Infertility Treatment Tied to Neural Tube Defects

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WASHINGTON — Infants born to women treated for infertility—particularly those treated with clomiphene citrate around the time of conception—have a significantly increased risk of neural tube defects, according to results of a study presented at the annual meeting of the Pediatric Academic Societies.

In the study, singleton infants with neural tube defects were almost five times (OR 4.8) as likely as were those in a healthy control group to have a mother with a history of infertility. Singletons with neural tube defects were 11.7 times more likely to have been exposed to clomiphene around the time of conception than were those in the control group, said Yvonne Wu, M.D., of the University of California, San Francisco.

Seventeen percent of the infants with defects were exposed to clomiphene, compared with 2% of infants in the control group.

Clomiphene citrate has been used to treat infertility since the 1960s. Beginning in the 1970s, some case reports suggested that the drug might be a risk factor for neural tube defects in offspring. Several observational studies conducted in the 1980s produced conflicting results. Animal studies have shown that clomiphene administration before ovulation leads to an increased risk of exencephaly in offspring.

The current case-control study was nested within the population of 110,624 singleton live births delivered at 36 weeks' gestation or later from 1994 to 1997. The data came from the Kaiser Permanente database for Northern California.

The researchers identified all infants in this group with a physician diagnosis of spina bifida, other spinal cord anomalies, or spinal cerebellar disease. Reviewers were blinded to maternal infertility.

In all, 18 cases of neural tube defects were identified, resulting in a birth prevalence of 1.6 per 10,000. These included 13 cases of spina bifida aperta (myelomeningocele and meningocele) and 5 cases of spina bifida occulta. A total of 1,608 control infants also were identified. These infants were free of cerebral palsy, genetic abnormalities, or congenital anomalies.

Univariate and multivariate odds ratios were calculated and adjusted for infant gender, maternal age, and maternal race. There were no demographic differences between the infants in the case and control groups.

A maternal history of infertility and clomiphene use were both independent predictors of neural tube defects.

Among the infants with neural tube defects, 22% of the mothers had a history of infertility, compared with only 6% of mothers of infants in the control group. Maternal history of infertility was determined from an infertility diagnosis in the Kaiser database, use of one of 23 infertility drugs documented in the Kaiser system, or evaluation at one of 11 infertility clinics in Northern California.

Seventeen percent of the infants with neural tube defects were exposed to clomiphene around the time of conception, compared with 2% of the infants in the control group. The periconceptional window was defined as 60 days before the date of conception to 15 days after. The date of conception was defined as the date of birth minus seven times the gestational age in weeks.

Eighty percent of the women who had been given clomiphene around the time of conception had received multiple courses of the drug before conception. Previous research has shown that the active component of clomiphene is present in the bloodstream for more than a month, meaning that clomiphene is still present for 3-4 weeks after conception—the period when the neural tube closes.

Three of the mothers of infants with neural tube defects had received an average of 5.7 courses of clomiphene, compared with 2.7 courses for the mothers of infants in the control group exposed to the drug. This difference was significant, suggesting that there may be a dose response.

The meeting was sponsored by the American Pediatric Society, the Society for Pediatric Research, the Ambulatory Pediatric Association, and the American Academy of Pediatrics. ■