

Periodontitis+High CRP Raise Preeclampsia Risk

The presence of both factors in pregnant women more than doubled the risk of either factor by itself.

BY KATE JOHNSON
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TORONTO — A combination of maternal periodontal disease and high levels of maternal C-reactive protein is associated with a significantly increased risk of preeclampsia, compared with either risk factor alone, according to a new analysis of the Oral Conditions and Pregnancy Study.

"There seems to be some type of synergy when both are combined," said Dr. Michael S. Ruma, who presented the findings at the annual meeting of the Society for Gynecologic Investigation.

A secondary analysis of 775 healthy pregnant women who had oral examinations and C-reactive protein (CRP) levels measured at enrollment (less than 26 weeks' gestation) found that preeclampsia was more common in those with high CRP levels alone (OR 2.6), and those with moderate to severe periodontal disease (PD) alone (OR 2.0)—but a combination of high CRP levels and moderate to severe PD increased the odds ratio to 7.0.

A total of 31 women (4%) developed preeclampsia in the cohort. The rate of preeclampsia was greater among women with a high CRP level (above the 75th percentile) than for women with a low CRP level (at or below the 75th percentile): 7% and 3%, respectively. The addition of mild PD to the elevated CRP level significantly increased the risk of preeclampsia from an odds ratio of 2.6 to 6.0 and moderate to severe PD increased it further (OR 7.0).

"Maternal systemic inflammation may be in the causal pathway between periodontal disease and the development of preeclampsia," said Dr. Ruma of the University of North Carolina at Chapel Hill. However, he said, future research is required to further understand this phenomenon. "Both periodontitis and preeclampsia are multifactorial, but the implication is

that inflammation in the mother is leading to systemic disease," he said in an interview.

A separate study presented at the meeting suggests that such maternal inflammation may also be transferred to the fetus—particularly in the setting of maternal smoking. In a study of 277 women, Dr. John P. Newnham of the Women and Infants Research Foundation at King Edward Memorial Hospital in Perth, Western Australia, and his colleagues found that 12% of women with PD had babies who were small for gestational age (SGA), compared with 2% of women who had healthy gums ("Gum Disease Again Tied to Pregnancy Outcomes," OB.GYN. NEWS, June 1, 2005, p. 28). Further analysis of this study, which was presented at the meeting, found this effect is significantly increased (25%) in women who smoke. Additionally, the researchers found that in smokers, both with and without PD, inflammatory markers (CRP and tumor necrosis factor- α) were significantly elevated in umbilical cord blood, indicating an inflammatory response in the fetus.

"The thing I found absolutely fascinating was this marked inflammation in the fetus at birth as a result of the woman smoking in pregnancy—and PD added further to it," Dr. Newnham said in an interview. "Smoking not only increases the risk of PD, which everyone has known for a long time, but smoking increased the inflammatory markers in the cord blood and PD added to this."

Although the absence of PD is associated with better obstetric outcomes, it is not known whether treating PD during pregnancy is beneficial or harmful, said Dr. Newnham. "We are in equipoise. We know inflamed periodontal tissue can release cytokines and prostaglandins," he said, leading some to hypothesize that the treatment of PD could temporarily increase maternal systemic inflammation. ■



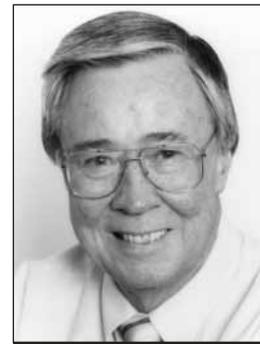
The mouth of a patient suffering from periodontal disease shows receding gums and a periodontal abscess (white, center). The disease is caused by bacteria in plaque.

DRUGS, PREGNANCY, AND LACTATION

Gastrointestinal Agents: Part III

The final part of this series covers the use of infliximab, anticholinergics/antispasmodics, gastrointestinal stimulants, and anorectal preparations in pregnant and lactating women.

► **Infliximab (Remicade):** Infliximab is a monoclonal antibody used to treat severe Crohn's disease and autoimmune diseases such as ankylosing spondylitis, rheumatoid arthritis, and psoriasis. It binds to and inhibits human tumor necrosis factor- α (TNF- α). Animal reproduction studies have not been conducted with the agent because it does not react with animal TNF- α . Human pregnancy exposure consists of about 30 cases, which are limited to case reports and observational studies. The drug does not appear to represent a significant risk for developmental toxicity. Still, if possible, the best course is to avoid its use in pregnancy. If pregnancy exposure does occur, health



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care providers are encouraged to register these patients in the Organization of Teratology Information Specialists (OTIS) Autoimmune Diseases in Pregnancy study by calling the toll-free number, 877-311-8972.

► **Anticholinergics/antispasmodics:** These agents have been used for many years for peptic ulcer and functional GI disorders such as diarrhea, hypermotility, neurogenic colon, irritable bowel syndrome, ulcerative colitis, biliary tract spasm, and similar conditions. The agents—available under numerous trade names—include atropine, belladonna, dicyclomine, glycopyrrolate, L-hyoscyamine, mepenzolate, methscopolamine, propantheline, and scopolamine.

Only atropine, scopolamine, and dicyclomine have sufficient data in pregnancy. There are no reports suggesting that these agents cause birth defects. However, an excessive dose of scopolamine in labor has been associated with newborn toxicity. The other drugs are also probably low risk, but cannot be classified as such because of the very limited or complete lack of human pregnancy experience. However, anticholinergic combinations formulated with phenobarbital or other sedatives should be avoided in pregnancy and lactation. Although the data are very limited, all anticholinergics, except dicyclomine, appear to be compatible with breast-feeding. Dicyclomine is concentrated in milk and has been associated with apnea in one nursing infant.

► **GI stimulants:** Dexpantenol (Ilopan) is given by intramuscular injection to prevent paralytic ileus after abdominal surgery. Although the drug has been promoted for constipation in pregnant women, there are no reports

of its use or studies in pregnant or lactating animals or humans. Thus, the drug should not be given during pregnancy or breast-feeding.

In contrast, another GI stimulant, metoclopramide (Reglan, Maxolon), has substantial human pregnancy experience, primarily as an antiemetic. Although it is considered compatible with pregnancy, its use during breast-feeding is controversial. It has been successfully used as a lactation stimulant at doses of 20-45 mg/day. The drug is excreted into milk, but the estimated dose ingested by a nursing infant from milk is much lower than the therapeutic infant dose.

However, mild intestinal discomfort has been observed in two infants. Because of its dopaminergic blocking action, the American Academy of Pediatrics classifies metoclopramide as a drug of potential concern during breast-feeding.

► **Anorectal preparations:** These include a large group of agents that are available in various topical formulations such as creams, ointments, foams, lotions, tissues and pads, and suppositories. With the exception of the hydrocortisone products, all are available over the counter, so you might not know that your patient is using them unless a careful history is taken. The OTC preparations are formulated with low concentrations of various drug mixtures, such as local anesthetics, vasoconstrictors, astringents, antiseptics, emollients/protectants, counterirritants, keratolytics, and wound healing agents. Only a few of these products and drugs have been studied in human pregnancy or lactation, but these preparations are used for their local effects and clinically significant systemic levels are not expected.

About 26% of the corticosteroid is absorbed from hydrocortisone suppositories, but the maximum strength of these products is only 30 mg, so the amount reaching the circulation is clinically insignificant. Therefore, at recommended doses, the use of anorectal preparations during pregnancy or breast-feeding can be considered low risk.

Of the drugs covered in this series, misoprostol and tetracycline cause structural defects, castor oil can induce labor, and mesalamine-containing agents and dicyclomine have caused toxicity in nursing infants. Most GI agents are safe in pregnancy and lactation, but many have insufficient data to judge their risk.

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