

Endometriosis: Surgery Alone Won't Tx Fertility

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EXPERT ANALYSIS FROM A MEETING
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FOUNDATION OF AMERICA

NEW YORK – Surgery alone won't completely treat infertility in women with endometriosis, according to one infertility expert.

Instead, physicians need to consider all of their options. In women with signifi-

cant endometriosis, the best course for improving pregnancy rates may be surgery plus some form of assisted reproductive technology (ART), Dr. Hugh S. Taylor, director of reproductive endocrinology and infertility at Yale University, New Haven, Conn., said at the meeting.

Prospective randomized trials examining surgical interventions in endometriosis do demonstrate improvements in pregnancy rates. In a study by the

Canadian Collaborative Group on Endometriosis that included 341 infertile women with mild endometriosis who underwent either a diagnostic laparoscopy or resection or ablation of visible endometriosis, pregnancy rates nearly doubled with removal of endometriotic lesions. Diagnostic laparoscopy resulted in a subsequent pregnancy rate of about 17.7%, while the pregnancy rate was 30.7% in women whose lesions were removed. The

pregnancy rates per month rose from about 2.4% in the control group to about 4.7% in the intervention group (N. Engl. J. Med. 1997;337:217-22).

Although the study showed an increase in pregnancy rates, those rates are still very low. Comparatively, without treatment, women with stage I or II endometriosis-associated infertility have a spontaneous monthly fecundity rate between 2% and 3%, Dr. Taylor said, and treatment with in vitro fertilization (IVF) can result in monthly pregnancy rates of 30%-50% in women with endometriosis.

One reason that surgery doesn't provide a meaningful boost in fertility is that surgeons often fail to identify endometriotic lesions and so don't perform a full resection. Adding to this problem, the staging system used for endometriosis isn't very accurate and doesn't correlate well with pain or infertility.

The biggest problem, however, in using surgery to correct fertility problems associated with endometriosis is that the disease creates epigenetic changes in the endometrium that may not be reversible, even if the endometriotic lesions are ful-

LYSTEDA™

(tranexamic acid) tablets

BRIEF SUMMARY OF PRESCRIBING INFORMATION

Please consult package insert for full Prescribing Information

INDICATIONS AND USAGE

LYSTEDA™ (tranexamic acid) tablets is indicated for the treatment of cyclic heavy menstrual bleeding. Prior to prescribing LYSTEDA, exclude endometrial pathology that can be associated with heavy menstrual bleeding.

DOSE AND ADMINISTRATION

Recommended Dosage

The recommended dose of LYSTEDA for women with normal renal function is two 650 mg tablets taken three times daily (3900 mg/day) for a maximum of 5 days during monthly menstruation. LYSTEDA may be administered without regard to meals. Tablets should be swallowed whole and not chewed or broken apart.

Renal Impairment: In patients with renal impairment, the plasma concentration of tranexamic acid increased as serum creatinine concentration increased. Dosage adjustment is needed in patients with serum creatinine concentration higher than 1.4 mg/dL (Table 1).

Table 1. Dosage of LYSTEDA in Patients with Renal Impairment

Serum Creatinine (mg/dL)	LYSTEDA	
	Adjusted Dose	Total Daily Dose
Cr above 1.4 and ≤ 2.8	1300 mg (two 650 mg tablets) two times a day for a maximum of 5 days during menstruation	2600 mg
Cr above 2.8 and ≤ 5.7	1300 mg (two 650 mg tablets) once a day for a maximum of 5 days during menstruation	1300 mg
Cr above 5.7	650 mg (one 650 mg tablet) once a day for a maximum of 5 days during menstruation	650 mg

CONTRAINDICATIONS

Thromboembolic Risk: Do not prescribe LYSTEDA to women who are known to have the following conditions: active thromboembolic disease (e.g., deep vein thrombosis, pulmonary embolism, or cerebral thrombosis), a history of thrombosis or thromboembolism, including retinal vein or artery occlusion, an intrinsic risk of thrombosis or thromboembolism (e.g., thrombotic valvular disease, thrombotic cardiac rhythm disease, or hypercoagulopathy). Venous and arterial thrombosis or thromboembolism, as well as cases of retinal artery and retinal vein occlusions, have been reported with tranexamic acid. **Hypersensitivity to Tranexamic Acid:** Do not prescribe LYSTEDA to women with known hypersensitivity to tranexamic acid [see *Warnings and Precautions* and *Adverse Reactions*].

WARNINGS AND PRECAUTIONS

Hormonal Contraceptives: Combination hormonal contraceptives are known to increase the risk of venous thromboembolism, as well as arterial thromboses such as stroke and myocardial infarction. Because LYSTEDA is antifibrinolytic, concomitant use of hormonal contraception and LYSTEDA may further exacerbate this increased thrombotic risk. Women using hormonal contraception were excluded from the clinical trials supporting the safety and efficacy of LYSTEDA, and there are no clinical trial data on the risk of thrombotic events with the concomitant use with hormonal contraceptives. Therefore, women using hormonal contraception should use LYSTEDA only if there is a strong medical need and the benefit of treatment will outweigh the potential increased risk of a thrombotic event. **Severe Allergic Reaction:** A case of severe allergic reaction to LYSTEDA was reported in the clinical trials, involving a subject who experienced dyspnea, tightening of her throat, and facial flushing that required emergency medical treatment. A case of anaphylactic shock has also been reported in the literature, involving a patient who received an intravenous bolus of tranexamic acid. **Ocular Effects:** Retinal venous and arterial occlusion has been reported in patients using tranexamic acid. Patients should be instructed to report visual and ocular symptoms promptly. In the event of such symptoms, patients should be instructed to discontinue LYSTEDA immediately and should be referred to an ophthalmologist for a complete ophthalmic evaluation, including dilated retinal examination, to exclude the possibility of retinal venous or arterial occlusion. Lignous conjunctivitis also has been reported in patients taking tranexamic acid. The conjunctivitis resolved following cessation of the drug. **Factor IX Complex Concentrates or Anti-Inhibitor Coagulant Concentrates:** LYSTEDA is not recommended for women taking either Factor IX complex concentrates or anti-inhibitor coagulant concentrates because the risk of thrombosis may be increased [see *Drug Interactions*]. **All-Trans Retinoic Acid (Oral Retinoin):** Exercise caution when prescribing LYSTEDA to women with acute promyelocytic leukemia taking all-trans retinoic acid for remission induction because of possible exacerbation of the procoagulant effect of all-trans retinoic acid [see *Drug Interactions*]. **Subarachnoid Hemorrhage:** Cerebral edema and cerebral infarction may be caused by use of LYSTEDA in women with subarachnoid hemorrhage.

ADVERSE REACTIONS

Clinical Trial 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 clinical practice. **Short-term Studies:** The safety of LYSTEDA in the treatment of heavy menstrual bleeding (HMB) was studied in two randomized, double-blind, placebo-controlled studies. One study compared the effects of two doses of LYSTEDA (1950 mg and 3900 mg given daily for up to 5 days during each menstrual period) versus placebo over a 3-cycle treatment duration. A total of 304 women were randomized to this study, with 115 receiving at least one dose of 3900 mg/day of LYSTEDA. A second study compared the effects of LYSTEDA (3900 mg/day) versus placebo over a 6-cycle treatment duration. A total of 196 women were randomized to this study, with 117 receiving at least one dose of LYSTEDA. In both studies, subjects were generally healthy women who had menstrual blood loss of ≥80 mL. In these studies, subjects were 18 to 49 years of age with a mean age of approximately 40 years, had cyclic menses every 21-35 days, and a BMI of approximately 32 kg/m². On average, subjects had a history of HMB for approximately 10 years and 40% had fibroids as determined by transvaginal ultrasound. Approximately 70% were Caucasian, 25% were Black, and 5% were Asian, Native American, Pacific Islander, or Other. Seven percent (7%) of all subjects were of Hispanic origin. Women using hormonal contraception were excluded from the trials. The rates of discontinuation due to adverse events during the two clinical trials were comparable between LYSTEDA and placebo. In the 3-cycle study, the rate in the 3900 mg LYSTEDA dose group was 0.8% as compared to 1.4% in the placebo group. In the 6-cycle study, the rate in the LYSTEDA group was 2.4% as compared to 4.1% in the placebo group. Across the studies, the combined exposure to 3900 mg/day LYSTEDA was 947 cycles and the average duration of use was 3.4 days per cycle. The following adverse events occurred in ≥5% of subjects and more frequently in LYSTEDA-treated subjects receiving 3900 mg/day (N = 232) compared to placebo (N = 139). The total number of adverse events reported with LYSTEDA was 1500 versus 923 with placebo. The number of subjects with at least one adverse event was 208 (89.7%) with LYSTEDA versus 122 (87.8%) with placebo. The following adverse events reported in LYSTEDA-treated subjects receiving 3900 mg/day and placebo, respectively, were (n/%):

headache (includes headache and tension headache): 17 (50.4%), 65 (46.8%); nasal & sinus symptoms (includes nasal, respiratory tract and sinus congestion, sinusitis, acute sinusitis, sinus headache, allergic sinusitis and sinus pain, and multiple allergies and seasonal allergies): 59 (25.4%), 24 (17.3%); back pain: 48 (20.7%), 21 (15.1%); abdominal pain (includes abdominal tenderness and discomfort): 46 (19.8%), 25 (18.0%); musculoskeletal pain (includes musculoskeletal discomfort and myalgia): 26 (11.2%), 4 (2.9%); arthralgia (includes joint stiffness and swelling): 16 (6.9%), 7 (5.0%); muscle cramps & spasms: 15 (6.5%), 8 (5.8%); migraine: 14 (6.0%), 8 (5.8%); anemia: 13 (5.6%), 5 (3.6%); and fatigue: 12 (5.2%), 6 (4.3%). **Long-term Studies:** Long-term safety of LYSTEDA was studied in two open-label studies. In one study, subjects with physician-diagnosed heavy menstrual bleeding (not using the alkaline hematin methodology) were treated with 3900 mg/day for up to 5 days during each menstrual period for up to 27 menstrual cycles. A total of 781 subjects were enrolled and 239 completed the study through 27 menstrual cycles. A total of 12.4% of the subjects withdrew due to adverse events. Women using hormonal contraception were excluded from the study. The total exposure in this study to 3900 mg/day LYSTEDA was 10,213 cycles. The average duration of LYSTEDA use was 2.9 days per cycle. A long-term open-label extension study of subjects from the two short-term efficacy studies was also conducted in which subjects were treated with 3900 mg/day for up to 5 days during each menstrual period for up to 9 menstrual cycles. A total of 288 subjects were enrolled and 196 subjects completed the study through 9 menstrual cycles. A total of 2.1% of the subjects withdrew due to adverse events. The total exposure to 3900 mg/day LYSTEDA in this study was 1,956 cycles. The average duration of LYSTEDA use was 3.5 days per cycle. The types and severity of adverse events in these two long-term open-label trials were similar to those observed in the double-blind, placebo-controlled studies although the percentage of subjects reporting them was greater in the 27-month study, most likely because of the longer study duration. A case of severe allergic reaction to LYSTEDA was reported in the extension trial, involving a subject on her fourth cycle of treatment who experienced dyspnea, tightening of her throat, and facial flushing that required emergency medical treatment.

Postmarketing Experience: The following adverse reactions have been identified from postmarketing experience with tranexamic acid. 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. Based on worldwide postmarketing reports, the following have been reported in patients receiving tranexamic acid for various indications: nausea, vomiting, and diarrhea, allergic skin reactions, anaphylactic shock and anaphylactoid reactions, thromboembolic events (e.g., deep vein thrombosis, pulmonary embolism, cerebral thrombosis, acute renal cortical necrosis, and central retinal artery and vein obstruction), impaired color vision and other visual disturbances, dizziness.

DRUG INTERACTIONS

No drug-drug interaction studies were conducted with LYSTEDA. **Hormonal Contraceptives:** Because LYSTEDA is antifibrinolytic, concomitant use of hormonal contraception and LYSTEDA may further exacerbate the increased thrombotic risk associated with combination hormonal contraceptives. Women using hormonal contraception should use LYSTEDA only if there is a strong medical need and the benefit of treatment will outweigh the potential increased risk of a thrombotic event [see *Warnings and Precautions*]. **Factor IX Complex Concentrates or Anti-Inhibitor Coagulant Concentrates:** LYSTEDA is not recommended for women taking either Factor IX complex concentrates or anti-inhibitor coagulant concentrates because the risk of thrombosis may be increased [see *Warnings and Precautions*]. **Tissue Plasminogen Activators:** Concomitant therapy with tissue plasminogen activators may decrease the efficacy of both LYSTEDA and tissue plasminogen activators. Therefore, exercise caution if a woman taking LYSTEDA therapy requires tissue plasminogen activators.

All-Trans Retinoic Acid (Oral Retinoin): Exercise caution when prescribing LYSTEDA to women with acute promyelocytic leukemia taking all-trans retinoic acid for remission induction because of possible exacerbation of the procoagulant effect of all-trans retinoic acid [see *Warnings and Precautions*].

USE IN SPECIFIC POPULATIONS

Pregnancy: (Category B) LYSTEDA is not indicated for use in pregnant women. Reproduction studies have been performed in mice, rats and rabbits and have revealed no evidence of impaired fertility or harm to the fetus due to tranexamic acid. However, tranexamic acid is known to cross the placenta and appears in cord blood at concentrations approximately equal to the maternal concentration. There are no adequate and well-controlled studies in pregnant women. An embryo-fetal developmental toxicity study in rats and a perinatal developmental toxicity study in rats were conducted using tranexamic acid. No adverse effects were observed in either study at doses up to 4 times the recommended human oral dose of 3900 mg/day based on mg/m² (actual animal dose 1500 mg/kg/day). **Nursing Mothers:** Tranexamic acid is present in the mother's milk at a concentration of about one hundredth of the corresponding serum concentration. LYSTEDA should be used during lactation only if clearly needed. **Pediatric Use:** LYSTEDA is indicated for women of reproductive age and is not intended for use in premenarcheal girls. LYSTEDA has not been studied in adolescents under age 18 with heavy menstrual bleeding. **Geriatric Use:** LYSTEDA is indicated for women of reproductive age and is not intended for use by postmenopausal women.

Renal Impairment: The effect of renal impairment on the pharmacokinetics of LYSTEDA has not been studied. Because tranexamic acid is primarily eliminated via the kidneys by glomerular filtration with more than 95% excreted as unchanged in urine, dosage adjustment in patients with renal impairment is needed. [see *Dosage and Administration*]. **Hepatic Impairment:** The effect of hepatic impairment on the pharmacokinetics of LYSTEDA has not been studied. Because only a small fraction of the drug is metabolized, dosage adjustment in patients with hepatic impairment is not needed.

OVERDOSAGE

There are no known cases of intentional overdose with LYSTEDA and no subjects in the clinical program took more than 2 times the prescribed amount of LYSTEDA in a 24-hour period (>7800 mg/day). However, cases of overdose of tranexamic acid have been reported. Based on these reports, symptoms of overdose may include gastrointestinal (nausea, vomiting, diarrhea); hypotensive (e.g., orthostatic symptoms); thromboembolic (arterial, venous, embolic); visual impairment; mental status changes; myoclonus; or rash. No specific information is available on the treatment of overdose with LYSTEDA. In the event of overdose, employ the usual supportive measures (e.g., clinical monitoring and supportive therapy) as dictated by the patient's clinical status.

Rx only

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Lysteda™
(tranexamic acid) tablets



Endometriosis creates epigenetic changes in the endometrium that may not be reversible.

DR. TAYLOR

ly removed. "Once that DNA is modified, it stays that way," Dr. Taylor said. "So we can be removing all of the endometriosis, and yet that change in the uterus won't revert simply by treating the endometriosis."

In an effort to get a better handle on this phenomenon, Dr. Taylor has been studying the effect of the HOXA10 gene – which is required for an embryo to attach to the uterus – in mouse and primate models. In mouse models, when the gene is not expressed the uterus will not be receptive to embryos, even normal embryos. In humans, expression of the HOXA10 gene varies with the menstrual cycle. It increases at the time of implantation and is regulated by estrogen and progesterone. "It looks like it's playing an important role in that implantation process." In women with endometriosis, the HOXA10 gene generally fails to increase, suggesting that there is an implantation defect in women with endometriosis. Dr. Taylor has shown that this failure is due to epigenetic reprogramming of the HOXA10 gene (Semin. Reprod. Med. 2010;28:69-74).

But there is some hopeful news for women with endometriosis who want to conceive, Dr. Taylor said. Researchers are looking at ways to use stem cells to replace the damaged cells. The idea is that placing new cells in the endometrium can restore fertility by making the endometrium more receptive to implantation. ■

Disclosures: Dr. Taylor said he had no conflicts of interest to disclose.