

Hormonal Contraceptives May Affect GDM Risk

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The androgenicity of the progestin component of hormonal contraceptives used before pregnancy may affect risk for gestational diabetes mellitus, suggests a recent study.

In a nested case-control study of 724 women with a live singleton birth, the use of only low-androgen hormonal contraceptives for at least 6 months in the 5 years

before pregnancy was associated with a 16% reduction in gestational diabetes mellitus (GDM) risk (adjusted odds ratio 0.84), compared with no hormonal contraceptive use. In addition, the use of a high-androgen hormonal contraceptive for at least 6 months—regardless of whether low-androgen contraceptives were also used—in the 5 years before pregnancy was associated with a 43% increase in GDM risk (adjusted odds ratio 1.43), reported Monique M. Hedderson, Ph.D., of the Kaiser Per-

manente Medical Care Program of Northern California, Oakland, and her colleagues.

Women who used Loestrin—the highest-androgen oral contraceptive—had the greatest increase in GDM risk (adjusted odds ratio 1.99), the investigators noted (Diabetes Care 2007;30:1062-8).

The findings remained essentially unchanged when the data analyses were repeated after excluding women who used nonoral hormonal contraceptives.

The 356 case patients and 368 controls

were part of a multiethnic cohort of more than 14,000 women who delivered between Jan. 1, 1996, and June 30, 1998, and who were screened for GDM between 24 and 28 weeks' gestation. Patients were diagnosed with GDM if at least two of four plasma glucose values obtained during a 100-g, 3-hour oral glucose tolerance test were abnormal by National Diabetes Data Group criteria.

For oral contraceptives, high androgenicity was defined as androgenic activity of at least 0.47 mg of methyl testosterone equivalents per 28 days. Among nonoral hormonal contraceptives, Norplant was considered high androgen because it contains levonorgestrel, which has high androgenic activity; depot-medroxyprogesterone acetate contraceptives were considered low androgen because they contain medroxyprogesterone, which has low androgenic activity.

There was some evidence in this study that the duration of contraceptive use also played a role in GDM risk: A greater reduction in GDM risk was seen with longer duration of low-androgen contraceptives. No clear trend emerged in regard to duration of use of high-androgen contraceptives. "However, the statistical precision of our results was not great, and, given no true associations, chance alone plausibly could have been responsible for those we did observe," the authors noted.

The risk reduction associated with low-androgen contraceptives was greatest when use was discontinued within 6 months before pregnancy, and the risk increase associated with high-androgen contraceptives was greatest when use was discontinued at least 1 year before pregnancy.

The effect of hormonal contraceptives on GDM risk may vary based on the androgenicity of the progestin component of the contraceptives, but the findings of this study should be interpreted with caution pending additional study, the investigators concluded.

Van Kerrebroeck et al.¹ A 12-week, randomized, double-blind, placebo-controlled, multicenter trial that compared the efficacy and safety of tolterodine tartrate capsules (4 mg qd) and tolterodine tartrate tablets (2 mg bid) with placebo in 1529 adults with urinary frequency and urgency incontinence. Primary objective of this study was to evaluate the effect of active drugs or placebo on incontinence episodes using a 7-day bladder diary. Mean urgency incontinence episodes at baseline per week were 22.1 for patients treated with tolterodine tartrate capsules (4 mg qd), 23.2 for patients treated with tolterodine tartrate tablets (2 mg bid), and 23.3 for placebo-treated patients. Secondary objectives included other diary variables such as pad usage and various patient-reported outcomes.

Landis et al.² A post hoc subgroup analysis of 986 patients from the Van Kerrebroeck study that compared the efficacy of tolterodine tartrate capsules (4 mg qd) with placebo in severe urgency incontinence. Severe urgency incontinence was defined as 21 to 168 urgency incontinence episodes/week. Median urgency incontinence episodes at baseline per week were 34 for patients treated with tolterodine tartrate capsules (4 mg qd) and 31.5 for placebo-treated patients.

References: 1. Van Kerrebroeck P, Kreder K, Jonas U, Zinner N, Wein A, for the Tolterodine Study Group. Tolterodine once-daily: superior efficacy and tolerability in the treatment of the overactive bladder. *Urology*. 2001;57:414-421.

2. Landis JR, Kaplan S, Swift S, Versi E. Efficacy of antimuscarinic therapy for overactive bladder with varying degrees of incontinence severity. *J Urol*. 2004;171:752-756.

Detrol LA[®]

tolterodine tartrate
extended release capsules

PHARMACIA

Brief Summary of Prescribing Information

INDICATIONS AND USAGE

DETROL LA Capsules are once daily extended release capsules indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency.

CONTRAINDICATIONS

DETROL LA Capsules are contraindicated in patients with urinary retention, gastric retention, or uncontrolled narrow-angle glaucoma. DETROL LA is also contraindicated in patients who have demonstrated hypersensitivity to the drug or its ingredients.

PRECAUTIONS

General

Risk of Urinary Retention and Gastric Retention: DETROL LA Capsules should be administered with caution to patients with clinically significant bladder outflow obstruction because of the risk of urinary retention and to patients with gastrointestinal obstructive disorders, such as pyloric stenosis, because of the risk of gastric retention (see **CONTRAINDICATIONS**).

Controlled Narrow-Angle Glaucoma: DETROL LA should be used with caution in patients being treated for narrow-angle glaucoma.

Reduced Hepatic and Renal Function: For patients with significantly reduced hepatic function or renal function, the recommended dose for DETROL LA is 2 mg daily (see **CLINICAL PHARMACOLOGY, Pharmacokinetics in Special Populations** in full prescribing information).

Patients with Congenital or Acquired QT Prolongation

In a study of the effect of tolterodine immediate release tablets on the QT interval (see **CLINICAL PHARMACOLOGY, Cardiac Electrophysiology** in full prescribing information), the effect on the QT interval appeared greater for 8 mg/day (two times the therapeutic dose) compared to 4 mg/day and was more pronounced in CYP2D6 poor metabolizers (PMs) than extensive metabolizers (EMs). The effect of tolterodine 8 mg/day was not as large as that observed after four days of therapeutic dosing with the active control moxifloxacin. However, the confidence intervals overlapped. These observations should be considered in clinical decisions to prescribe DETROL LA for patients with a known history of QT prolongation or patients who are taking Class IA (eg, quinidine, procainamide) or Class III (eg, amiodarone, sotalol) antiarrhythmic medications (see **PRECAUTIONS, Drug Interactions**). There has been no association of Torsade de Pointes in the international postmarketing experience with DETROL or DETROL LA.

Information for Patients

Patients should be informed that antimuscarinic agents such as DETROL LA may produce the following effects: blurred vision, dizziness, or drowsiness. Patients should be advised to exercise caution in decisions to engage in potentially dangerous activities until the drug's effects have been determined.

Drug Interactions

CYP3A4 Inhibitors: Ketoconazole, an inhibitor of the drug metabolizing enzyme CYP3A4, significantly increased plasma concentrations of tolterodine when coadministered to subjects who were poor metabolizers (see **CLINICAL PHARMACOLOGY, Variability in Metabolism and Drug-Drug Interactions** in full prescribing information). For patients receiving ketoconazole or other potent CYP3A4 inhibitors such as other azole antifungals (eg, itraconazole, miconazole) or macrolide antibiotics (eg, erythromycin, clarithromycin) or cyclosporine or vinblastine, the recommended dose of DETROL LA is 2 mg daily (see **DOSAGE AND ADMINISTRATION**).

Drug-Laboratory-Test Interactions

Interactions between tolterodine and laboratory tests have not been studied.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies with tolterodine immediate release were conducted in mice and rats. At the maximum tolerated dose in mice (30 mg/kg/day), female rats (20 mg/kg/day), and male rats (30 mg/kg/day), AUC values obtained for tolterodine were 355, 291, and 462 µg • h/L, respectively. In comparison, the human AUC value for a 2-mg dose administered twice daily is estimated at 34 µg • h/L. Thus, tolterodine exposure in the carcinogenicity studies was 9- to 14-fold higher than expected in humans. No increase in tumors was found in either mice or rats. No mutagenic effects of tolterodine were detected in a battery of in vitro tests, including bacterial mutation assays (Ames test) in 4 strains of *Salmonella typhimurium* and in 2 strains of *Escherichia coli*, a gene mutation assay in L5178Y mouse lymphoma cells, and chromosomal aberration tests in human lymphocytes. Tolterodine was also negative in vivo in the bone marrow micronucleus test in the mouse. In female mice treated for 2 weeks before mating and during gestation with 20 mg/kg/day (corresponding to AUC value of about 500 µg • h/L), neither effects on reproductive performance or fertility were seen. Based on AUC values, the systemic exposure was about 15-fold higher in animals than in humans. In male mice, a dose of 30 mg/kg/day did not induce any adverse effects on fertility.

Pregnancy

Pregnancy Category C. At oral doses of 20 mg/kg/day (approximately 14 times the human exposure), no anomalies or malformations were observed in mice. When given at doses of 30 to 40 mg/kg/day, tolterodine has been shown to be embryolethal and reduce fetal weight, and increase the incidence of fetal abnormalities (cleft palate, digital abnormalities, intra-abdominal hemorrhage, and various skeletal abnormalities, primarily reduced ossification) in mice. At these doses, the AUC values were about 20- to 25-fold higher than in humans. Rabbits treated subcutaneously at a dose of 0.8 mg/kg/day achieved an AUC of 100 µg • h/L, which is about 3-fold higher than that resulting from the human dose. This dose did not result in any embryotoxicity or teratogenicity. There are no studies of tolterodine in pregnant women. Therefore, DETROL LA should be used during pregnancy only if the potential benefit for the mother justifies the potential risk to the fetus.

Nursing Mothers

Tolterodine immediate release is excreted into the milk in mice. Offspring of female mice treated with tolterodine 20 mg/kg/day during the lactation period had slightly reduced bodyweight gain. The offspring regained the weight during the maturation phase. It is not known whether tolterodine is excreted in human milk; therefore, DETROL LA should not be administered during nursing. A decision should be made whether to discontinue nursing or to discontinue DETROL LA in nursing mothers.

Pediatric Use

Efficacy in the pediatric population has not been demonstrated. A total of 710 pediatric patients (486 on DETROL LA, 224 on placebo) aged 5-10 with urinary frequency and urge incontinence were studied in two Phase 3 randomized, placebo-controlled, double-blind, 12-week studies. The percentage of patients with urinary tract infections was higher in patients treated with

DETROL LA (6.6%) compared to patients who received placebo (4.5%). Aggressive, abnormal and hyperactive behavior and attention disorders occurred in 2.9% of children treated with DETROL LA compared to 0.9% of children treated with placebo.

Geriatric Use

No overall differences in safety were observed between the older and younger patients treated with tolterodine (see **CLINICAL PHARMACOLOGY, Pharmacokinetics in Special Populations** in full prescribing information).

ADVERSE REACTIONS

The Phase 2 and 3 clinical trial program for DETROL LA Capsules included 1073 patients who were treated with DETROL LA (n=537) or placebo (n=536). The patients were treated with 2, 4, 6, or 8 mg/day for up to 15 months. 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. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates. The data described below reflect exposure to DETROL LA 4 mg once daily every morning in 505 patients and to placebo in 507 patients exposed for 12 weeks in the Phase 3, controlled clinical study.

Adverse events were reported in 52% (n=263) of patients receiving DETROL LA and in 49% (n=247) of patients receiving placebo. The most common adverse events reported by patients receiving DETROL LA were dry mouth, headache, constipation, and abdominal pain. Dry mouth was the most frequently reported adverse event for patients treated with DETROL LA occurring in 23.4% of patients treated with DETROL LA and 7.7% of placebo-treated patients. Dry mouth, constipation, abnormal vision (accommodation abnormalities), urinary retention, and dry eyes are expected side effects of antimuscarinic agents. A serious adverse event was reported by 1.4% (n=7) of patients receiving DETROL LA and by 3.6% (n=18) of patients receiving placebo.

The frequency of discontinuation due to adverse events was highest during the first 4 weeks of treatment. Similar percentages of patients treated with DETROL LA or placebo discontinued treatment due to adverse events. Treatment was discontinued due to adverse events and dry mouth was reported as an adverse event in 2.4% (n=12) of patients treated with DETROL LA and in 1.2% (n=6) of patients treated with placebo.

Table 4 lists the adverse events reported in 1% or more of patients treated with DETROL LA 4 mg once daily in the 12-week study. The adverse events were reported regardless of causality.

Table 4. Incidence* (% of Adverse Events Exceeding Placebo Rate and Reported in ≥1% of Patients Treated with DETROL LA (4 mg daily) in a 12-week, Phase 3 Clinical Trial

Body System	Adverse Event	% DETROL LA n=505	% Placebo n=507
Autonomic Nervous	dry mouth	23	8
General	headache	6	4
	fatigue	2	1
	dizziness	2	1
Central/Peripheral Nervous	dizziness	2	1
Gastrointestinal	constipation	6	4
	abdominal pain	4	2
	dyspepsia	3	1
Vision	xerophthalmia	3	2
	vision abnormal	1	0
Psychiatric	somnolence	3	2
	anxiety	1	0
Respiratory	sinusitis	2	1
Urinary	dysuria	1	0

* in nearest integer.

Postmarketing Surveillance

The following events have been reported in association with tolterodine use in worldwide post-marketing experience: **General:** anaphylactoid reactions, including angioedema; **Cardiovascular:** tachycardia, palpitations, peripheral edema; **Gastrointestinal:** diarrhea; **Central/Peripheral Nervous:** confusion, disorientation, memory impairment, hallucinations. Reports of aggravation of symptoms of dementia (eg, confusion, disorientation, delusion) have been reported after tolterodine therapy was initiated in patients taking cholinesterase inhibitors for the treatment of dementia. Because these spontaneously reported events are from the worldwide postmarketing experience, the frequency of events and the role of tolterodine in their causation cannot be reliably determined.

OVERDOSAGE

A 27-month-old child who ingested 5 to 7 tolterodine immediate release tablets 2 mg was treated with a suspension of activated charcoal and was hospitalized overnight with symptoms of dry mouth. The child fully recovered.

Management of Overdosage

Overdosage with DETROL LA Capsules can potentially result in severe central anticholinergic effects and should be treated accordingly. ECG monitoring is recommended in the event of overdosage. In dogs, changes in the QT interval (slight prolongation of 10% to 20%) were observed at a suprapharmacologic dose of 4.5 mg/kg, which is about 68 times higher than the recommended human dose. In clinical trials of normal volunteers and patients, QT interval prolongation was not observed with tolterodine immediate release at doses up to 8 mg (4 mg bid) and higher doses were not evaluated (see **PRECAUTIONS, Patients with Congenital or Acquired QT Prolongation**).

DOSAGE AND ADMINISTRATION

The recommended dose of DETROL LA Capsules is 4 mg daily. DETROL LA should be taken once daily with liquids and swallowed whole. The dose may be lowered to 2 mg daily based on individual response and tolerability, however, limited efficacy data is available for DETROL LA 2 mg (see **CLINICAL STUDIES** in full prescribing information). For patients with significantly reduced hepatic or renal function or who are currently taking drugs that are potent inhibitors of CYP3A4, the recommended dose of DETROL LA is 2 mg daily (see **CLINICAL PHARMACOLOGY and PRECAUTIONS, Drug Interactions** in full prescribing information).

Rx only



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Androgenic Activity of Methyltestosterone Equivalents per 28 Days (in mg)

Selected Low-Androgenicity Contraceptives

Ovrette	0.12
Micronor/Nor.Q.D.	0.12
Ovcom-35	0.14
Modicon, Brevicon	0.17
Ovulen 50, Demulen 1/50	0.21
Demulin 1/35	0.21
Ortho-Novum 10/11	0.26
Ortho-Novum 7/7	0.26
Tri-Levlen, Triphasil	0.29
Ovcon-50	0.34
Ortho-Novum 1/50	0.34
Ortho-Novum 1/35	0.34

Selected High-Androgenicity Contraceptives

Nordette, Levlen	0.47
Lo/Ovral 28-day	0.47
Loestrin 1/20	0.52
Loestrin 1.5/30	0.79

Source: Dr. Hedderson

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