Migraine Tip of the Month

Pregnant and migraine out of control? Consider Botox

OnabotulinumtoxinA (BotoxA) has been with us for over 30 years, was FDA-approved for the treatment of chronic migraine in 2010 and in recent years has become a mainstay for managing that prevalent and often otherwise difficult to treat disorder.

Given how safe, tolerable and effective it appears to be in comparison with many of the oral medications used for migraine, many headache specialists now routinely use BotoxA for pregnant patients with chronic migraine. While for a significant proportion of migraineurs their headaches improve in the second or third trimester, many pregnant patients suffer for months on end because they are told they can't take their usual migraine medications. Commonly used medications for migraine such as sodium valproate (*Depakote*), nortriptyline (*Pamelor*), and topiramate (*Topamax*) are either known to cause harm to the growing fetus, or as with propranolol (*Inderal*) and verapamil (*Calan*), to have uncertain effects on fetal development.

At least in the case of BotoxA, this may be overly restrictive. Botulinum toxin, derived from bacteria, causes paralysis of muscles, and in large doses the toxin can cause botulism, a serious medical disease. The medication, BotoxA, does not contain the bacteria, and for chronic migraine it is used in tiny doses which are administered into the muscles of the head and neck. Along with relaxing those muscles, its downstream effect serves to stabilize the nervous system circuit that, when activated, generates migraine.

In more than 600 pregnant women who have had known exposure to Botox during pregnancy, there was no increase in risk to the pregnancy or to the resulting baby. Even if BotoxA were accidentally to get into the bloodstream, the molecule is too large to cross from the mother's circulation through the placenta and into the fetal circulation. Remarkably, in reported cases of pregnant patients critically ill with botulism, the full-blown paralytic infection caused by the *Clostridium botulinum* bacteria, fetal movement remained normal even when the pregnant mother was completely paralyzed. This demonstrates the incredible ability of the placenta to filter out large particles and likewise supports the argument that the BotoxA molecule does not pose any risk to the pregnancy and fetus.

Given the scarcity of attractive alternatives, the clinical observations indicated above and the implications inherent in the large size of the BotoxA molecule, I highly recommend that providers strongly consider BotoxA as a treatment option for their pregnant (or attempting to become pregnant) patients who are suffering from chronic migraine.

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Some general comments about migraine and pregnancy…

Dr. Smirnoff addresses a highly relevant clinical issue. The target demographic for migraine is females of childbearing potential, and - not surprisingly - individuals within that demographic group frequently desire to conceive, become pregnant and then often to breast-feed. And while it's true that many patients experience a vacation from migraine during pregnancy, especially during the latter stages, the hallmark of migraine is that nothing about the headache disorder is "always". Unfortunately, many females experience a profound worsening of their migraine during pregnancy, and for some it may persist throughout all three trimesters and make for a truly miserable experience.

Even if her migraine lessens during pregnancy, following delivery the female migraineur may experience a rather abrupt resurgence of headache. Breast-feeding may suppress migraine…or it may not. When it does not and migraine burden is high, the afflicted female finds herself facing much the same issue as exists in pregnancy-aggravated migraine: what medication can I use to help control my headaches without potentially harming my infant?

Unless there is some major change in the way we evaluate medications used for treatment of migraine, there will never be a prospective, randomized, placebo-controlled and large-scale whiz-bang of a clinical trial that will firmly establish the safety to the fetus or breast-feeding infant of a given medication taken by the mother for her migraine. This is one of those areas where the "art of medicine" and common sense therefore must take precedence over science.

*A few migraine medications are absolutely contraindicated for females at risk for pregnancy or known to be pregnant. Perhaps the most notable is divalproex sodium (**Depakote**), a drug that is FDA-approved for migraine prevention and often quite helpful when pregnancy is not a concern. Especially if the developing fetus is exposed to divalproex early in pregnancy, serious malformations of the central nervous system may result.*

For most migraine medications, however, we just don't know. Adequate data pertaining to safety of use during pregnancy or breast-feeding simply do not exist. What data are available are derived from animal models typically involving doses of the given medication far higher proportionately than what is prescribed for human patients or from pregnancy registries that are highly susceptible to selection bias (who bothers to phone in the information vs who doesn't). Left with this uncertainty, clinicians tend to avoid prescribing altogether or stick to those medications which have been available the longest. The triptans serve as a good example: available in the United States for three decades, they gradually have evolved from being rarely used in pregnancy to being commonly prescribed despite no change in their original labeling: "…should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus". This oft-invoked precaution is not much help; the "potential benefit" (relief from acute migraine headache) is obvious, but as for "potential risk", who knows?

So, time for a little art of medicine blended with common sense and a dash of pharmacology. Dr. Smirnoff makes the very good point that the BotoxA molecule is so large that it is unlikely to pass from mother to fetus through the placental blood circulation. Similarly, the concentration of BotoxA in breastmilk is, if detectable at all, so low that it seems overly meticulous to deny BotoxA to breast-feeding mothers with chronic migraine. The pregnancy-related labelling for BotoxA is unlikely to change, but – as with the triptans – use of BotoxA for chronic migraine during attempted conception, pregnancy and breast-feeding is becoming commonplace and now can be said to fall within "the range of acceptable medical management."

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Dr. Smirnoff's comments do not necessarily reflect the opinions and clinical policies of her colleagues and parent institution, Stanford University. In any event, the decision of what medications to use for migraine treatment during pregnancy or imminent pregnancy should involve a fully informed patient and all relevant providers, along with careful analysis of existing data from clinical experience and research.