

# Study Finds No Link in OC Exposure, Birth Defects

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ST. PETE BEACH, FLA. — Periconceptional exposure to oral contraceptives was not associated with increased risk of adverse fetal outcomes in a recent prospective study.

None of the 45 women who were exposed to oral contraceptives during the periconceptional period and were followed until after delivery gave birth to an

infant with congenital malformations, compared with 6 of 225 controls.

The difference in the congenital malformation rate between the exposed group and control group was not significant, according to H.K. Ahn, M.D., and colleagues of the Motherisk Program at Sungkyunkwan University, Seoul, South Korea, during a poster presentation at the annual meeting of the Teratology Society.

The groups were also similar in regard

to mean gestational age at delivery (39 weeks in both groups) and birth weight (3,257g in the exposed group, and 3,268g in the controls), the investigators said.

Women who were in the exposed group took oral contraceptives that contained either combined ethinyl estradiol and progesterone, or high-dose progesterone.

Although some earlier studies suggested a link between oral contraceptive use during pregnancy and increased risk of

birth defects, later studies—including the current study—have failed to reproduce these findings.

“Exposure to oral contraceptives, including high doses of progesterone ... did not increase adverse fetal outcomes,” the investigators said. ■

## Neurocognition Is Unimpaired By Diclectin

ST. PETE BEACH, FLA. — Diclectin used for nausea and vomiting of pregnancy does not appear to affect the later neurocognitive development of children who are exposed to the drug in utero, Irene Nulman, M.D., and her colleagues at the Hospital for Sick Children, Toronto, reported at the annual meeting of the Teratology Society.

The drug, available in Canada but not in the United States at this time, has proved safe in terms of fetal dysmorphology, but its effects on the developing central nervous system have been unclear, the investigators reported in a poster presentation at the meeting.

In a prospective, randomized, double-blind study, they compared the children's neurocognitive development and measures of child behavior and language development. The study included 42 mother-child pairs exposed to nausea and vomiting of pregnancy (NVP) and diclectin, 37 pairs exposed to NVP but not to pharmacotherapy, and 25 pairs not exposed to NVP.

No significant differences were found among groups in any of these measures. Children in all groups had scores in the normal range on total indexes of IQ and on measures of temperament, behavior, and language. For example, performance IQ scores were a mean of 119.76 in the NVP/diclectin-exposed group, 111.75 in the NVP-only group, and 110.08 in the unexposed group.

NVP affects 70%-80% of pregnant women and can lead to hyperemesis gravidarum, the investigators noted.

“Exposure to diclectin does not adversely affect child long-term full-scale IQ. ... When indicated, diclectin therapy should be instituted to prevent hyperemesis gravid[ar]um and improve pregnant women's life style,” they concluded.

Diclectin, manufactured by Duchesnay Inc., is a generic form of the drug Bendectin, which was marketed in the United States until 1983 when it was voluntarily withdrawn by its manufacturer, Merrell Dow Pharmaceuticals Inc., following a series of lawsuits claiming the drug caused birth defects. Although the company won every case and numerous studies have confirmed the drug's safety, the drug was never put back on the U.S. market. Duchesnay Inc. is currently attempting to gain Food and Drug Administration clearance to market diclectin in the United States.

—Sharon Worcester

### Treatment of osteoporosis Postmenopausal women

In two identically designed, three-year, placebo-controlled, double-blind, multicenter studies (United States and Multinational; n=994), discontinuation of therapy due to any clinical adverse experience occurred in 4.1% of 196 patients treated with FOSAMAX® (alendronate sodium) 10 mg/day and 6.0% of 397 patients treated with placebo. In the Fracture Intervention Trial (n=6459), discontinuation of therapy due to any clinical adverse experience occurred in 9.1% of 3236 patients treated with FOSAMAX 5 mg/day for 2 years and 10 mg/day for either one or two additional years and 10.1% of 3223 patients treated with placebo. Discontinuations due to upper gastrointestinal adverse experiences were: FOSAMAX, 3.2%; placebo, 2.7%. In these study populations, 49-54% had a history of gastrointestinal disorders at baseline and 54-89% used nonsteroidal anti-inflammatory drugs or aspirin at some time during the studies. Adverse experiences from these studies considered by the investigators as possibly, probably, or definitely drug related in B1% of patients treated with either FOSAMAX or placebo are presented in the following table.

	United States/Multinational Studies		Fracture Intervention Trial	
	FOSAMAX* % (n=196)	Placebo % (n=397)	FOSAMAX** % (n=3236)	Placebo % (n=3223)
<b>Gastrointestinal</b>				
abdominal pain	6.6	4.8	1.5	1.5
nausea	3.6	4.0	1.1	1.5
dyspepsia	3.6	3.5	1.1	1.2
constipation	3.1	1.8	0.0	0.2
diarrhea	3.1	1.8	0.6	0.3
flatulence	2.0	0.5	0.2	0.3
acid regurgitation	2.0	4.3	1.1	0.9
esophageal ulcer	1.5	0.0	0.1	0.1
vomiting	1.0	1.5	0.2	0.3
dysphagia	1.0	0.0	0.1	0.1
abdominal distention	1.0	0.8	0.0	0.0
gastritis	0.5	1.3	0.6	0.7
<b>Musculoskeletal</b>				
musculoskeletal (bone, muscle or joint) pain	4.1	2.5	0.4	0.3
muscle cramp	0.0	1.0	0.2	0.1
<b>Nervous System/Psychiatric</b>				
headache	2.6	1.5	0.2	0.2
dizziness	0.0	1.0	0.0	0.1
<b>Special Senses</b>				
taste perversion	0.5	1.0	0.1	0.0

\*10 mg/day for three years  
\*\*5 mg/day for 2 years and 10 mg/day for either 1 or 2 additional years

Rarely, rash and erythema have occurred. One patient treated with FOSAMAX (10 mg/day), who had a history of peptic ulcer disease and gastrectomy and who was taking concomitant aspirin developed an anastomotic ulcer with mild hemorrhage, which was considered drug related. Aspirin and FOSAMAX were discontinued and the patient recovered.

The adverse experience profile was similar for the 401 patients treated with either 5 or 20 mg doses of FOSAMAX in the United States and Multinational studies. The adverse experience profile for the 296 patients who received continued treatment with either 5 or 10 mg doses of FOSAMAX in the two-year extension of these studies (treatment years 4 and 5) was similar to that observed during the three-year placebo-controlled period. During the extension period, of the 151 patients treated with FOSAMAX 10 mg/day, the proportion of patients who discontinued therapy due to any clinical adverse experience was similar to that during the first three years of the study.

In a one-year, double-blind, multicenter study, the overall safety and tolerability profiles of once weekly FOSAMAX 70 mg and FOSAMAX 10 mg daily were similar. The adverse experiences considered by the investigators as possibly, probably, or definitely drug related in B1% of patients in either treatment group are presented in the following table.

	Once Weekly FOSAMAX		FOSAMAX	
	70 mg % (n=519)	10 mg/day % (n=370)	70 mg % (n=519)	10 mg/day % (n=370)
<b>Gastrointestinal</b>				
abdominal pain	3.7	3.0	3.7	3.0
dyspepsia	2.7	2.2	2.7	2.2
acid regurgitation	1.9	2.4	1.9	2.4
nausea	1.9	2.4	1.9	2.4
abdominal distention	1.0	1.4	1.0	1.4
constipation	0.8	1.6	0.8	1.6
flatulence	0.4	1.6	0.4	1.6
gastritis	0.2	1.1	0.2	1.1
gastric ulcer	0.0	1.1	0.0	1.1
<b>Musculoskeletal</b>				
musculoskeletal (bone, muscle, joint) pain	2.9	3.2	2.9	3.2
muscle cramp	0.2	1.1	0.2	1.1

### Men

In two placebo-controlled, double-blind, multicenter studies in men (a two-year study of FOSAMAX 10 mg/day and a one-year study of once weekly FOSAMAX 70 mg) the rates of discontinuation of therapy due to any clinical adverse experience were 2.7% for FOSAMAX 10 mg/day vs. 10.5% for placebo, and 6.4% for once weekly FOSAMAX 70 mg vs. 8.6% for placebo. The adverse experiences considered by the investigators as possibly, probably, or definitely drug related in B2% of patients treated with either FOSAMAX or placebo are presented in the following table.

	Two-year Study		One-year Study	
	FOSAMAX 10 mg/day % (n=146)	Placebo % (n=95)	Once Weekly FOSAMAX 70 mg % (n=109)	Placebo % (n=58)
<b>Gastrointestinal</b>				
acid regurgitation	4.1	3.2	0.0	0.0
flatulence	4.1	1.1	0.0	0.0
gastroesophageal reflux disease	0.7	3.2	2.8	0.0
dyspepsia	3.4	0.0	2.8	1.7
diarrhea	1.4	1.1	2.8	0.0
abdominal pain	2.1	1.1	0.9	3.4
nausea	2.1	1.1	0.0	0.0

### Concomitant use with estrogen/hormone replacement therapy

In two studies (of one and two years' duration) of postmenopausal osteoporotic women (total: n=853), the safety and tolerability profile of combined treatment with FOSAMAX 10 mg once daily and estrogen ± progestin (n=354) was consistent with those of the individual treatments.

### Other studies with FOSAMAX® (alendronate sodium) Prevention of osteoporosis in postmenopausal women

The safety of FOSAMAX 5 mg/day in postmenopausal women 40-60 years of age has been evaluated in three double-blind, placebo-controlled studies involving over 1,400 patients randomized to receive FOSAMAX for either two or three years. In these studies the overall safety profiles of FOSAMAX 5 mg/day and placebo were similar. Discontinuation of therapy due to any clinical adverse experience occurred in 7.5% of 642 patients treated with FOSAMAX 5 mg/day and 5.7% of 648 patients treated with placebo.

In a one-year, double-blind, multicenter study, the overall safety and tolerability profiles of once weekly FOSAMAX 35 mg and FOSAMAX 5 mg daily were similar. The adverse experiences from these studies considered by the investigators as possibly, probably, or definitely drug related in B1% of patients treated with either once weekly FOSAMAX 35 mg, FOSAMAX 5 mg/day or placebo are presented in the following table.

	Two/Three-Year Studies		One-Year Study	
	FOSAMAX 5 mg/day % (n=642)	Placebo % (n=648)	Once Weekly FOSAMAX 5 mg/day % (n=361)	Once Weekly FOSAMAX 35 mg % (n=362)
<b>Gastrointestinal</b>				
dyspepsia	1.9	1.4	2.2	1.7
abdominal pain	1.7	3.4	4.2	2.2
acid regurgitation	1.4	2.5	4.2	4.7
nausea	1.4	1.4	2.5	1.4
diarrhea	1.1	1.7	1.1	0.6
constipation	0.9	0.5	1.7	0.3
abdominal distention	0.2	0.3	1.4	1.1
<b>Musculoskeletal</b>				
musculoskeletal (bone, muscle or joint) pain	0.8	0.9	1.9	2.2

### Treatment of glucocorticoid-induced osteoporosis

In two, one-year, placebo-controlled, double-blind, multicenter studies in patients receiving glucocorticoid treatment, the overall safety and tolerability profiles of FOSAMAX 5 and 10 mg/day were generally similar to that of placebo. The adverse experiences considered by the investigators as possibly, probably, or definitely drug related in B1% of patients treated with either FOSAMAX 5 or 10 mg/day or placebo are presented in the following table.

	FOSAMAX 10 mg/day % (n=157)	FOSAMAX 5 mg/day % (n=161)	Placebo % (n=159)
	<b>Gastrointestinal</b>		
abdominal pain	3.2	1.9	0.0
acid regurgitation	2.5	1.9	1.3
constipation	1.3	0.6	0.0
melena	1.3	0.0	0.0
nausea	0.6	1.2	0.6
diarrhea	0.0	0.0	1.3
<b>Nervous System/Psychiatric</b>			
headache	0.6	0.0	1.3

The overall safety and tolerability profile in the glucocorticoid-induced osteoporosis population that continued therapy for the second year of the studies (FOSAMAX: n=147) was consistent with that observed in the first year.

### Paget's disease of bone

In clinical studies (osteoporosis and Paget's disease), adverse experiences reported in 175 patients taking FOSAMAX 40 mg/day for 3-12 months were similar to those in postmenopausal women treated with FOSAMAX 10 mg/day. However, there was an apparent increased incidence of upper gastrointestinal adverse experiences in patients taking FOSAMAX 40 mg/day (17.7% FOSAMAX vs. 10.2% placebo). One case of esophagitis and two cases of gastritis resulted in discontinuation of treatment.

Additionally, musculoskeletal (bone, muscle or joint) pain, which has been described in patients with Paget's disease treated with other bisphosphonates, was considered by the investigators as possibly, probably, or definitely drug related in approximately 6% of patients treated with FOSAMAX 40 mg/day versus approximately 1% of patients treated with placebo, but rarely resulted in discontinuation of therapy. Discontinuation of therapy due to any clinical adverse experience occurred in 6.4% of patients with Paget's disease treated with FOSAMAX 40 mg/day and 2.4% of patients treated with placebo.

### Laboratory Test Findings

In double-blind, multicenter, controlled studies, asymptomatic, mild, and transient decreases in serum calcium and phosphate were observed in approximately 18% and 10%, respectively, of patients taking FOSAMAX versus approximately 12% and 3% of those taking placebo. However, the incidences of decreases in serum calcium to <8.0 mg/dL (2.0 mM) and serum phosphate to <2.0 mg/dL (0.65 mM) were similar in both treatment groups.

### FOSAMAX PLUS D™ (alendronate sodium/cholecalciferol)

In a fifteen week double-blind, multinational study in osteoporotic postmenopausal women (n=682) and men (n=35), the safety profile of FOSAMAX PLUS D was similar to that of FOSAMAX once weekly 70 mg.

### Post-Marketing Experience

The following adverse reactions have been reported in post-marketing use with alendronate:

**Body as a Whole:** hypersensitivity reactions including urticaria and rarely angioedema. Transient symptoms of myalgia, malaise and rarely, fever have been reported with alendronate, typically in association with initiation of treatment. Rarely, symptomatic hypocalcemia has occurred, generally in association with predisposing conditions.

**Gastrointestinal:** esophagitis, esophageal erosions, esophageal ulcers, rarely esophageal stricture or perforation, and oropharyngeal ulceration. Gastric or duodenal ulcers, some severe and with complications have also been reported (see WARNINGS, PRECAUTIONS, Information for Patients, and DOSAGE AND ADMINISTRATION).

**Localized osteonecrosis of the jaw,** generally associated with tooth extraction and/or local infection, often with delayed healing, has been reported rarely (see PRECAUTIONS, Dental).

**Musculoskeletal:** bone, joint, and/or muscle pain, occasionally severe, and rarely incapacitating (see PRECAUTIONS, Musculoskeletal Pain).

**Skin:** rash (occasionally with photosensitivity), pruritus, rarely severe skin reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis.

**Special Senses:** rarely uveitis, scleritis or episcleritis.

For more detailed information, please read the Prescribing Information.

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