Cytokine Tied to Depression in Pregnant Women

Macrophage migration inhibitory factor is a fairly recent discovery and has attracted wide attention.

BY ERIK GOLDMAN
Contributing Writer

NEW YORK — Macrophage migration inhibitory factor, a newly characterized cytokine that inhibits cortisol and increases production of inflammatory cytokines, may be the key to understanding depression during pregnancy, Brad D. Pearce, Ph.D., said at a symposium sponsored by the National Alliance for Research on Schizophrenia and Depression.

Pregnant women seeking treatment for major depression have markedly higher levels of macrophage migration inhibitory factor (MIF) than do nondepressed pregnant women of similar age. In general, MIF levels are slightly elevated in pregnant vs. nonpregnant women, but the difference is insignificant compared with the difference between depressed and nondepressed pregnant women, said Dr. Pearce of the department of psychology at Emory University, Atlanta.

"We all hear that pregnancy is a time of joy, a natural high, and that pregnancy-related hormones are protective. The data, however, collide with these truisms," said Dr. Pearce, noting that roughly 7% of all American women experience episodes of major depression during their first pregnancies. The proportion increases to 12%-14% for second and third pregnancies.

The prevalence of major depression among nonpregnant women is roughly 8%. So, on a statistical basis, pregnancy is hardly protective and may actually increase the incidence of depression, he said.

"There are some very big changes in body chemistry during pregnancy. The shift in the balance of hormones, cytokines, cortisol, and many other things can be huge and complex. Some women feel bliss; many others become depressed," he noted.

Depression during pregnancy can have significant complications: It is predictive of preterm labor and delivery, as well as other obstetrical complications, and is linked to an increased risk of behavioral and social problems in the children. "The physiological changes caused by depression during pregnancy result in changes in maternal–fetal interaction, which can have adverse effects on the fetal brain," Dr. Pearce said.

Antidepressant drug therapy, however, is not a neutral, risk-free proposition. Although none of the major antidepressant drug classes is considered strongly teratogenic, many commonly used agents have been linked to adverse obstetrical outcomes, including preterm delivery.

Dr. Pearce and his colleagues at Emory have been looking at potential biologic mediators involved in depression during pregnancy. They've focused largely on inflammatory cytokines, many of which are consistently elevated in people with major depression. Patients with chronic inflammatory disorders, characterized by elevated cytokine levels, often have comorbid depression. Some cytokines used as drugs in the treatment of cancer can induce symptoms of depression if given intravenously.

MIF is a fairly recent discovery, and it has attracted wide attention among immunologists and infectious-disease researchers. "It is a very unique protein. It is not like any of the other cytokines. It is really in its own family," Dr. Pearce said.

MIF is produced by different immune cells and appears to block the action of cortisol. This results in an overall up-regulation of inflammation because cortisol normally inhibits inflammatory signaling molecules. MIF is also modulates catecholamine metabolism. Interestingly, MIF is also produced in large quantities by the hippocampus. "Nobody knows yet what it is doing there in the brain," he said.

If studies bear out the connection between higher MIF levels and depression, he believes MIF may be useful as a prognostic marker for both depression and pregnancy complications like preterm labor. Prepregnancy depression predicts depression during and after pregnancy, Dr. Pearce said. ■

Drug Tx May Be Appropriate for Depression During Pregnancy

BY NORRA MACREADY
Los Angeles Bureau

LOS ANGELES — Caring for a pregnant woman with a history of depression means weighing the risks of fetal exposure to psychotropic medication against the consequences of the untreated illness, Vivien Burt, M.D., said at a psychopharmacology update sponsored by the University of California, Los Angeles.

Abruptly discontinuing antidepressants during pregnancy is not necessarily best for the woman or her baby, said Dr. Burt, professor of psychiatry and biobehavioral sciences at the university.

In a review of 1,861 pregnancies among inner-city women, preterm delivery was significantly higher in women whose scores on the Center for Epidemiologic Studies Depression Scale were in the 91st to 100th percentile, than in patients with lower scores (Epidemiol. Rev. 1995;17:165-71).

In an earlier study by different investigators, the risk of a negative pregnancy outcome among inner-city adults rose 5%-7% for every point they scored on the Beck Depression Inventory (J. Clin. Epidemiol. 1992;45:1093-9). Other research has linked maternal depression to neurobehavioral sequelae in the neonate, including decreased motor and vagal tone, lower activity levels, and poorer orienting skills, compared with infants born to women who were not depressed.

There may be dangers to the mother as well. The risks of untreated depression during pregnancy include poor self-care, including sleep disruption and poor judgment regarding nutrition and use of alcohol, tobacco, and illicit drugs. Depression and anxiety are associated with a higher risk of preeclampsia and postpartum depression.

Dr. Burt recommended this approach to treatment:

► **For mild to moderate depression.** Consider nonpharmacologic interventions such as psychotherapy, stress-reduction techniques, and a reliable support system.

► **For serious depression marked by suicidality, psychosis, poor weight gain, impaired self-care, or impaired bonding with the fetus.** Consider medication.

► **When a change of medication is indicated.** If the patient is not yet pregnant, make sure she is stable and put her on the safest possible agent. If the patient is pregnant, consider her prior history of response before switching her medication. Many antidepressants have been widely studied during pregnancy, so doctors and patients can make an informed decision about which ones are safest to take, Dr. Burt said.

In general, pregnant women should avoid mirtazapine, bupropion, and MAO inhibitors. Mirtazapine and bupropion haven't been studied sufficiently in this patient population, and limited evidence associates bupropion with fetal cardiovascular defects. MAO inhibitors may produce a hypertensive crisis when used with tocolytic agents and have been associated with congenital anomalies in animal studies.

Dr. Burt said she feels "fairly comfortable" prescribing tricyclic antidepressants and selective serotonin reuptake inhibitors; many studies have shown they do not cause major congenital anomalies even when taken in the first trimester. These agents have been associated with negative obstetric outcomes in a few studies, including a slight decrease in mean 5-minute Apgar score and transient tachypnea in newborns, but these effects don't seem to produce any long-term damage.

As delivery approaches, Dr. Burt schedules additional appointments so she can monitor the patient more closely. She may prescribe a lower dose during the final month of pregnancy, then restore it to its usual level immediately thereafter.

Whatever drug is prescribed, make sure peer-reviewed studies support the choice, should it become necessary to justify the decision in court. These will carry more weight than the letter grades assigned by the Food and Drug Administration, Dr. Burt warned. ■

VBAC Has More Risks Than Second Elective Cesarean Section

BY JANE SALODOF MACNEIL
Southwest Bureau

LOS ANGELES — Women who choose vaginal birth after a cesarean section have a 2.5 times greater risk of major complications than if they were to opt for a second elective cesarean section, according to a poster presentation at the annual meeting of the Society for Gynecologic Investigation.

The adjusted odds ratio of 2.5 for major morbidities comes from a retrospective cohort study, comparing 5,299 women who attempted vaginal birth after a cesarean (VBAC) section with 4,065 women who elected a second cesarean delivery. Major complications occurred in 295 women (6%) in the VBAC group and 101 women (3%) who delivered by a second C-section.

"I think we are … seeing a swing where more people are getting sectioned, and now we are going to see complications from the sections," investigator Heather S. Lipkind, M.D., said in presenting the data.

Cesarean deliveries accounted for 27.3% of all births in 2003, while the VBAC rate plunged to a low of 10.6%, according to Dr. Lipkind, a fellow in maternal-fetal medicine at Columbia University College of Physicians and Surgeons in New York City, and her colleagues.

Dr. Lipkind and her associates reported that numerous studies have looked at VBAC complication rates, but none has been a randomized, controlled trial. Therefore, the researchers used propensity scores, a statistical technique, to approximate a trial by controlling for confounders resulting from the nonrandomized assignment of women to the VBAC or repeat C-section cohorts.

The patients came from a 5-year database of births at 17 university and community hospitals. All had a single gestation and one prior low-transverse cesarean delivery. None had previously given birth vaginally. Dr. Lipkind said the success rate was 68% for the women who attempted VBAC.

Rupture was the most common major complication, occurring in 106 (2%) VBAC patients, compared with 19 (less than 1%) patients who elected C-sections (adjusted odds ratio 4.8).

Although the other major complications occurred in less than 1% of both groups, bladder injury more than tripled in the VBAC cohort; it occurred in 27 VBACs and 7 repeat C-sections (adjusted odds ratio 3.5). Other major complications were hemorrhage (29 VBACs vs. 17 repeat cesareans; adjusted odds ratio 1.5) and abruption (65 VBACs vs. 39 repeat cesareans: adjusted odds ratio 1.4).

Minor complications were similar between groups: 757 (14%) in the VBAC cohort and 489 (12%) in the elective C-section patients (adjusted odds ratio 1.0). Fever was the most common, occurring in 626 (12%) women who chose VBAC and 424 (10%) women who had repeat C-sections (adjusted odds ratio 0.9). ■