

PCOS Appears to Be Manifesting at Younger Ages

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FROM THE JOURNAL OF PEDIATRIC AND ADOLESCENT GYNECOLOGY

VITALS

Major Finding: Of 58 female patients who were between the ages of 9 and 18 years and were diagnosed with PCOS, 15 (26%) of them were preadolescents aged 9-12 years and 43 (74%) of them were adolescents aged 13-18 years.

Data Source: A cross-sectional retrospective chart study of 58 females aged 9-18 years with PCOS.

Disclosures: No funding sources or financial conflicts of interest were reported.

Polycystic ovary syndrome appears to be manifesting at younger ages than previously thought, a study has shown.

The disorder should be considered and a thorough work-up performed in prepubertal girls who have risk factors suggestive of PCOS, with particular attention given to hyperinsulinemia and early pubarche and thelarche, said Dr. Jason

Bronstein and his associates at New York University.

In what they described as the largest pediatric PCOS study to date, the researchers found "a large subgroup of young PCOS girls with characteristic metabolic derangements at a younger age, suggesting a need for early therapeutic interventions."

Early onset of PCOS does not portend well for future complications such as infertility, metabolic syndrome, and vascular disease.

However, earlier recognition and treatment of PCOS might reduce morbidity in later adolescence and adulthood, they noted.

The investigators performed a retrospective, cross-sectional chart study of 58 patients from diverse ethnic backgrounds who attended two large, urban tertiary care centers and were diagnosed as having PCOS between ages 9 and 18 years. Fifteen (26%) of these subjects were preadolescents aged 9-12 years, and 43 (74%) were adolescents aged 13-18 years.

The severity of PCOS was similar between preadolescents and adolescents. Hyperinsulinemia was present in similar proportions of both groups, indicating that metabolic derangement is already present in the youngest girls with PCOS.

However, preadolescent girls were different in that they had significantly earlier pubarche and thelarche than did adolescent girls with PCOS, and the disorder developed much sooner after thelarche in the younger girls.

Clinicians should look for early pubarche and thelarche in girls predisposed to PCOS, the investigators said (J. Pediatr. Adolesc. Gynecol. 2011;24:15-20).

The two groups also had similar risk factors.

Mothers or other relatives had PCOS in approximately 14% of the study subjects, and there were no significant differences between preadolescents and adolescents in historical risk factors such as gestational age at birth, birth weight, childhood obesity, or family history of obesity, diabetes, or hypertension.

There also were no differences between preadolescents and adolescents in clinical risk factors such as body mass index, acne, hirsutism, alopecia, or hyperandrogenism, and no differences in biochemical risk factors such as serum total testosterone and free testosterone levels, insulin resistance, HDL levels, triglyceride levels, or fasting glucose levels.

These findings show that a high index of suspicion is needed to diagnose PCOS in preadolescents.

"We recommend that pediatricians ascertain risk for PCOS in their patients, including maternal factors, family history, birth weight, metabolic factors, and history of premature pubarche and/or early thelarche," Dr. Bronstein and his colleagues concluded. ■

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.

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., thrombogenic valvular disease, thrombogenic 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

Thromboembolic Risk: Concomitant Use of 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, the risk of venous thromboembolism, as well as arterial thromboses such as stroke, may increase further when hormonal contraceptives are administered with LYSTEDA. This is of particular concern in women who are obese or smoke cigarettes, especially smokers over 35 years of age [see *Contraindications and Drug Interactions*]. 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 of LYSTEDA with hormonal contraceptives. There have been US postmarketing reports of venous and arterial thrombotic events in women who have used LYSTEDA concomitantly with combined hormonal contraceptives. Women using hormonal contraception, especially those who are obese or smoke, 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. Do not use LYSTEDA in women who are taking more than the approved dose of a hormonal contraceptive. **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 Tretinoin):** 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*]. **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. **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. **Subarachnoid Hemorrhage:** Cerebral edema and cerebral infarction may be caused by use of LYSTEDA in women with subarachnoid hemorrhage. **Ligneous Conjunctivitis:** Ligneous conjunctivitis has been reported in patients taking tranexamic acid. The conjunctivitis resolved following cessation of the drug.

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 $\geq 5\%$ 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): 117 (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 US and 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*]. **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. **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*]. **All-Trans Retinoic Acid (Oral Tretinoin):** 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 patient with renal impairment is needed. **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.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility: **Carcinogenesis:** Carcinogenicity studies with tranexamic acid in male mice at doses as high as 6 times the recommended human dose of 3900 mg/day showed an increased incidence of leukemia which may have been related to treatment. Female mice were not included in this experiment. The dose multiple referenced above is based on body surface area (mg/m²). Actual daily dose in mice was up to 5000 mg/kg/day in food. Hyperplasia of the biliary tract and cholangioma and adenocarcinoma of the intrahepatic biliary system have been reported in one strain of rats after dietary administration of doses exceeding the maximum tolerated dose for 22 months. Hyperplastic, but not neoplastic, lesions were reported at lower doses. Subsequent long-term dietary administration studies in a different strain of rat, each with an exposure level equal to the maximum level employed in the earlier experiment, have failed to show such hyperplastic/neoplastic changes in the liver. **Mutagenesis:** Tranexamic acid was neither mutagenic nor clastogenic in the *in vitro* Bacterial Reverse Mutation Assay (Ames test), *in vitro* chromosome aberration test in Chinese hamster cells, and in *in vivo* chromosome aberration tests in mice and rats. **Impairment of Fertility:** Reproductive studies performed in mice, rats and rabbits have not revealed any evidence of impaired fertility or adverse effects on the fetus due to tranexamic acid. In a rat embryo-fetal developmental toxicity study, tranexamic acid had no adverse effects on embryo-fetal development when administered during the period of organogenesis (from gestation days 6 through 17) at doses 1, 2 and 4 times the recommended human oral dose of 3900 mg/day. In a perinatal-postnatal study in rats, tranexamic acid had no adverse effects on pup viability, growth or development when administered from gestation day 6 through postnatal day 20 at doses 1, 2 and 4 times the recommended human oral dose of 3900 mg/day. The dose multiples referenced above are based on body surface area (mg/m²). Actual daily doses in rats were 300, 750 or 1500 mg/kg/day. **Animal Toxicology and/or Pharmacology:** **Ocular Effects:** In a 9-month toxicology study, dogs were administered tranexamic acid in food at doses of 0, 200, 600, or 1200 mg/kg/day. These doses are approximately 2, 5, and 6 times, respectively, the recommended human oral dose of 3900 mg/day based on AUC. At 6 times the human dose, some dogs developed reversible reddening and gelatinous discharge from the eyes. Ophthalmologic examination revealed reversible changes in the nictitating membrane/conjunctiva. In some female dogs, the presence of inflammatory exudate over the bulbar conjunctival mucosa was observed. Histopathological examinations did not reveal any retinal alteration. No adverse effects were observed at 5 times the human dose. In other studies, focal areas of retinal degeneration were observed in cats, dogs and rats following oral or intravenous tranexamic acid doses at 6-40 times the recommended usual human dose based on mg/m² (actual animal doses between 250-1600 mg/kg/day).

Rx only

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