

# No Red Flags Seen for Etanercept in Pregnancy

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WASHINGTON — Preliminary data suggest no increased risk for adverse pregnancy outcomes in women exposed to etanercept during the first trimester, Christina Chambers, Ph.D., reported in a poster at the annual meeting of the American Academy of Dermatology.

Although the numbers are small thus far, no worrisome pattern has emerged. "Based on preliminary data at the present time, we don't see any big red flags," said Dr. Chambers, a perinatal epidemiologist at the University of California, San Diego, who specializes in drug safety during pregnancy.

The prospective cohort data come from the Organization of Teratology Information Specialists (OTIS), a network of telephone-based teratology counseling services based at hospitals and universities throughout the United States and Canada. Since 1999, network members have collaborated on the OTIS Autoimmune Diseases in Pregnancy Project, a registry study focused on the safety of medications used to treat a variety of autoimmune diseases.

The project is sponsored in part by research grants from several pharmaceutical companies, including Amgen Inc., the manufacturer of etanercept (Enbrel), and Abbott Laboratories, maker of adalimumab (Humira).

Etanercept is a self-injectable anti-TNF- $\alpha$  monoclonal antibody medication approved in the United States for the treatment of rheumatoid arthritis (RA) and psoriatic arthritis.

Etanercept also is approved for treating psoriasis and ankylosing spondylitis.

In an ongoing study, 82 women were enrolled between March 2005 and October 2006.

Of those, 48 were exposed to etanercept: 28 for RA, 14 for psoriasis or psoriatic arthritis, and 6 for ankylosing spondylitis.

Another 34 women who did not take etanercept were also enrolled: 18 with RA, 14 with psoriasis or psoriatic arthritis, and 2 with ankylosing spondylitis.

Mean age was about 33 years in both groups, and mean gestational age at enrollment was 11.4 weeks for the etanercept-exposed group and 12.2 weeks for the disease-matched comparison group.

Outcome was known for 42 preg-

nancies as of October 2006. No stillbirths occurred in either group. There was one spontaneous abortion among the 22 in the etanercept group (4.5%), far below both the 3 of 20 (15%) in the disease-matched comparison group and the 10%-15% pregnancy loss rate in the general population, Dr. Chambers noted.

Gestational age was 37.5 weeks for the etanercept group, which was not significantly different from the 37.8 weeks for the disease-matched controls.

Gestational age in both groups, however, was about a week less than normal, a phenomenon that has been documented previously in patients with RA.

Similarly, birth weights—which were 3,323 g for the etanercept group and 3,317 g for the nonexposed disease-matched women—were slightly

lower than the 3,400- to 3,500-g average birth weight in the general population, but were not decreased in those infants with etanercept exposure, Dr. Chambers said.

Of the 21 infants born alive in the etanercept group, 3 had major defects. One of those three infants, a twin, was born with malrotation of the stomach, which required surgery; a preterm infant had a unilateral inguinal hernia that required surgery; and a third infant, whose mother had Hashimoto's thyroiditis, was born with congenital hypothyroidism.

In the comparison group, one pregnancy was terminated following a prenatal diagnosis of Down syndrome.

All of the infants will be evaluated up to 1 year of age for major and minor anomalies by pediatric specialists, Dr. Chambers said.

Final results for preterm delivery, birth weight, and congenital malformations should be available in 1-2 years.

In the meantime, even these small preliminary numbers are reassuring because they don't show any particular pattern. "All the major teratogens are associated with very specific patterns of abnormal outcomes. When you don't see a pattern and you just see one of this and one of that, it makes you a little more confident that this is not an Accutane," she said. ■

Physicians who prescribe etanercept to women of childbearing age are encouraged to enroll patients in OTIS. For more information, e-mail Dr. Chambers at [chchambers@ucsd.edu](mailto:chchambers@ucsd.edu) or call 877-311-8972.

## DRUGS, PREGNANCY, AND LACTATION

### Cocaine Use by Pregnant Women

Concerns about the adverse effects of maternal cocaine use during pregnancy on children exposed in utero have been the focus of many studies since the 1980s, when cocaine use began to increase, first among more affluent socioeconomic groups, then shifting to lower-income groups with the advent of cheap crack cocaine.

During the mid to late 1980s, reports suggested that cocaine use during pregnancy caused congenital malformations, which were followed by other reports suggesting that cocaine had adverse effects on long-term neurodevelopment in children exposed in utero. However, more recent systematic reviews of a large number of cases have not found an association between in utero exposure to cocaine and an increase in malformations of any kind, and these original concerns have not been borne out.

Women who use cocaine have many other risk factors for poor neonatal outcome and adverse long-term effects on the child than women who don't use cocaine, which may include low socioeconomic class, smoking, poor nutrition, and abuse of other drugs.

Over the years, studies have more carefully controlled for these other factors, comparing women who used cocaine during pregnancy to women in similar environments who had the same risk factors but did not use cocaine, and these studies have not found any association between maternal cocaine use and congenital defects or long-term effects in children.

In 2001, investigators performing a review of 36 prospective studies of prenatal cocaine exposure in children aged 6 years and younger found no convincing consistent evidence that in utero cocaine exposure was associated with negative effects on physical growth, developmental test scores, or receptive or expressive language.

They concluded that "many findings once thought to be specific effects of in utero cocaine exposure can be explained in whole or in part by other factors, including prenatal exposure to tobacco, marijuana, or alcohol and the quality of the child's environment" (JAMA 2001;285:1613-25).

While these and later studies constitute the overall picture, some well-designed studies have suggested that prenatal cocaine exposure does have some serious adverse effects, most notably, a greater risk of prematurity and higher rates of placenta previa.

There are also reports that some addicted women take high doses of cocaine near the end of pregnancy because they believe it may induce labor, which can result in placental bleeding and shock, potentially resulting in adverse, long-term effects on brain development in the baby.

An important consideration for obstetricians and other health care professionals who follow women who may use cocaine during pregnancy and those who follow their children is that continuing use of cocaine after a woman knows she is pregnant is recognized

as essentially a sine qua non for addiction.

Many women may not disclose they use cocaine during a history, but our laboratory and others have developed methods of ascertaining whether a baby has been exposed to cocaine in utero, such as analysis of neonatal hair and meconium, biomarkers for maternal cocaine use that are validated and widely used by social services and clinicians in the United States and Canada.

Cocaine and its metabolite benzoylecgonine accumulate in fetal hair during the last trimester, so a positive test is a strong indicator that the mother used cocaine during the sixth or seventh month.

Cocaine and benzoylecgonine also accumulate in meconium, which is produced in midpregnancy, so a positive meconium test is an indication of use earlier in pregnancy. The meconium analysis can be used during the first few days post partum, while the hair analysis can be used for up to 3 months after the baby's birth.

Studies have documented damage to the brain in monkeys exposed in utero to cocaine at doses equivalent to doses that are typically used in humans.

Why similar findings have not been found in human studies speaks volumes to the plasticity of the newborn's or young child's brain and the ability to recover, if early environmental factors, with optimal stimulation, are favorable. This is an important area of research that is not yet fully resolved.

We conducted a study comparing children exposed in utero to cocaine who had been adopted by stable families, where presumably, environmental factors were normal, with biologic children of mothers from the same socioeconomic class.

The IQs of the adopted children were significantly lower than those of the comparator group, although the families were not aware of any neurodevelopmental problems with the children. This suggests that even in an optimal situation, however, not all damage can be reversed by brain plasticity.

Some studies have suggested that there may be an effect of fetal cocaine exposure on some specialized executive functions, such as the ability to perform complex tasks, or more refined functions, but the verdict on this issue is still out.

We and others continue to follow children who have been exposed in utero to cocaine, and are trying to understand sources of variability and why some children are affected and others are not.

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