CNS Defects Linked to Parvovirus in Pregnancy

Subtle neurobehavioral effects in normal children may be tied to mild maternal parvovirus B19 infections.

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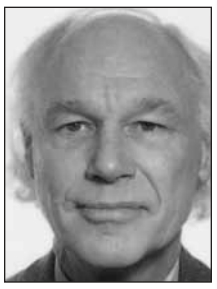
ST. PETE BEACH, FLA. — Typical primary effects of parvovirus B19 infection during pregnancy include hydrops fetalis, fetal death, and spontaneous abortion, but a recent case and a review of the literature suggest that central nervous system abnormalities are a rare but possible effect of such infection, Dr. Kenneth Lyon Jones reported at the annual meeting of the Teratology Society.

Dr. Jones' case involved an 11-year-old boy whose mother had documented parvovirus B19 infection early in her first trimester. The child had severe brain development defects secondary to the prenatal exposure. Mental retardation was severe; he had not learned to speak and had been diagnosed with hypertonic cerebral palsy.



Diagnosis of maternal infection was made during the first trimester. An ultrasound at 20.5 weeks' gestation indicated fetal ventricular enlargement, and at birth the boy weighed 2,898 g. At day 5 he received a blood transfusion because he had severe anemia, said Dr. Jones of the University of California, San Diego.

During the newborn period, ultrasound showed severe cerebral atrophy.

At age 11, his height was 122 cm (below the 3rd percentile) and his weight was 27.3 kg (10th percentile).

The child was markedly hirsute and had a frontal hair upsweep, a large hemangioma over the helix of his right ear, a large space between his upper central incisors, and clinodactyly of the index and fifth fingers of his left hand, Dr. Jones noted.

In addition, his inner canthal distance was 2.7 cm (25th percentile), and his palpebral fissure was 2.3 cm (below the 2nd percentile).

Valproic acid and carbamazepine treatment failed to control seizures, which he began having at birth.

A search of the literature revealed three publications documenting CNS abnormalities after maternal parvovirus B19 infection, Dr. Jones said.

The first, which was published as an abstract, involved three cases. In one case the fetus died, and in the other two cases the fetuses survived but had severe mental retardation.

Neuropathology at the time of death in the nonsurviving fetus, which was exposed to infection at 24 weeks' gestation, showed brain atrophy with widespread dysplasia and focal destruction of spinal cord and piriform cells, among other abnormal findings noted Dr. Jones.

One of the survivors was exposed to infection at 18 weeks' gestation. The child had cerebral palsy, developmental delay, and infantile spasms. Neuroimaging revealed enlarged ventricles with small periventricular calcifications, cortical dysplasia with polymicrogyria, and periventricular hypodensity.

The final case in that report involved a fetus exposed at 23 weeks' gestation. A CT scan of the brain revealed periventricular calcifications.

The second publication was a case report involving a fetus that was exposed at 15 weeks' gestation and died 7 hours after birth. Neuropathology showed multinucleated giant cells, macrophages, microglia, and many small calcifications around the vessels, predominantly in the cerebral white matter. Polymerase chain reaction amplification showed that parvovirus DNA was present in the nuclei of the multinucleated giant cells and endothelial cells, Dr. Jones said.

The most likely mechanisms of action include infection of cells in the CNS and hypoxia secondary to severe anemia.

DR. JONES

The final publication involved a series of 92 consecutive singleton pregnancies with serologic evidence of parvovirus B19 infection. There were 3 therapeutic abortions, 64 fetal deaths, 10 premature births (8 of the babies subsequently died), and 15 term births (1 baby subsequently died).

Of the 73 fetal or neonatal deaths, 21 had adequate histologic evaluation of the brain, and 9 of these showed CNS abnormalities. Of the 16 surviving babies, 5 had CNS abnormalities.

One of the 14 with CNS abnormalities had trisomy 13 syndrome; no etiology was determined in the remaining cases, but the findings suggested anemia might be an important mechanism for CNS abnormalities, Dr. Jones noted.

Based on the findings of the published reports, it appears three patterns of abnormalities are associated with maternal parvovirus B19 infection: positional limb deformities, radiographic evidence of intercranial calcifications, and dysplastic changes, including agyria, macrogyria, polymicrogyria, and dysgenesis of the corpus callosum, he said.

"CNS involvement is a rare occurrence following maternal parvovirus infection, but it clearly occurs, and when it does, it's clearly significant," Dr. Jones said, noting that the mechanism of action most likely includes both infection of cells in the central nervous system and hypoxia secondary to severe anemia.

It is possible that subtle neurobehavioral effects in otherwise normal children result from a mild case of maternal parvovirus B19 infection, he added. ■

Maternal Citalopram Treatment Prompts Adverse Event Reports

ST. PETE BEACH, FLA. — A total of 228 adverse events associated with the use of citalopram (Celexa) during pregnancy has been reported to the Food and Drug Administration's Adverse Event Reporting System since the drug was approved in 1998, J. Edward Fisher, Jr., Ph.D., reported at the annual meeting of the Teratology Society.

Of these reports, 120 involved adverse developmental events, and 38 of those events occurred during the peri- or postnatal period.

A total of 31 of the 38 cases occurred in the early neonatal period during the first week of life, and 18 of these involved neonatal withdrawal symptoms, including jitteriness, rigidity, tremor, and confusion associated with citalopram exposure in either the third trimester or throughout pregnancy.

The doses used by the pregnant women ranged from 20 to 40 mg/day, said Dr. Fisher, a pharmacologist with the FDA Center for Drug Evaluation and Research, Rockville, Md.

Reports of symptoms consistent with neonatal withdrawal syndrome and associated with maternal use of selective serotonin reuptake inhibitors (SSRIs) and selective norepinephrine reuptake inhibitors (SNRIs) prompted the FDA last year to require labeling changes warning of the risk associated with their use during pregnancy.

Possible cases of neonatal withdrawal syndrome have been reported with all SSRIs, but in at least one study, the majority of cases were associated with paroxetine.

In that study of 93 cases, 64 were associated with paroxetine, 14 with fluoxetine, 9 with sertraline, and 7 with citalopram, which is marketed as Celexa by Forest Laboratories. (One patient received both paroxetine and fluoxetine.) Another large study showed that the association between paroxetine and neonatal symptoms was no greater than that of other SSRIs.

The citalopram reports noted by Dr. Fisher and the other reports involving various SSRIs and SNRIs and their association with neonatal withdrawal symptoms suggest a class effect. But the data remain insufficient for determining whether there are significant differences among the individual drugs in this class, he told this newspaper.

As a rule, "the use of this agent has to be balanced with respect to the benefit to the mother if she is depressed. There is a general consensus that SSRIs and SNRIs are preferable to tricyclics in terms of safety and efficacy," said Jeffrey Jonas, M.D., senior vice president of Forest Research Institute, a division of Forest Labs.

Experts continue to urge clinicians to weigh the risks and benefits of SSRI and SNRI use in pregnancy and to consider the increased risk of maternal morbidity associated with untreated maternal depression. ■

Diclectin Exposure Held Harmless To Neurocognitive Development

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, Irena 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 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 who were 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. ■