

THE PREGNANT PATIENT WITH HEADACHES

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Objectives

- To understand how to counsel women with migraine contemplating pregnancy
- To understand which treatments are safe to use during pregnancy
- To understand what secondary headaches may occur during pregnancy

Pre-pregnancy Considerations

- Migraine medications ideally should be discontinued before pregnancy
- Woman can attempt pregnancy as soon as the medications are discontinued
- However, at least 50% of pregnancies are unplanned

Pre-pregnancy Considerations

- Folic acid supplementation
 - In the general population, folate < incidence of MCMs (major congenital malformations)
 - Insufficient information to address dose of folic acid but should be at least 400 ug (0.4 mg)
 - Divalproex & barbiturates interfere with folate metabolism

- Use of NSAIDs during attempted conception may inhibit implantation

Pennell, P from annual course at the meeting of the American Epilepsy Society, 2007

Pre-Pregnancy Considerations

- A woman wants to know if her baby will be normal if she takes meds during pregnancy.
- Important that woman understands that just by getting pregnant there is:
 - 30-50% risk of miscarriage
 - 3-5% risk of birth defects in the baby
 - 1% risk of mental retardation in the child

Pre-Pregnancy Considerations

- Therefore, the correct question about a medication exposure during pregnancy is not, will my baby be normal, but will the exposure increase the background risk?

Scialli A.Counseling. From www.reprotox.org

Pre-pregnancy Considerations

- Beware of using divalproex sodium (VPA) in women during the childbearing years
 - VPA dose-related risk for MCMs in 1st trimester supported by 2 class II studies and 6 class III studies
 - Daily dose cutoff not consistent but approximated 1000 mg/day in 5 studies
 - Recent report that women taking valproate during pregnancy may increase their child's risk of autism

Pennell P. From the annual course at the American Epilepsy Society Meeting, 2007.

Bromley RL, et al. Neurology 2008; 71:1923-1924.

Outcome of Pregnancy in Migraineurs

- Risk of miscarriage, MCM, & stillbirth not increased
- Controversial whether migraine is associated with low birth weight
- Scher found that migraineurs have a higher risk of gestational hypertension

Olesen, et al 2000

Banhidy 2006

Scher et al 2005

Outcome of Pregnancy in Migraineurs

- The risk of preeclampsia appears to increase in proportion to disease severity and may occur earlier and be more severe
- Migraine is a risk factor for stroke in pregnancy with odds ratio of 16.9
 - Risk higher in women over 35
 - Ergot derivatives eg bromocriptine & methylergonovine as well as triptans have been implicated in post-partum stroke and RCVCS (reversible cerebral vasoconstrictive syndrome)

Adeny and Williams 2006

What happens to migraine during pregnancy?

- Spontaneous improvement of headache in 50-80% of women with migraines
- Prospective study in 47 pregnant women in migraine without aura:
 - >50% decrease in 57% of patients first trimester
 - 83% during the second trimester
 - 87% during the third trimester

Sances, et al Cephalalgia, 2003

What happens to migraine during pregnancy?

- Marcus, et al in a study in Headache 1999 showed that women still having headaches at the end of the first trimester are unlikely to have significant headache improvement during the remainder of the pregnancy.
- Migraines tend to recur soon after delivery-58% have return first post-partum week.

What happens to migraine during pregnancy?

- Migraine can occur for the first time during pregnancy
 - Most commonly occur during 1st trimester
 - Most often migraine with aura

Evaluation of headache during pregnancy

- Headache that begins or changes during pregnancy needs further evaluation
- MRI is preferred over CT & considered safe
 - No negative sequelae noted in 3 year-olds exposed to MRI during mom's pregnancy
 - No negative sequelae seen in pregnant MRI techs
- MRA & MRV offers non-invasive methods for visualizing vasculature
- Avoid Gadolinium since it crosses that placenta & is excreted by the fetal kidneys

Levine, et al, Radiology, 1999

Kanal, et al, Radiology, 1993

Secondary headaches during pregnancy

- Low or high pressure headache
- Eclampsia/preelampsia
- Cerebral venous thrombosis
- Subarachnoid hemorrhage
- Tumors
- Meningitis

Challenges of Treating Headache in Pregnancy

- The risk of safety in pregnancy only established for a few drugs
- Drugs aren't tested in pregnant women
- No drug has FDA approval for use during pregnancy
- Ideal to avoid drugs during pregnancy but dehydration/vomiting bad for mother and baby

US FDA Categories of Medication Risk in Pregnancy

- A- Controlled human studies show no risk
- B- No evidence of risk in humans, but no controlled studies
- C- Risk to humans has not been ruled out
- D- Positive evidence of risk to humans from human or animal studies
- X- Contraindicated in pregnancy

Why doesn't the system work?

QUIZ

- The categories represent a gradation of risk: A is safer than B, which is safer than C, etc. (True/False)
- Category D drugs have been shown to cause birth defects in humans. (True/False)
- Category X drugs have been shown to cause birth defects in humans. (True/False)

Quiz

- A drug can only get into a Category X with human studies. (True/False)
- Category X drugs cause birth defects than Category D. (True/False)

Scialli, A. The Perils of the Pregnancy Label. Reprotox website.

Are the categories dangerous?

- The labels may not be up-to-date.
- The manufacturer , not the FDA owns the label.
- Bad advice is bad advice, no matter what the source.
- The label may be a tool of the drug company to limit its own liability.
- Withholding important medication because of pregnancy fears may result in adverse outcome.

Teratogen Informational Service (TERIS)

- Online, automated database of teratogen information
- Drugs are classified into 1 of 7 risk categories
- The categories are meant to assess teratogenic risk
- Agreement between TERIS & FDA ratings no greater than would be expected by chance alone

Sources of Information on Meds During Pregnancy

- www.reprotox.org
- OTIS (organization of Teratology Information Specialists)
www.otispregnancy.org
- Pharmaceutical company registries
- North American AED Pregnancy Registry

Drugs to Avoid

- Avoid ergot-related drugs
 - Dihydroergotamine
 - Methysergide
 - Ergotamine
- Valproic acid is a known teratogen & recent study shows that children exposed to valproate in utero were 7X more likely to develop autism
- NSAIDs should be avoided after 32 weeks

Principles of acute treatment

- Need to balance risks vs benefits
- Still need to limit acute treatment to 2-3 days a week.
- Safe medications:
 - Acetaminophin
 - Opioids
 - Antiemetics
- NSAIDS
 - Avoid during attempted conception
 - Avoid after week 32

Principles of acute treatment

- Triptans still controversial:
 - Small registries not associated with malformations
 - Galaxo Smith Kline's registry failed to find any negative associations with triptans during pregnancy
 - Two European studies showed trend toward early delivery & lower birth weight but no increase in MCM

Schuhaiber, Neurology 1998

O'Quinn, Arch Gynecol Obstetrics, 1999

Acute Treatment

- Best to avoid barbiturates
 - Often associated with overuse
 - Neonatal withdrawal has been reported
 - In utero exposure may have long-term neurodevelopmental effects
- Corticosteroids may be helpful for prolonged attacks
 - Prednisone preferred over dexamethasone
 - Even first trimester thought to be safe

Holmes 2005

Treatment of Pregnant Migraineur in the ER

- IV fluid for hydration
- Prochlorperazine 10 mg IV-can help with both nausea & headache
- If not effective can use MgSO₄—1 GM IVP or rapid infusion BID
- Narcotics

Preventive medications

- Divalproex sodium contraindicated
- TCA—use in psychiatric patients during pregnancy associated with risk of cardiovascular abnormalities
- Betablockers considered safe
- Neurontin can be used early in pregnancy but should be discontinued later in pregnancy
- Not much info on calcium channel blockers

Preventative medications

- Topamax-recent info from the UK Epilepsy & Pregnancy Register shows clefting abnormalities 11 X higher than the background rate
 - Hypospadias 14 X higher than the background rate
 - Of the 3 infants who had MCM with exposure to just topiramate, the average dose was 400 mg vs 238 mg without MCM

Craig J, et al. Neurology 2008

Nonpharmacologic treatment

- Don't forget the basics
 - No Smoking or alcohol
 - Healthy diet
 - Adequate sleep
- Effects of herbal or vitamin & mineral supplementation unknown, although Mg probably safe
- Stress management
- Relaxation
- Biofeedback

Nonpharmacologic Treatment

- Marcus looked at the effect of 4 1-hr sessions for relaxation & thermal biofeedback reduced headaches 50-79% in pregnant women with migraine &/or tension headaches
- Benefits were maintained for 12 months after delivery
- Unfortunately, often not covered by insurance

Marcus, Psychosom Med 1995

Scharff, Headache, 1996

Conclusions

- Ideal to counsel women before pregnancy
 - Encourage women to take folate
 - Avoid known teratogens
 - Remind women that the background rate of congenital malformations is 2-5%
- There are limited data on what drugs are safe during pregnancy
- Take advantage of nonpharmacologic treatments
- If headaches increase in frequency and/or severity consider a secondary cause of headache

THANK YOU!