

FSH in Unexplained Infertility Means More Twins

BY SUSAN LONDON

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

VANCOUVER, B.C. — Multiple pregnancy occurs in about one-fifth of women with unexplained infertility who become pregnant after treatment with follicle-stimulating hormone to induce superovulation, the largest study to look

at this outcome found.

Investigators at the University of British Columbia, Vancouver, retrospectively studied 759 women whose infertility had no identifiable cause after a full work-up and who received FSH, with or without intrauterine insemination (IUI), a treatment that is a less costly and less invasive alternative to in vitro fertilization (IVF).

In all, 22% of the women became pregnant, according to results reported at the

meeting. Although 18% of the pregnant women had a multiple pregnancy, in most cases these were twin gestations. Multiple pregnancy was most common among women younger than 30 years of age.

“This study definitely provides information for patients when we are counseling them on the different treatment choices that are available, specifically for the group with unexplained infertility,” commented first author Dr. Melica

Nourmoussavi, a resident in the department of ob.gyn. at the university. “And it’s also very important for gynecologists who are concerned about the risks of multiple pregnancies when treating with FSH, with or without IUI.”

She acknowledged that such concerns are justified, and offered some guidance, based in part on the study’s findings, for minimizing the likelihood of this outcome. “First of all, [make] appropriate patient selection; for example, [be] cautious when treating younger women

Zyclara® [zi-clar-a] (imiquimod) Cream 3.75%

BRIEF SUMMARY OF PRESCRIBING INFORMATION
SEE PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION
INDICATIONS AND USAGE

External Genital Warts

ZYCLARA Cream is indicated for the treatment of external genital and perianal warts (EGW)/condyloma acuminata in patients 12 years or older.

Limitations of Use

Treatment with ZYCLARA has not been studied for prevention or transmission of HPV.

Unevaluated Populations

The safety and efficacy of ZYCLARA Cream have not been established in the treatment of:

- urethral, intra-vaginal, cervical, rectal or intra-anal human papilloma viral disease.
- actinic keratosis when treated with more than one 2-cycle treatment course in the same area.
- patients with xeroderma pigmentosum.
- superficial basal cell carcinoma.
- immunosuppressed patients.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Local Skin Reactions

Intense local skin reactions including skin weeping or erosion can occur after a few applications of ZYCLARA Cream and may require an interruption of dosing. ZYCLARA Cream has the potential to exacerbate inflammatory conditions of the skin, including chronic graft versus host disease.

Administration of ZYCLARA Cream is not recommended until the skin is healed from any previous drug or surgical treatment.

Systemic Reactions

Flu-like signs and symptoms may accompany, or even precede, local skin reactions and may include fatigue, nausea, fever, myalgias, arthralgias, malaise and chills. An interruption of dosing and assessment of the patient should be considered.

Lymphadenopathy occurred in 2% of subjects with actinic keratosis treated with ZYCLARA Cream. This reaction resolved in all subjects by 4 weeks after completion of treatment.

Ultraviolet Light Exposure Risks

Exposure to sunlight (including sunlamps) should be avoided or minimized during use of ZYCLARA Cream. Patients should be warned to use protective clothing (e.g., a hat) when using ZYCLARA Cream. Patients with sunburn should be advised not to use ZYCLARA Cream until fully recovered. Patients who may have considerable sun exposure, e.g. due to their occupation, and those patients with inherent sensitivity to sunlight should exercise caution when using ZYCLARA Cream.

In an animal photo-carcinogenicity study, imiquimod cream shortened the time to skin tumor formation. The enhancement of ultraviolet carcinogenicity is not necessarily dependent on phototoxic mechanisms. Therefore, patients should minimize or avoid natural or artificial sunlight exposure.

Increased Risk of Adverse Reactions with Concomitant Imiquimod Use

Concomitant use of ZYCLARA and any other imiquimod products, in the same treatment area, should be avoided since they contain the same active ingredient (imiquimod) and may increase the risk for and severity of local skin reactions.

The safety of concomitant use of ZYCLARA and any other imiquimod products has not been established and should be avoided since they contain the same active ingredient (imiquimod) and may increase the risk for and severity of systemic reactions.

Immune Cell Activation in Autoimmune Disease

ZYCLARA Cream should be used with caution in patients with pre-existing autoimmune conditions because imiquimod activates immune cells.

ADVERSE REACTIONS

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 rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Clinical Trials Experience: External Genital Warts

In two double-blind, placebo-controlled studies 602 subjects applied up to one packet of ZYCLARA Cream or vehicle daily for up to 8 weeks.

The most frequently reported adverse reactions were application site reactions and local skin reactions. Selected adverse reactions are listed in Table 1.

Table 1: Selected Adverse Reactions Occurring in ≥2% of ZYCLARA Treated Subjects and at a Greater Frequency than with Vehicle in the Combined Trials (EGW)

Preferred Term	ZYCLARA Cream 3.75% (N=400)	Vehicle Cream (N=202)
Application site pain	28 (7%)	1 (<1%)
Application site irritation	24 (6%)	2 (1%)
Application site pruritus	11 (3%)	2 (1%)
Vaginitis bacterial*	6 (3%)	2 (2%)
Headache	6 (2%)	1 (<1%)

*Percentage based on female population of 6/216 for ZYCLARA Cream 3.75% and 2/106 for vehicle cream. Local skin reactions were recorded as adverse reactions only if they extended beyond the treatment area, if they required any medical intervention, or they resulted in patient discontinuation from the study. The incidence and severity of selected local skin reactions are shown in Table 2.

Table 2: Selected Local Skin Reactions in the Treatment Area Assessed by the Investigator (EGW)

All grades*, (%)	Severe, (%)	ZYCLARA Cream 3.75% (N=400)	Vehicle Cream (N=202)
Erythema*		70%	27%
	Severe erythema	9%	<1%
Edema*		41%	8%
	Severe edema	2%	0%
Erosion/ulceration*		36%	4%
	Severe erosion/ulceration	11%	<1%
Exudate*		34%	2%
	Severe exudate	2%	0%

*Mild, Moderate, or Severe

The frequency and severity of local skin reactions were similar in both genders, with the following exceptions: a) flaking/scaling occurred in 40% of men and in 26% of women and b) scabbing/crusting occurred in 34% of men and in 18% of women.

In the clinical trials, 32% (126/400) of subjects who used ZYCLARA Cream and 2% (4/202) of subjects who used vehicle cream discontinued treatment temporarily (required rest periods) due to adverse local skin reactions, and 1% (3/400) of subjects who used ZYCLARA Cream discontinued treatment permanently due to local skin/application site reactions.

Other adverse reactions reported in subjects treated with ZYCLARA Cream include: rash, back pain, application site rash, application site cellulitis, application site excoriation, application site bleeding, scrotal pain, scrotal erythema, scrotal ulcer, scrotal edema, sinusitis, nausea, pyrexia, and influenza-like symptoms.

Postmarketing Experience

The following adverse reactions have been identified during post-approval use of imiquimod. 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.

Application Site Disorders: tingling at the application site.

Body as a Whole: angioedema.

Cardiovascular: capillary leak syndrome, cardiac failure, cardiomyopathy, pulmonary edema, arrhythmias (tachycardia, supraventricular tachycardia, atrial fibrillation, palpitations), chest pain, ischemia, myocardial infarction, syncope.

Endocrine: thyroiditis.

Gastro-Intestinal System Disorders: abdominal pain.

Hematological: decreases in red cell, white cell and platelet counts (including idiopathic thrombocytopenic purpura), lymphoma.

Hepatic: abnormal liver function.

Infections and Infestations: herpes simplex.

Musculo-Skeletal System Disorders: arthralgia.

Neuropsychiatric: agitation, cerebrovascular accident, convulsions (including febrile convulsions), depression, insomnia, multiple sclerosis aggravation, paresis, suicide.

Respiratory: dyspnea.

Urinary System Disorders: proteinuria, urinary retention, dysuria.

Skin and Appendages: exfoliative dermatitis, erythema multiforme, hyperpigmentation, hypertrophic scar, hypopigmentation.

Vascular: Henoch-Schönlein purpura syndrome.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category C:
There are no adequate and well-controlled studies in pregnant women. ZYCLARA Cream should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

The animal multiples of human exposure calculations were based on daily dose comparisons for the reproductive toxicology studies described in this label. The animal multiples of human exposure were based on weekly dose comparisons for the carcinogenicity studies described in this label. For the animal multiple of human exposure ratios presented in this label, the Maximum Recommended Human Dose (MRHD) was set at 2 packets (500 mg cream) per treatment of actinic keratosis with ZYCLARA Cream (imiquimod 3.75%, 18.75 mg imiquimod) for BSA comparison. The maximum human AUC value obtained in the treatment of external genital and perianal warts was higher than that obtained in the treatment of actinic keratosis and was used in the calculation of animal multiples of MRHD that were based on AUC comparison.

Systemic embryofetal development studies were conducted in rats and rabbits. Oral doses of 1, 5 and 20 mg/kg/day imiquimod were administered during the period of organogenesis (gestational days 6 – 15) to pregnant female rats. In the presence of maternal toxicity, fetal effects noted at 20 mg/kg/day (163X MRHD based on AUC comparisons) included increased resorptions, decreased fetal body weights, delays in skeletal ossification, bent limb bones, and two fetuses in one litter (2 of 1567 fetuses) demonstrated exencephaly, protruding tongues and low-set ears. No treatment related effects on embryofetal toxicity or teratogenicity were noted at 5 mg/kg/day (28X MRHD based on AUC comparisons).

Intravenous doses of 0.5, 1 and 2 mg/kg/day imiquimod were administered during the period of organogenesis (gestational days 6 – 18) to pregnant female rabbits. No treatment related effects on embryofetal toxicity or teratogenicity were noted at 2 mg/kg/day (2.1X MRHD based on BSA comparisons), the highest dose evaluated in this study, or 1 mg/kg/day (115X MRHD based on AUC comparisons).

A combined fertility and peri- and post-natal development study was conducted in rats. Oral doses of 1, 1.5, 3 and 6 mg/kg/day imiquimod were administered to male rats from 70 days prior to mating through the mating period and to female rats from 14 days prior to mating through parturition and lactation. No effects on growth, fertility, reproduction or post-natal development were noted at doses up to 6 mg/kg/day (25X MRHD based on AUC comparisons), the highest dose evaluated in this study. In the absence of maternal toxicity, bent limb bones were noted in the F1 fetuses at a dose of 6 mg/kg/day (25X MRHD based on AUC comparisons). This fetal effect was also noted in the oral rat embryofetal development study conducted with imiquimod. No treatment related effects on teratogenicity were noted at 3 mg/kg/day (12X MRHD based on AUC comparisons).

Nursing Mothers

It is not known whether imiquimod is excreted in human milk following use of ZYCLARA Cream. Because many drugs are excreted in human milk, caution should be exercised when ZYCLARA Cream is administered to nursing women.

Pediatric Use

Safety and efficacy in patients with external genital/perianal warts below the age of 12 years have not been established.

Geriatric Use

Clinical studies of ZYCLARA Cream for EGW did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Of the 400 subjects treated with ZYCLARA Cream in the EGW clinical studies, 5 subjects (1%) were 65 years or older.

OVERDOSAGE

Topical overdosing of ZYCLARA Cream could result in an increased incidence of severe local skin reactions and may increase the risk for systemic reactions.

Hypotension was reported in a clinical trial following multiple oral imiquimod doses of >200 mg (equivalent to ingestion of the imiquimod content of more than 21 packets of ZYCLARA). The hypotension resolved following oral or intravenous fluid administration.

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VITALS

Major Finding: Overall, 22% of women became pregnant, and 18% of this group had a multiple pregnancy (usually a twin gestation).

Data Source: A retrospective analysis of 759 women with unexplained fertility who were treated with FSH, with or without intrauterine insemination

Disclosures: Dr. Nourmoussavi reported that she had no relevant financial disclosures.

because of their increased risk of multiple pregnancies,” she said. “Second, [consider] conversion to IVF or even cancellation of cycles when there are signs of overstimulation,” such as more than three mature follicles or multiple medium-size follicles. “And third, [use] minimal ovarian stimulation protocols for more controlled treatment.”

In the so-called stair-step approach to unexplained infertility (in which physicians work their way up from the least expensive, invasive, and stressful – but also least successful – treatments to those that are the most expensive, invasive, and stressful), FSH-induced superovulation, with or without IUI, comes after clomiphene, with or without IUI, but before IVF.

She and her colleagues retrospectively reviewed the charts of women with unexplained infertility who were treated with FSH, with or without IUI, at the university in 2002-2008.

The 759 women identified had a total of 1,387 cycles of treatment. Some 73% were aged 35 years or older.

Study results showed that the pregnancy rate was 22% in the study population as a whole, but it ranged from 12% among women aged 40 years or older to 31% among those aged 30-34 years.

In the group who became pregnant, the multiple pregnancy rate was 18%, with a range spanning from 9% among women aged 40 years or older to 33% among those younger than 30 years of age.

Most of these multiple pregnancies (87%) were twin gestations, whereas the rest were triplet gestations. In all, 16% of the multiple pregnancies were reduced to singleton pregnancies.

An analysis of the cumulative pregnancy rate with treatment showed that although the pregnancy rate did increase with each cycle regardless of a woman’s age, the increase was much smaller in women older than 40 years. ■