Cytokines, Fetal Growth, and RA

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Circulating cytokines appear to influence fetal growth in pregnant women who have rheumatoid arthritis, results of a Dutch study suggest.

High levels of interleukin-10, IL-6, and TNF-alpha might all play a role, each acting independently – and at different stages of pregnancy – to increase the risk of low birth weight among infants born to these mothers, Dr. Radboud Dolhain and colleagues wrote (J. Reprod. Immunol. 2010 [doi: 10.1016/j.jri.2010.08.010]).

VITALS

Major Finding: IL-10 in the first trimester seems to protect against low birth weight, while IL-6 seems to increase the risk. TNF-alpha exerts its influence in the third trimester, when higher levels also seem to protect against lower birth weights.

Data Source: A study of 302 pregnant women with rheumatoid arthritis and 33 controls.

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Dr. Dolhain of Erasmus University Medical Centre, Rotterdam, the Netherlands, and his coinvestigators examined circulating cytokines in 134 pregnant patients with rheumatoid arthritis during their first trimester, 168 in their third trimester, and 33 healthy controls. Birth weights were analyzed using standard deviation scores.

Disease activity in the women was based on the disease activity score for 28 joints (DAS28); the scale runs from 0-10, with higher numbers indicating greater disease activity.

Since IL-10, IL-6 and TNF-alpha generally decrease during pregnancy, the investigators sought to determine if any increasing gestational levels correlated with birth weight. Among the first trimester patients, 12 had detectable IL-10; all of these women had a higher disease activity score than did those with no IL-10 (mean DAS28 4.4 vs. 3.6).

Birth weights were compared between the two groups, which were matched with regard to disease activity, parity, and prednisone use.

The mean birth weight standard deviation was significantly greater in the IL-10 positive group (0.92) than in the matched negative group (0.15), Dr. Dolhain and his associates reported.

This association with IL-10 was not seen in the third trimester pregnancies.

The investigators then examined the effect of IL-6 by stratifying IL-6 levels and disease activity scores in the first and third trimester.

In the two groups with high disease activity (DAS28 3.8 or higher), birth weight standard deviation was significantly lower in mothers with high IL-6.

In the high IL-6 group, the birth weight standard deviation was –0.19, compared with 0.36 in the low IL-6 group.

Again, the authors found no such association in the third trimester.

"In the first trimester, elevated IL-10 seems to protect against the negative influence of RA disease activity on birth weight, [while] IL-6 seems to amplify this negative influence," the investigators wrote.

"Both cytokines create a birth weight standard deviation of more than 0.50, which is considered clinically relevant. In the third trimester, there is no influence, suggesting an early critical window."

TNF-alpha, however, did exert an influence in the third trimester of pregnancy, Dr. Dolhain and his colleagues noted. Stratifying TNF-alpha in the same way, they concluded that the birth weight standard deviation was lower in the group with low TNF-alpha (0.05) than in the group with high TNF-alpha (0.52).

This association was not present in the first trimester.

The finding that increased TNF-alpha is associated with better birth weights may require a rethinking of anti–TNF-alpha therapy for pregnant women, they suggested.

This implies that "TNF blockers, which are more and more prescribed during pregnancy to treat rheumatoid arthritis, should be used with caution," Dr. Dolhain and his associates said. ■

DRUGS, PREGNANCY, AND LACTATION

Perceived Risks of Folic Acid Supplementation

The current recommendation in the United States and Canada is that women of reproductive age consume at least 400 mcg/day, or 0.4 mg/day, of folic acid by ingesting a multivitamin, foods fortified with folic acid, or both to reduce their risk of having a baby with a neural tube defect; and 4 mg/day for women who have already had an NTD pregnancy.

Since 2007, the Society of Obstetricians and Gynecologists of Canada has recommended that in cases in which clinicians believe that their patients do not comply with taking a daily prenatal vitamin containing 0.8-1.1 mg of folate, those women should take a supplement that contains 5 mg of folic acid. This recommendation is based on evidence that compliance with prenatal vitamins is quite low, including a large study of reproductive-age women in Ontario that my colleagues and I conducted, which found that 40% did not achieve the level of red blood folate needed to prevent NTDs, despite folic acid supplementation and folic acid fortification of food products in North America that began in 1998 (Reprod. Toxicol. 2008;25:408-12).

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Other evidence includes an analysis of all cohort studies that concluded that 5 mg/day of folic acid would prevent almost 90% of NTDs, based on the level of serum folate achieved at this dose, and that 0.4 mg/day or even 0.8 mg/day was not adequate for many women (Lancet 2001;358:2069-73).

The 2007 Canadian guidelines also recommended that certain groups of women who need more than 0.8-1 mg/day also take the higher folic acid dose, including those taking antiepileptic drugs or folic antagonists such as sulfa drugs or methotrexate, those who have malabsorption syndrome, and obese women with a body mass index greater than 35 kg/m^2, as well as women who smoke and those with diabetes.

However, many women are wary of increasing the amount of folic acid during the preconception period and pregnancy. At Motherisk, we often receive questions from women who are concerned about the possible adverse effects of higher folic acid doses. A major concern is that higher doses can mask vitamin B_{12} deficiency and result in pernicious anemia, which affects people older than women of childbearing age who are taking the larger folic acid dose for a relatively short period of time. Moreover, because foods have been fortified with folic acid for over a decade and there is no evidence that the rate of pernicious anemia in the general population has increased overall, this is probably not a risk in the context of pregnancy. But if a clinician has any doubts or concerns, he or she can check the patient's B_{12} status.

Perhaps a more prominent concern is that too much folic acid could increase the risk for cancer, which is based on a lab experiment showing that exposing precancerous cells to folic acid increased the likelihood they would become cancerous. This is clearly an important question that needs to be addressed and has been the focus of recently published studies that provide reassuring data.

More reassuring evidence was provided by a randomized study of more than 600 men and women who had already been diagnosed with and treated for colorectal cancer and who then received either 1 mg/day of folic acid or placebo for 3-6.5 years. The relative risk of adenoma recurrence among those in the folic acid supplementation arm was 0.82, compared with placebo, which was not statistically significant but was suggestive of a mild protective effect. In addition, there was a significant protective effect (relative risk, 0.61) among the people who had low plasma folate levels at baseline (Am. J. Clin. Nutr. 2009;90:1623-31).

In a meta-analysis of 27 studies on the risk of colorectal cancer and folic acid, published in January, we also found an inverse association between folic acid intake and the incidence of colorectal cancer, which was suggestive of a mild protective effect overall of high folic acid intake, ranging from 8% to 15% reductions in risk, which were statistically significant (Cancer Epidemiol. 2011;35:2-10). The evidence available to date, therefore, strongly suggests that increasing folic acid for those who need a higher dose does not increase the risk for colorectal cancer – and clearly reduces the risk of NTDs.

One explanation that was proposed for the theoretical increase in cancer risk was that high levels of unmetabolized folic acid resulting from excessive folic acid intake may be toxic to natural killer cells. But this theory was not supported by a study we conducted in women aged 18-45 years who were not pregnant and who were randomized to receive either 1.1 mg/day or 5 mg/day of folic acid for 30 weeks. The study determined that the concentrations of unmetabolized folic acid were not significantly different between the two groups, and that levels were low (Am. J. Clin. Nutr. 2009;89:844-52). Another concern is the potential risk of taking folic acid supplements for an extended period of time among women of reproductive age who could become pregnant or are taking a long time to conceive. For those cases in which it is unclear whether a patient is taking more than is needed to reach protective levels, or in which reassurance is needed, I would recommend measuring folate in red blood cells. Levels above 900 nmol are protective against NTDs, so if the patient's level is 2,000 nmol, for example, a lower folic acid dose can be recommended. The test is not available in every hospital, but it is accessible and can provide reassuring information for patients.

There are not many sure ways to reduce the risk of birth defects, so women should be encouraged to take folic acid supplements and – if they are in the higher risk groups for NTDs – to take the higher doses recommended, without fearing long-term adverse effects.

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