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Pregnancy, anti-seizure medications, and seizures

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In their article, "Antiepileptic drug clearances during pregnancy and clinical implications for women with epilepsy," Voinescu et al.[1] looked at a very specific problem. They wanted to see how the changes that occur in a woman's body during pregnancy affects the strength of seizure medication in the bloodstream. The idea is straightforward. If the changes in the body during pregnancy cause the strength of the medication to go down, more seizures might happen during pregnancy. It was because of this that they looked at medication levels before, during, and for 1 year after the pregnancy. They also looked at the person's seizures, measuring whether the seizures worsened during pregnancy.

This idea is not new. In fact, there have been similar studies looking at the levels of 2 commonly used seizure medications, carbamazepine[2] and lamotrigine[3,4] during pregnancy. In these studies, it was found that carbamazepine levels changed very little while lamotrigine levels changed quite a bit when a person is pregnant. The problem is that there are many medications available for the treatment of seizures. We have information on only 2: carbamazepine and lamotrigine. What about all of the others? Do levels change during pregnancy? Should doctors be monitoring levels for all of these medications?

The reason this is so important is that there have been studies which have shown that when seizure medication levels fall below 65% of the pre-pregnancy values, seizure get worse.[5] Seizures that occur during pregnancy could injure the baby. Keeping the levels as constant as possible throughout the pregnancy lessens the risk of seizures getting worse. However, for doctors to do this, they need to know which medications are affected by pregnancy. Further, doctors need to know *how soon* in the course of the pregnancy the levels change. Does it happen right away, or does it happen at the end of the pregnancy?

There are many changes that occur in a woman's body when she is pregnant. Perhaps the most obvious is that mom gains weight. However, many body functions change. One is that kidney function increases. Since the kidneys filter many seizure medications *out* of the bloodstream, increased kidney function means that the seizure medicine stays in the system shorter. Another is an increase in liver function. Many seizure medications are broken down by the liver. When liver function increases, the blood level of a medication goes down.

How was the study done?

Dr. Voinescu gathered information from 44 women with epilepsy. Most of them were taking only one medicine for their seizures (also called *monotherapy*). In most of these women, Dr. Voinescu had blood levels of the seizure medication *before* the woman became pregnant. In the instances where this information was not available, a blood level within 1 month *after* pregnancy was used as a comparison to the pregnancy levels. Blood levels of the medications were measured every 1–3 months. Because *adherence* (adherence refers to how consistently a person takes their medicine) to taking medication can affect blood levels, Dr. Voinescu also looked at how often a person might miss their seizure medicine. In women who were taking just one medicine, Dr. Voinescu counted seizures, in order to see if the changes in the blood levels correlated with a worsening of seizures.

The women were takin different medications. Eighteen were taking levetiracetam, 4 were taking oxcarbazepine, 10 were on topiramate, 5 on valproate, and 7 were taking phenytoin. The

authors followed these women through their pregnancies, and for 1 year after the baby was born.

What did the study show?

Levetiracetam, oxcarbazepine, and topiramate levels went down during the pregnancy. This was due to increased clearance of the medication. Pregnant women cleared these drugs 1.4–2.0 times faster than non-pregnant women. For each of the above medicines, the clearance rates were different. Further, this study showed that the clearance increased in the first or second trimester. In other words, the changes in the levels of these medications occurred early or in the middle of the pregnancy. For levetiracetam, clearance increased 1.71 times in the first trimester. For oxcarbazepine, it increased by 1.63 in the second trimester. Topiramate clearance increased 1.39-fold, also in the second trimester.

As for changes in seizures, in 15 women, seizures worsened when the medication levels decreased. However, this study was too small to factor out other possible causes of seizures like poor sleep or stress. Because of its small size, the authors could not clearly assess whether the women experienced a worsening of seizure severity. In other words, if their seizures increased in number, did they also turn into longer, more serious seizure types?

What does this mean?

Doctors have a lot to learn about seizures, seizure medications, and pregnancy. Studies like this help doctors to know how to best evaluate and manage women with epilepsy who are pregnant. There are many issues to consider: will the medicine affect the baby? What is the best way to minimize the risk of seizures during pregnancy? What is the best way to manage seizure medications? Studies like this one start to answer some important questions. First, not all medication s show changes in blood levels during pregnancy. For those that do, the changes may occur very early in pregnancy (the first trimester). For these medications, it will be important to start measuring blood levels as soon as he woman becomes pregnant. Adjustments in the dose of the medicine can be made, maintaining constant levels throughout the pregnancy. In keeping the levels constant, seizure control can be maintained. By preventing seizures during pregnancy, the risk of injury to the baby from seizures is eliminated.

This was a small study. Only a few medications could be studied. The authors admit that a larger study is needed, one that looks at all medications. Further, a bigger study needs to assess blood levels throughout the pregnancy. If possible, such a study should also carefully measure the changes in seizures that occur due to changes in blood levels.

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About epilepsy

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What is a seizure?

Nerve cells "talk" to each other constantly. They send both electrical messages and chemical ones, which we call neurotransmitters. Sometimes, brain cells send the "wrong" messages. Our brains have their own autocorrect, but just like a cell phone, sometimes an error still goes through. When the wrong signal is sent, other brain cells respond to the error by sending abnormal signals. If enough brain cells start sending the same, wrong message, a seizure occurs.

One way to think of this is that the brain works like an orchestra. There are different sections in an orchestra, each with its own instruments. Although each instrument plays its own part, it is only when they all play together that complex music is made. While playing, each member of the orchestra has to listen to the other members. As a team, playing together and listening to one another, the best music is made. In other words, when all of the brain cells are working together, a person can think clearly and logically.

However, what if one person in the orchestra began playing a different tune? At first, no one would notice that someone was playing the "wrong" tune. Nearby orchestra members would become confused: which tune were they supposed to play? As more members of the orchestra began playing the "different" tune, it would eventually become noticeable. At some point, the "different" tune might become louder than the original music.

This is similar to how a seizure gets started, and keeps going. The nearby brain cells start playing the wrong tune. They encourage other brain cells to do the same thing. Eventually, 2 different tunes are being played at the same time. For an orchestra, the combined music would be confusing and might turn into "noise" as opposed to "music." When a person has a seizure, at some point, the seizure is "loud" enough that they can no longer think clearly and logically. If this worsens, a person can no longer stay aware of what is going on around them. It is at this point that they lose consciousness.

What is epilepsy?

There are many kinds of seizures. There are many kinds of epilepsy. Using a combination of medical tests in combination with a detailed medical history and examination, a doctor can narrow down the list of possibilities to arrive at the correct *epilepsy* diagnosis. Saying this, epilepsy is diagnosed in a person has had 2 or more *unprovoked* seizures in their lifetime.

How is epilepsy diagnosed?

The doctor will need to know as much as possible about what happened immediately before, during, and after the seizure. How often do the seizures occur? Is there a warning sign? Does the person remember anything about the seizure? All of these questions help the doctor to better understand the kind of seizures and the kind of epilepsy that the person is experiencing. In addition, asking someone who has *seen* the person's seizure to describe them can provide valuable information. For instance, if the person who had the seizure cannot remember their seizures, the observer may be able to provide information that the patient may not know.

Medical testing can also help to better understand a person's seizures. Electroencephalography (EEG) is a simple and painless study that records the brain's electrical activity. The brain waves

are picked up by tiny electrodes that are put on the person's scalp. The EEG is reviewed, looking for specific brain wave patterns in people with epilepsy. These patterns provide critical information about the person's epilepsy, and help with the diagnosis.

Imaging studies are critical in understanding the cause of a person's seizures. The 2 most common studies are MRI and CT. Modern CT and MRI provide very detailed pictures of the brain, and are critical in locating tumors, scars, or other abnormalities that may cause seizures.

How are seizures treated?

There are many treatments for seizures. Medicines are tried first. If these do not work, your doctor may consider special diets, brain surgery, or devices for the treatment of seizures. Usually, the physician tries to stop all seizures while causing no side effects. In women who are considering becoming pregnant (or who are pregnant), the choice of medication is smaller. For instance, there are certain medications which are known to have a higher association with birth defects. Often, in women who are thinking about starting a family, these medications are avoided. It is very important to tell your doctor about the kinds of problems you might experience while on a medication (or any treatment). In addition, it is important to have a discussion with your doctor about your life plans: work, exercise, and the desire to start a family. Taking all of these things into consideration, together you will make the best choice of treatment(s).

For more information

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Epilepsy Foundation
epilepsy.com

Citizens United for Research in Epilepsy
CUREepilepsy.org

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