The glow of pregnancy is no shield against depression. Millions of expectant mothers rely on antidepressant medication for help. But treating mom with drugs at this time in her life may have long-term consequences for baby.

Around 10 percent of women suffer bouts of despair during the hormonal chaos of pregnancy or in the months after delivery. Some women are already being treated with antidepressants such as Prozac and Zoloft, while others get new prescriptions. For many adults these drugs, known collectively as selective serotonin reuptake inhibitors or SSRIs, work as advertised: lifting mood by temporarily boosting the availability of the brain chemical serotonin. But SSRIs may have a different, more long-lasting effect on a developing baby’s brain.

Over the past few years, a handful of studies have found that mice and rats exposed to antidepressants shortly before birth or just afterward grow up anxious and depressed. Other animal studies link early exposure to SSRIs to improved decision-making and spatial-learning abilities. Though many of the documented reactions fall within the normal range of behavior, the drugs can influence how an animal experiences and relates to its surroundings, says Judith Homberg of Radboud University in Nijmegen, the Netherlands.

No one knows for sure if people experience the same risks or benefits over the long haul, but a new study shows that children exposed to antidepressants in the womb are more likely to appear sad or withdrawn at age 3 than those whose moms didn’t take the drugs.

Though the mechanism underlying such changes is still unknown, a picture is beginning to emerge. In the February Trends in Pharmacological Sciences, Homberg and her colleagues outline research in animals linking exposure to SSRIs during early development to faulty brain organization and abnormalities. And recent studies in fruit flies support a theory that sensitivity to serotonin can be set early in life.

“You don’t necessarily get ill because of a change in brain development by serotonin, but it may change your personality traits,” Homberg says. “We may be changing the brain in subtle ways that we still don’t understand.”

Despite these recent findings, doctors caution women against stopping treatment, because the risks of depression — for mom and baby — may outweigh...
those of the medication. Recent studies grapple with how to separate the effects of SSRIs exposure from the damage wrought by depression in mothers.

**It’s all in the timing**

Serotonin works like a nerve cell lubricant that keeps life running smoothly. It excites neurons that control muscle activity and soothes neurons that mediate pain. It takes the edge off neurons in the brain’s limbic system, tempering impulses related to behaviors such as sex, aggression and overeating.

Specialized cells in a part of the brain called the raphe nuclei produce serotonin. Located near the base of the skull, these neurons send out branches that extend throughout the brain and spinal cord to connect with other neurons. When a nerve impulse reaches a branch ending, the neuron passes along the message by releasing serotonin into the synapse, a tiny space between one neuron and the next. Within a millisecond, the neuron that released the serotonin takes it back, vacuuming it up in a process known as reuptake.

Serotonin’s mood-boosting effects occur while the chemical is in the synapse. The longer it remains there, the better the prospects for pleasant feelings. Antidepressants such as Prozac and other SSRIs work by blocking the protein that accomplishes reuptake — called serotonin transporter protein, or 5-HTT.

In developing brains, serotonin has a much broader role. During brief but critical periods of early development — before and after birth — the 5-HTT protein shows up in various parts of the brain. Scientists believe that some nerve cells temporarily draw on serotonin to help guide the growth and connections of other young cells, a process that lays down circuits crucial for touch, vision, smell, thought and memory.

Changing the level of serotonin in the growing brain by blocking the reuptake process may alter the way these sensory systems develop, a growing number of animal studies suggest. SSRIs can readily cross the placenta, which nourishes the fetus, and the drugs are also detectable in breast milk and in breast-fed children.

In 2004, Columbia University scientists showed that both mice exposed to SSRIs and mice engineered to lack a gene for the 5-HTT protein grew up to exhibit anxiety traits in adulthood, such as a reluctance to eat in or explore unfamiliar places.

Since then, studies have found faulty brain organization in mice lacking the 5-HTT protein. Some of the most convincing evidence comes from studies of the barrel cortex, a brain region associated with processing information that mice gather with their whiskers.

Mice use whiskers like fingertips to feel around in the dark, passing the information to the barrel cortex. If exposed to SSRIs early in development — while neurons in the barrel cortex are being laid down — mice show abnormalities in this region. The neurons are smaller, with fewer branchlike structures, Homberg says.

Though humans don’t have a barrel cortex, they do have a brain region, called the primary somatosensory cortex, that processes delicate sensations received from the fingertips.

“It’s hard to translate the findings on the barrel cortex in rodents to the role that serotonin plays in development in humans,” Homberg says. “There is a kind of gap in between, and we should try to fill it.” She now plans to study this brain region in children whose mothers took SSRIs during pregnancy to see if similar structural abnormalities exist.

**Getting set up for life**

Serotonin may play another important role in growing brains: Organizing the circuitry by which the chemical itself operates throughout life. Serotonin is so essential to life that critters — from flies to frogs to humans — set up elaborate distribution systems to ensure its flow throughout the central nervous system. This is achieved, in part, by parceling out the sites where serotonin is released. But scientists have wondered how a developing brain knows what the density of release sites should be.

One possibility is that the sites are set up according to how much serotonin is in the system, says neuroscientist Barry Condron of the University of Virginia in Charlottesville. So neurons producing serotonin would have their own receptors that sense how much of the neurotransmitter is out there and adjust accordingly. A lack of serotonin would prompt more release sites to grow; too much would cause release sites to retract.

During development, when the serotonin system is “under installation,” it may be especially sensitive to serotonin levels in the brain, Condron says. In 2005, he and then doctoral student Paul Sykes found that developing flies were quick to adjust the number of release sites in response to changes in serotonin levels. But the response depended on the timing: Adding serotonin to the system decreased the overall density of release sites in older larvae, while increasing the density in very young larvae.

“It’s all about timing,” Condron says. “There’s a fine ballet of timing in serotonin levels and the need for the
neurochemical during various stages of development.”

The levels of serotonin early in development may help determine how the serotonin system responds throughout life, he says. “Which brings with it the fact that if you change that level of serotonin in some artificial way, by taking drugs or experiencing stress, then those circuits could be forever altered.”

In a series of experiments directed by doctoral student Elizabeth Daubert, Condron’s team engineered fruit flies capable of making either high or low levels of serotonin. Early in development, the flies with excess serotonin showed signs of degeneration in the area around the release sites. The flies had large swellings along the branches that extend from neurons — swellings that resemble structures found in Alzheimer’s patients or ecstasy users.

Decreasing the fly’s serotonin levels led to a recovery over time, Condron says. Still, the findings, published online April 13 in the journal *Molecular and Cellular Neuroscience*, suggest that nerve cells in the developing brain may be more sensitive to surges in serotonin than are those in the adult brain, he says.

“What it’s indicating to us is that the serotonin system goes through a critical period of development where the level of serotonin is gauged, and the neurons determine their sensitivity to serotonin in order to self-regulate the system,” Condron says. The study also suggests that the serotonin system has a “set” point, he says. “If you get to a certain high level, it starts to fall apart on you.”

**From mice to men**

Even if the preliminary findings in rodents and flies hold up in people, SSRIs are but one factor that may alter serotonin levels in the brain of a developing baby. Factors such as the child’s genetics and the mother’s mood can also play a role.

Depressed women are less likely to take care of themselves, sleep well or exercise, leading to higher levels of stress, says Tim Oberlander, a developmental pediatrician at the University of British Columbia in Vancouver. They’re also more likely to engage in reckless behavior, such as drinking or using illicit drugs. All of these activities work to change serotonin levels in a growing brain.

Distinguishing between the impact of prenatal SSRI exposure and the fallout of the mother’s mental illness, Oberlander says, remains a key challenge.

Over the past few years, Oberlander has conducted a number of studies to sort out effects. In 2006, he examined roughly 120,000 birth records and linked the births to mothers who were diagnosed as depressed during pregnancy. Some of the women in the group used SSRIs and others did not. He then compared records with a third group of women who were not diagnosed with depression and not treated with medication during pregnancy. The findings, published in the *Archives of General Psychiatry*, showed that babies born with SSRIs in their systems had lower birth weights and were more likely to experience respiratory distress.

Oberlander’s group began a long-term study in 2007. When the researchers looked at behaviors such as aggression, they found that children who had been exposed to SSRIs in the womb had an increased risk for aggressive behaviors at 4 years of age — but only when their mothers were still reporting high levels of depression.

“It didn’t matter that kids were exposed prenatally, but it did matter what the mother was feeling at the time of the follow-up study,” Oberlander says. That finding fits with long-established
literature that says children who grow up in a household with someone who has a mood disorder are more likely to act out, showing more aggressive or impulsive behaviors, he says.

Still, the story is complicated. The latest study by Oberlander suggests that both SSRI exposure and a mother’s current anxiety level matter. Oberlander and his colleagues recruited a group of 33 pregnant women who were taking SSRIs for mood disorders. The team followed the progress of the women and their children over a three-year period, comparing them with a group of pregnant women with a range of mood symptoms who were not on SSRIs.

When controlling for anxiety during late pregnancy, the researchers were able to link prenatal SSRI exposure with sad and withdrawn behavior in kids at 3 years of age. Mom’s anxiety at the time of the study was also associated with these behaviors. When controlling for prenatal and postnatal depressed mood, however, only the mother’s current mood seemed to matter.

The study, published in the May issue of Archives of Pediatric and Adolescent Medicine, also points to a genetic effect. The team found that among the 3-year-olds with mothers who were depressed during pregnancy, only children who had two short copies of a gene called SLC6A4 tended to be more anxious and depressed. The gene is called the “master modulator” of the serotonin system because variations lead to changes in the amount of serotonin available both inside and outside the cell: A short version leads to less efficient serotonin reuptake, while a long version leads to more rapid reuptake.

Oberlander’s group also found that children with two long copies of the gene whose mothers experienced elevated anxiety during the third trimester of pregnancy showed an increased risk for aggressive behavior at 3 years of age — whether mom had been treated with antidepressants or not. No interactions were noted among child genotype and SSRI exposure.

Oberlander says the work shows that SSRIs and mother’s mood can have an emotional impact on a child’s development, but the child’s genetic makeup also plays a role. “These findings might give us some insight into who might be at increased risk and who might not be,” he says.

The bad and the good

While Oberlander’s study shows that early exposure to SSRIs may have lingering aftereffects, Homberg says it is important to keep in mind that work in rodents suggests the outcome may not always be negative.

While some studies show that mice and rats exposed to SSRIs during development are anxious, a handful of others suggest that, when put in environments with changing conditions, these rodents are quicker to pick up on new routines and make decisions better and faster than those that haven’t been exposed. These positive reactions closely resemble behaviors found in people who carry two short forms of the SLC6A4 gene, Homberg says. People with this genetic variation are less likely to take risks and are more sensitive to social threats. The common denominator, she says, is increased vigilance and sensitivity to environmental stimuli.

“It could be that they respond emotionally when conditions are stable, but rely on their cognitive skills when conditions are changing,” she says. “During changing conditions there are additional stimuli that might distract their attention, drawing it away from the one that is inducing an emotional response.”

Homberg is now pursuing studies in animals and humans to see how seemingly positive effects play out over time. “Being sensitive to the environment can be bad, as you may develop an illness,” she says. “But if exposed to more positive stimuli, which are also in the environment, you may even come out better.”

So where does this research leave women who are concerned about how antidepressants might affect the neurodevelopment of their children?

“None of our findings suggest that pregnant women should not be treated for depression,” Oberlander says. “But we have a lot to learn about who can benefit from pharmacological treatment with an SSRI and its impact on child development. And at the end of day, we need to understand that there is no free lunch, nor an easy route that is totally risk free.”

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