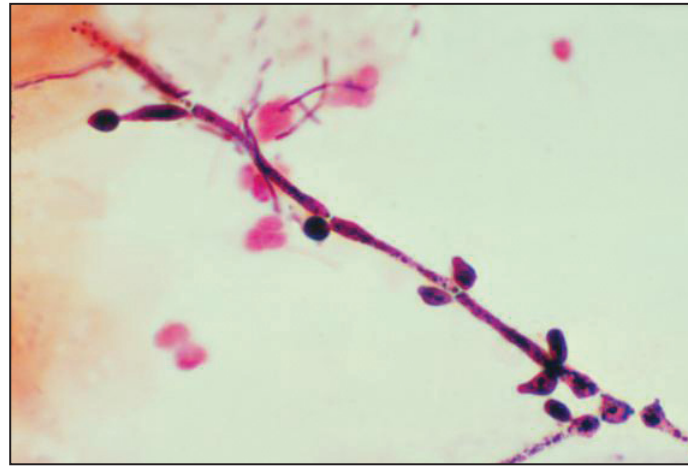
One patient required daily gentian violet for 14 days, with cure, and three patients were controlled on boric acid three times per week.

The novel, oral broad-spectrum antifungal, voriconazole (Vfend) is a possibility, but is rarely used because it is so poorly tolerated, Dr. Sobel said.

Audience members questioned whether flucytosine (Ancobon), a synthetic antimycotic, can be employed. Specialty pharmacies can formulate it, but at \$1,500 to \$2,000 per tube is out of reach for most women. The ancient antifungal antibiotic nystatin is a far cheaper alternative, but should be given at 100,000 units daily per vagina only, Dr. Sobel said.

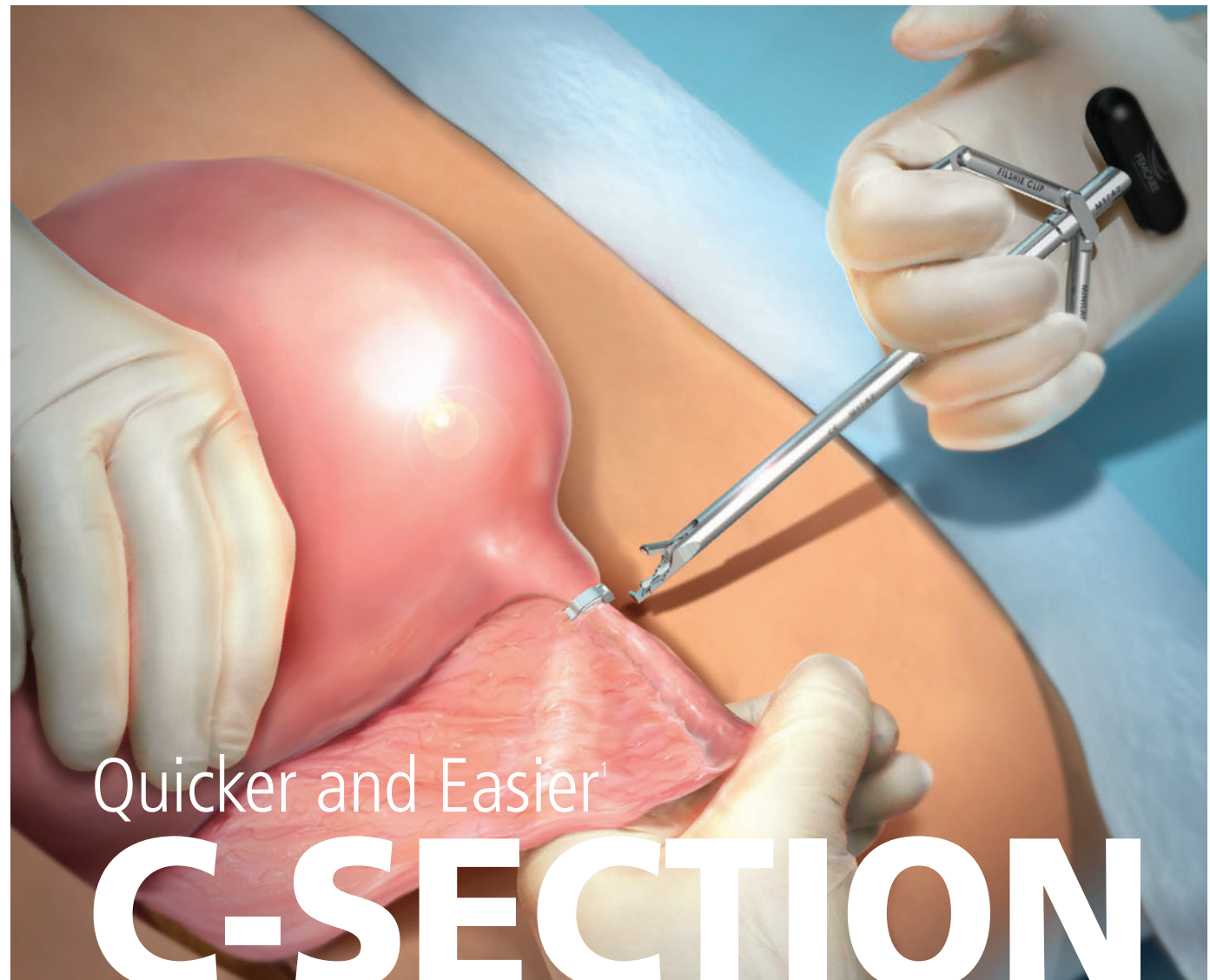
"We urgently need new classes of antifungal agents for *Candida* vaginitis," he said.

Dr. Sobel and his colleagues reported no relevant financial disclosures. ■



COURTESY CDC/DR. STUART BROWN

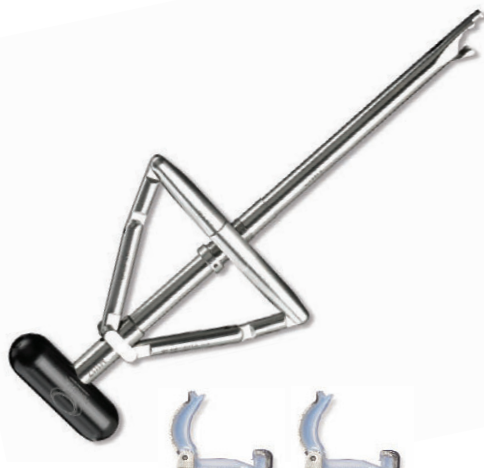
This is a photomicrograph of a vaginal smear identifying *Candida albicans* using a Gram-stain technique.



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