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Folic acid recommendations have little effect on birth defects ►

For more than a decade, we've known that folic acid supplementation in reproductive-age women can reduce the incidence of neural tube defects in infants by as much as 80%. Study results have shown that folic acid fortification of flour can be effective, but the effectiveness of recommendations alone has not been determined. These investigators examined data from birth-defect registries to determine whether public recommendations to increase folic acid intake through diet or supplements—but not through food fortification—have reduced the incidence of neural tube defects.

From 1988 through 1998, 8636 cases of anencephaly and spina bifida occurred among more than 13 million births in nine European countries and Israel (areas without mandated fortification of flour). Trends in incidence rates did not change significantly after local recommendations to increase folic acid intake were issued in eight of these countries.

Comment ► These findings seem to validate the U.S. and Canadian decisions to fortify flour with folic acid, which were followed by reduced incidence of neural tube defects in those countries. Additionally, practitioners are encouraged to recommend use of multivitamins that contain folic acid to all reproductive-aged women, and especially to those contemplating pregnancy. Recommendations alone are unlikely to be effective in reducing the incidence of neural tube defects.

Robert W. Rebar, MD
Published in *Journal Watch* May 6, 2005

▲ Botto LD *et al.* International retrospective cohort study of neural tube defects in relation to folic acid recommendations: are the recommendations working? *BMJ* 2005;**330**:571–3.

Neonatal behavioral complications from SRI exposure: fairly common, rarely serious ►

Use of serotonin reuptake inhibitors (SRIs) during pregnancy is not associated with fetal anomalies, but concerns about behavioral signs led the Food and Drug Administration to require labels warning about potential neonatal complications from late-pregnancy exposure. Researchers performed a meta-analysis of all relevant studies published from 1966 to 2005 and uncovered 13 case reports that described 18 patients, as well as 9 prospective cohort studies in which newborns of about 1000 women exposed to SRIs late in pregnancy were compared with those of controls (either unexposed women or those exposed early in pregnancy).

Behavioral signs were reported more often for paroxetine and fluoxetine than for other drugs, although exposure-normalized rates for specific SRIs could not be compared directly. An SRI-related neonatal behavioral syndrome was defined that included jitteriness, tachypnea, hypothermia, poor tone, weak cry, and feeding difficulties; the syndrome was more common among infants born to late-exposed women than among those born to unexposed or early-exposed women (relative risk, 3.0). Late-exposed infants also were more likely to be admitted to a special care nursery (RR, 2.6) and to have some respiratory difficulty (RR, 2.3). Behavioral signs almost always resolved within 2 weeks, risk for more serious problems did not appear to be increased, and supportive care usually was sufficient. Analyses could not be controlled for the severity of maternal psychiatric illness.

Comment ► These results are consistent with the biologic plausibility of serotonin withdrawal and confirm clinical experience, but the behavioral signs do not appear to be sufficiently severe to warrant withholding SRIs from severely depressed women in late pregnancy. Further studies are needed to determine the effect of the neonatal behavioral syndrome on future behavior and risk associated with specific SRIs.

Thomas L. Schwenk, MD
Published in *Journal Watch* May 20, 2005

▲ Moses-Kolko EL *et al.* Neonatal signs after late in utero exposure to serotonin reuptake inhibitors: literature review and implications for clinical applications. *JAMA* 2005;**293**:2372–83.

Natural history of Raynaud phenomenon ►

Raynaud phenomenon (RP) is common in people who do not have underlying connective tissue diseases. In this prospective community-based study of the natural history of RP, 1358 people (mean age, 54) in the Framingham Offspring Study cohort were interviewed at baseline and again 7 years later. RP was diagnosed based on responses to a validated questionnaire.

The baseline prevalence of RP was 11% in women and 8% in men; RP persisted in 36% and remitted in 64% of these people during the 7-year follow-up. The incidence of new RP was 2% at the 7-year follow-up interviews. Responses to other questions suggested that RP rarely interfered with daily activities.

Comment ► The authors believe that this is the first prospective community-based study of the natural history of Raynaud phenomenon. Although RP occasionally is debilitating in people without underlying connective tissue disease, it usually is mild, and the frequency of remission is high in this population.

Allan S. Brett, MD
Published in *Journal Watch* May 6, 2005

▲ Suter LG *et al.* The incidence and natural history of Raynaud's phenomenon in the community. *Arthritis Rheum* 2005;**52**:1259–63.

A black-box warning for tacrolimus and pimecrolimus ►

Recently, the FDA mandated a "black-box" warning label for the topical nonsteroidal anti-inflammatory agents tacrolimus and pimecrolimus. The reasons for that decision, and the implications for clinicians, are summarized below.

Background ► Tacrolimus ointment (Protopic 0.03, 0.1%) and pimecrolimus cream (Elidel 1%) are topical nonsteroidal anti-inflammatory agents indicated for atopic dermatitis in patients aged 2 years and older in whom conventional therapy is either ineffective or inadvisable because of concerns about adverse effects. On March 10, 2005, the FDA, acting on concerns voiced by its Pediatric Advisory Committee that this class of drugs is associated with a theoretical risk for lymphoma, ordered a black-box warning label.

FDA concerns ► Systemic tacrolimus (Prograf) is used as an immunosuppressive agent to prevent graft rejection in transplant patients. (Systemic pimecrolimus is not commercially available but may be supposed to have a risk profile similar to systemic tacrolimus because of molecular and receptor similarities between the two drugs.) Post-transplant lymphoproliferative disorder (PTLD),

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sometimes progressing to frank lymphoma, is a well-recognized complication of the intensive immunosuppression in transplant recipients. The risk for PTLD appears to be related to primary Epstein-Barr virus infection in seronegative patients with sustained immunosuppression (indicated by tacrolimus levels ⩾3 ng/mL).

Graft-related concerns are not directly relevant in the context of atopic dermatitis. In fact, numerous pre- and postmarketing pharmacokinetic, safety, and efficacy studies of tacrolimus and pimecrolimus in atopic dermatitis patients have repeatedly demonstrated very low levels of absorption, no accumulation, and no evidence of systemic immunosuppression as measured by response to childhood immunizations or delayed hypersensitivity. However, two sets of findings have raised concern: First, rare occurrences of lymphoma—both cutaneous (e.g., cutaneous T-cell lymphoma; mycosis fungoides) and noncutaneous—have been reported in patients using tacrolimus and pimecrolimus, although the specifics of each case and the numbers involved do not suggest an increased risk for lymphoma relative to the general population. Second, data from animal studies (including a positive dose-effect study in monkeys) suggest an increased risk for lymphoma with exposure to these drugs.

Definitive findings from clinical trials on the safety of these agents may not be forthcoming for up to 10 years. In the meantime, confronted with the troubling findings in animal studies and a biologically plausible risk in humans from agents that have been widely used off-label in infants (13% of pimecrolimus and 8% of tacrolimus prescriptions from June 2003 through May 2004 were written for children younger than 2 years), the FDA adopted the black-box warning.

Comment ► Topical tacrolimus and pimecrolimus are still available and recommended for use in appropriately selected patients with atopic dermatitis. The preponderance of evidence from clinical trials and postmarket studies suggests that these medications are safe and efficacious. Nevertheless, and even when parents exert pressure for nonsteroidal treatment, pediatricians should still consider these agents as second-line therapy—an option for patients older than 2 who have had protracted or ineffective topical steroid treatment. Every effort should be made to minimize the use of both these agents and topical steroids and to emphasize maintenance skin care including emollients. Thicker, fragrance-free ointments or creams are preferable.

Robert Sidbury, MD

Published in *Journal Watch Pediatrics and Adolescent Medicine* May 6, 2005

▲ FDA public health advisory: Elidel (pimecrolimus) cream and Protopic (tacrolimus) ointment. Accessed May 2, 2005, at http://www.fda.gov/cder/drug/advisory/elidel_protopic.htm.

▲ FDA talk paper: FDA issues public health advisory informing health care providers of safety concerns associated with the use of two eczema drugs, Elidel and Protopic. Accessed May 2, 2005, at http://www.fda.gov/bbs/topics/ANSWERS/2005/ANS01343.html.

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▲ Fonacier L *et al*. Report of the calcineurin task force of the ACAAI and AAAI (publication forthcoming).

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