

Contraceptive Component 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, a recent study suggested.

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, 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 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. ■

Digoxin

There was a slight increase in the area under the curve (AUC, 11%) and mean peak drug concentration (C_{max} , 18%) of digoxin with the coadministration of 100 mg sitagliptin for 10 days. These increases are not considered likely to be clinically meaningful. Digoxin, as a cationic drug, has the potential to compete with metformin for common renal tubular transport systems, thus affecting the serum concentrations of either digoxin, metformin or both. Patients receiving digoxin should be monitored appropriately. No dosage adjustment of digoxin or JANUMET is recommended.

Glyburide

In a single-dose interaction study in type 2 diabetes patients, coadministration of metformin and glyburide did not result in any changes in either metformin pharmacokinetics or pharmacodynamics. Decreases in glyburide AUC and C_{max} were observed, but were highly variable. The single-dose nature of this study and the lack of correlation between glyburide blood levels and pharmacodynamic effects make the clinical significance of this interaction uncertain.

Furosemide

A single-dose, metformin-furosemide drug interaction study in healthy subjects demonstrated that pharmacokinetic parameters of both compounds were affected by coadministration. Furosemide increased the metformin plasma and blood C_{max} by 22% and blood AUC by 15%, without any significant change in metformin renal clearance. When administered with metformin, the C_{max} and AUC of furosemide were 31% and 12% smaller, respectively, than when administered alone, and the terminal half-life was decreased by 32% without any significant change in furosemide renal clearance. No information is available about the interaction of metformin and furosemide when coadministered chronically.

Nifedipine

A single-dose, metformin-nifedipine drug interaction study in normal healthy volunteers demonstrated that coadministration of nifedipine increased plasma metformin C_{max} and AUC by 20% and 9%, respectively, and increased the amount excreted in the urine. T_{max} and half-life were unaffected. Nifedipine appears to enhance the absorption of metformin. Metformin had minimal effects on nifedipine.

The Use of Metformin with Other Drugs

Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. When such drugs are administered to a patient receiving JANUMET the patient should be closely observed to maintain adequate glycemic control.

In healthy volunteers, the pharmacokinetics of metformin and propranolol, and metformin and ibuprofen were not affected when coadministered in single-dose interaction studies.

Metformin is negligibly bound to plasma proteins and is, therefore, less likely to interact with highly protein-bound drugs such as salicylates, sulfonamides, chloramphenicol, and probenecid, as compared to the sulfonylureas, which are extensively bound to serum proteins.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category B:

JANUMET

There are no adequate and well-controlled studies in pregnant women with JANUMET or its individual components; therefore, the safety of JANUMET in pregnant women is not known. JANUMET should be used during pregnancy only if clearly needed.

Merck & Co., Inc. maintains a registry to monitor the pregnancy outcomes of women exposed to JANUMET while pregnant. Health care providers are encouraged to report any prenatal exposure to JANUMET by calling the Pregnancy Registry at (800) 986-8999.

No animal studies have been conducted with the combined products in JANUMET to evaluate effects on reproduction. The following data are based on findings in studies performed with sitagliptin or metformin individually.

Sitagliptin

Reproduction studies have been performed in rats and rabbits. Doses of sitagliptin up to 125 mg/kg (approximately 12 times the human exposure at the maximum recommended human dose) did not impair fertility or harm the fetus. There are, however, no adequate and well-controlled studies with sitagliptin in pregnant women.

Sitagliptin administered to pregnant female rats and rabbits from gestation day 6 to 20 (organogenesis) was not teratogenic at oral doses up to 250 mg/kg (rats) and 125 mg/kg (rabbits), or approximately 30 and 20 times human exposure at the maximum recommended human dose (MRHD) of 100 mg/day based on AUC comparisons. Higher doses increased the incidence of rib malformations in offspring at 1000 mg/kg, or approximately 100 times human exposure at the MRHD.

Sitagliptin administered to female rats from gestation day 6 to lactation day 21 decreased body weight in male and female offspring at 1000 mg/kg. No functional or behavioral toxicity was observed in offspring of rats.

Placental transfer of sitagliptin administered to pregnant rats was approximately 45% at 2 hours and 80% at 24 hours postdose. Placental transfer of sitagliptin administered to pregnant rabbits was approximately 66% at 2 hours and 30% at 24 hours.

Metformin hydrochloride

Metformin was not teratogenic in rats and rabbits at doses up to 600 mg/kg/day. This represents an exposure of about 2 and 6 times the maximum recommended human daily dose of 2000 mg based on body surface area comparisons for rats and rabbits, respectively. Determination of fetal concentrations demonstrated a partial placental barrier to metformin.

Nursing Mothers

No studies in lactating animals have been conducted with the combined components of JANUMET. In studies performed with the individual components, both sitagliptin and metformin are secreted in the milk of lactating rats. It is not known whether sitagliptin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when JANUMET is administered to a nursing woman.

Pediatric Use

Safety and effectiveness of JANUMET in pediatric patients under 18 years have not been established.

Geriatric Use

JANUMET

Because sitagliptin and metformin are substantially excreted by the kidney and because aging can be associated with reduced renal function, JANUMET should be used with caution as age increases. Care should be taken in dose selection and should be based on careful and regular monitoring of renal function [see *Warnings and Precautions*].

Sitagliptin

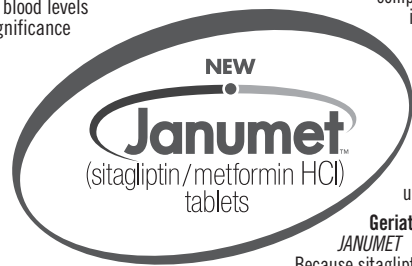
Of the total number of subjects (N=3884) in Phase II and III clinical studies of sitagliptin, 725 patients were 65 years and over, while 61 patients were 75 years and over. No overall differences in safety or effectiveness were observed between subjects 65 years and over and younger subjects. While this and other reported clinical experience have not identified differences in responses between the elderly and younger patients, greater sensitivity of some older individuals cannot be ruled out.

Metformin hydrochloride

Controlled clinical studies of metformin did not include sufficient numbers of elderly patients to determine whether they respond differently from younger patients, although other reported clinical experience has not identified differences in responses between the elderly and young patients. Metformin should only be used in patients with normal renal function. The initial and maintenance dosing of metformin should be conservative in patients with advanced age, due to the potential for decreased renal function in this population. Any dose adjustment should be based on a careful assessment of renal function [see *Contraindications; Warnings and Precautions*].



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

Selected Low-Androgen 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-Androgen 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