

Risks of Delayed-Interval Delivery Can Be High

VITALS

Major Finding: Of the 18 first-born infants, only 1 survived until discharge, while 13 survived among the 22 latter-born infants.

Data Source: A series of 17 premature multifetal deliveries in which the first fetus was born at least 24 hours before the others.

Disclosures: Dr. Murji reported no conflicts of interest.

BY KATE JOHNSON

FROM THE ANNUAL MEETING OF THE SOCIETY OF OBSTETRICIANS AND GYNAECOLOGISTS OF CANADA

MONTREAL – Delayed-interval delivery when the initial delivery is extremely premature carries high maternal and infant morbidity, as well as a high infant mortality, reported Dr. Ally Murji of the

University of Toronto's division of maternal-fetal medicine.

"Just because we can do something, it doesn't mean it should be done," he said in an interview.

In a study that he presented at the meeting, Dr. Murji described a series of 17 premature multifetal deliveries in which the first fetus was born at least 24 hours before the others. The mean gestational age of the

first delivery was 23 weeks and 2 days.

"In our series, this procedure was reserved for the threshold of viability – extremely premature infants," he said in an interview, explaining that the majority of the initial deliveries were precipitated by preterm premature rupture of membranes (PPROM).

Among the 17 pregnancies, 12 were twin gestations, 4 were triplets, and one was a quadruplet pregnancy, said Dr. Murji.

Forty-one percent of the pregnancies had been conceived spontaneously, with the remainder being a result of either in-vitro fertilization (47%) or ovulation induction (12%). All infants were born vaginally, except for two of the latter-born infants. In the quadruplet delivery, two babies were born within minutes of each other, followed by a latency interval and then the birth of the other two. During the interval, 88% of mothers received antibiotics and 47% received tocolysis.

Of the 18 first-born infants, only 1 survived until discharge; 13 survived among the 22 latter-born infants – a survival rate of 59%. Mean birth weight was 468 g for first-born infants and 674 g for latter-born infants.

"Clearly there is a survival benefit in having an asynchronous delivery," noted Dr. Murji. "But these babies are not out of the woods. When you look at the absolute weights these are very small babies – babies who are very fragile. The prognosis for these babies is already guarded."

Indeed, the infants' average stay in the neonatal intensive care unit was 104 days. Twelve of the 13 infants had at least one morbidity, including retinopathy of prematurity, intraventricular hemorrhage, patent ductus arteriosus, or sepsis, and many of them had multiple comorbidities.

Maternal morbidity also was significant. The average age of the mothers was 31 years, and complications occurred in 71% of them, with intraamniotic infection being the most common (59%). Almost half of the mothers (47%) experienced two or more complications, with abruptio placentae, postpartum hemorrhage, and blood transfusions each occurring in 18% and septic pelvic thrombophlebitis and pulmonary edema each occurring in 6%.

The findings underscore the decisions that parents and physicians must face in contemplating delayed interval delivery in the context of premature delivery of the first baby.

"Outcomes in extremely premature deliveries are meager, at best. Although we can do asynchronous delivery, is it really reasonable? Yes, there is a clear survival benefit for the latter-born infant, but this survival benefit comes at the risk of maternal morbidity and the interval in our experience has only been 1 week. And these latter-born infants have significant morbidity because they're born so prematurely," said Dr. Murji.

LYSTEDA™

(tranexamic acid) tablets

BRIEF SUMMARY OF PRESCRIBING INFORMATION

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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

LYSTEDA		
Serum Creatinine (mg/dL)	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., 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

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. Ligneous 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 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*]. **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): 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 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 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 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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