Drug tied to higher risk of birth defects

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Infants exposed in the womb to valproate – a common drug for seizures, migraines and mood disorders – have twice as many birth defects as previously thought, posing a troubling dilemma for doctors and mothers-to-be.

That's according to a new study, which found that 8.8 percent, or 11 of 123 babies born to mothers who took the drug, had serious abnormalities. Previously, the rate was thought to be 4 percent.

The report from a Harvard birth-defects registry has doctors and patients throughout the nation talking to and e-mailing one another about whether women of childbearing age should be discouraged from taking valproate, which has been in use for 30 years.

"There's every reason to be more concerned about this drug based on their study," said Dr. Kenneth Lyons Jones, director of the California Pregnancy Risk Information line at UC San Diego.

The state-funded database and hotline program follows women who take certain drugs, or who are exposed to pesticides or other chemicals during pregnancy.

"Doctors should be warning women in their childbearing years that the drug is associated with an increased prevalence of birth defects, and what those birth defects are," Jones said.
In healthy women not on valproate, the chance of having a baby with a major defect ranges from 1 percent to 2 percent.

"The previous messages tended to minimize the risks of this drug," said Dr. Lewis B. Holmes, who directed the Harvard-based Antiepileptic Drug Pregnancy Registry.
Holmes characterized the findings as "scary."

"What we're saying now is: 'Hey, this is really much more of a big deal than everyone was previously led to believe."

Holmes and others emphasized that neurologists, who frequently prescribe valproate, are well aware of the drug's dangers. But psychiatrists, obstetricians and other doctors who don't prescribe the drug as much may not be as well informed, he and others said.

In England, dozens of women who took valproate and delivered babies with defects and learning problems are suing the government health system, contending that they weren't told of the drug's dangers.

The Harvard registry has enrolled 3,100 women who took a variety of anti-convulsant drugs. Of those, 123 took Depakote, Depakene or Epivil, brand names of valproate, as single therapy during their pregnancies. Most took valproate for epileptic seizures, but some took it for bipolar disorders, pain, depression or migraine headaches.

Experts say it is unclear how many pregnant women with those conditions take valproate. But they estimate that 20,000 women with epilepsy get pregnant each year, and that between 5 percent and 25 percent of them take valproate.

Holmes said a Boston hospital survey of women who gave birth found that one in 250 had taken an anti-convulsant of some kind, but it was unknown what percentage of those women took valproate.

The abnormalities discovered in the Holmes study included four heart defects, two cases of spina bifida, a genital abnormality, a hernia, a club foot, too many fingers on one hand and a lethal kidney defect. Holmes blames valproate, rather than epileptic seizures, as the culprit because previous studies found no increase in birth defects in a similar group of women who did not take anti-seizure drugs.

Smaller studies have linked valproate with a 4 percent birth-defect rate, primarily spina bifida. Because of that, the drug is sold with a warning label.

But Holmes said doctors and patients generally ignore the warning because the chances seem relatively small, and the alternative – not taking the drug and having serious seizures – is unacceptable.

They are willing to risk a bad pregnancy outcome considering that, for many patients, there is no better drug, he said.

Dr. James Grisolia, a neurologist at Scripps Mercy Hospital and a member of the National Epilepsy Foundation board, agreed.

"For many women with epilepsy, migraines or psychiatric illness, valproate remains the best, most effective choice overall," Grisolia said.

He emphasized that "the majority of pregnant women who take it have normal pregnancies and healthy babies, and can lead full lives." Even some of the birth defects, such as an extra finger, don't have a major effect on a person's quality of life, he said.

Some women may be urged to take newer anti-seizure drugs in the hope the drugs cause fewer birth defects. But Holmes and others said it is too soon to know whether the newer drugs are really safer.

Susan Upchurch, client services director for the San Diego Epilepsy Foundation, said the new study will alarm many women already concerned that anti-seizure drugs will cause abnormal babies.

Generally, Upchurch said, physicians tell them not to worry, because the risk is small. If they don't take drugs and have severe seizures, they may fall and cause secondary harm to the fetus.

Holmes emphasized that women should not stop taking the drug on their own.

He and Grisolia urged women taking valproate to call their doctors even if they are just considering pregnancy. The defects are thought to occur during the first few weeks of gestation, before a woman knows she is pregnant.

And, Grisolia and Holmes emphasized, supplements of folic acid might reduce the risk.

Many doctors are as skeptical as they are worried about the study's results.

"This report is like saying the building is on fire," said Rodrigo Munoz, former president of the San Diego County Medical Society and a psychiatrist who prescribes the drug for manic depression. "It has put us in a bind, because many of our patients could not do well without this drug."

Since the registry report was released last month, Munoz said, e-mail among psychiatrists "has been red hot on this topic, because we ask each other have we seen any cases of birth defects in the infants of our patients, and the answer is always 'No.' "

Many psychiatrists wonder if the birth defects found in Holmes' registry aren't simply attributed to symptoms of epilepsy, Munoz said.

According to Holmes, that is unlikely.

Holmes reported in 2001 in the New England Journal of Medicine on a study that looked at 128,049 pregnant women in the Boston area who gave birth over a seven-year period.

Pregnant women who had seizures but did not take anti-seizure drugs had the same number of birth defects as healthy mothers, that study found.

Holmes said the valproate report is the first of many to come from the registry, which is financed by six pharmaceutical companies that make anti-seizure drugs. Because some companies have newer products, they hope to learn whether their drugs are as risky as valproate.

A spokesman for Abbott Labs, which makes Depakote, the best-selling type of valproate, said the increased risk from the drug is adequately covered by package warning labels. Abbott supports the registry and "the careful reporting of adverse events," the spokesman said.

Holmes' study was presented at a meeting of the Society for Maternal and Fetal Medicine last month in San Francisco and was published in the American Journal of Obstetrics and Gynecology. It comes two years after the Boston registry found that women who took phenobarbital, another anti-seizure drug, during pregnancy had a 7.8 percent chance of giving birth to babies with malformations such as heart defects and cleft lip and palate.

Registry staff conduct extensive interviews at the start of the callers' pregnancy, before any exams such as sonograms are performed. They keep track of medications, dosages and at what stages before and during the pregnancy the drugs were taken.

Holmes and Jones are working hard to publicize their registries and enroll more women who take drugs during their pregnancies in order to catalog birth abnormalities.

Carine Newberry, 36, of Oakton, Va., signed up for Holmes' study because she is on lamotrigine, a new anti-seizure drug on the market.

"If there's a good drug, I really want to help get that information out and make it safer for women who have to be on anti-epileptic drugs," she said.

While the Harvard registry focuses on epilepsy drugs, the University of California San Diego registry looks at hundreds of chemicals with an emphasis on drugs for asthma, depression, arthritis and epilepsy.

About 22 women a month are enrolled. Their children are followed for six years to see if any are diagnosed with
physical defects or learning and neurological problems.

Currently, UCSD is following about 1,500 women. The program is supported with $460,000 a year in state funds and a small grant from Aventis pharmaceutical company, which makes drugs for rheumatoid arthritis.
To enroll in UCSD's registry, call (800) 532-3749. To enroll in the Boston anti-seizure medicine registry, call (888) 233-2334.