

Ovarian Suppression Linked to More Migraines

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BOCA RATON, FLA. – Ovarian suppression to treat endometriosis might cause a woman to experience significantly more migraines, and more sleep disturbances, numbness, joint pain, hot

flashes, and heart palpitations, a study showed. Some women also experience more depression.

Migraines affect more than three times as many women as men in the United States. Decreases in hormone levels and sex steroids in the late luteal phase of the menstrual period, during the postpartum period, and during perimenopause, for example, can increase a woman's susceptibility to migraines. Researchers

noted that treatments that lower a woman's estrogen levels to tackle endometriosis might, at the same time, increase her risk for more severe and more frequent migraines and depressive symptoms.

Dr. Julia K. Warnock said that gonadotropin-releasing hormone (GnRH) agonists will decrease estrogen and increase the risk of headaches, including migraines, and increase the risk for depressive symptoms. Some women are

more sensitive to mood-related hormonal changes, said Dr. Warnock, professor of psychiatry and director of clinical research at the University of Oklahoma Health Science Center in Tulsa.

"As the patient transitions through the reproductive cycle, a number of [her] associated mood symptoms ... are influenced by fluctuations in estrogen," said study coauthor Dr. J. Clark Bundren, an ob.gyn. in private practice in Tulsa. "Proper supplementation of low-dose estradiol in this population can improve migraine headache, anxiety, and depression," Dr. Bundren said.

Dr. Warnock and colleagues evaluated baseline hormone levels, depression, and physical symptoms for 56 women with endometriosis. They completed the MENSEI (Menopause Symptom Index) and the HAM-D (Hamilton Rating Scale for Depression). They were then treated with 3.75 mg GnRH agonist via intramuscular

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injection daily for 28 days, and reevaluated at 1 month, 2 months, and 5 months.

A significant increase in the frequency of headaches was observed at each follow-up, according to an item level chi square analysis of MENSEI scores, compared with baseline. Total MENSEI scores likewise significantly increased at 1, 3, and 5 months, according to a t-test of dependent samples. Similarly, depressive symptoms significantly increased, compared with baseline, at months 1, 3, and 5, as reflected by the percentages of women who scored greater than 10 on the HAM-D.

"Psychiatrists should consider hormonal fluctuations in the treatment of women [with depression]," Dr. Warnock said, because decreases in estrogen levels can predispose some to worsening depression. Combination hormone and antidepressant treatment can have synergistic benefits. "Together is better." This dual approach also can mean lower doses of antidepressants and therefore, lower risk of associated adverse events.

As for the risks associated with hormone therapy, Dr. Bundren said, "Women on estrogen alone have a decreased risk of breast cancer, but it's not a simple message."

"It matters which estrogen, which patient, and how it's delivered," Dr. Warnock said. "In general, transdermal is better than oral. For women who are suffering, it's about their quality of life."

The study was limited by patient self-report of headache frequency on the MENSEI, and a lack of assessment of progesterone or its metabolites.

The study was unfunded. Dr. Warnock and Dr. Bundren said they had no relevant disclosures. ■

Makena[®]
hydroxyprogesterone
caproate injection

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, tizidine, 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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