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### **Migraine Headache and Pregnancy**

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More than 80% of women experience headaches during their childbearing years (Scharff, 1996). Some of these women experience migraine headache, defined as a severe, incapacitating headache accompanied by nausea, vomiting, photophobia, and phonophobia. While reports suggest that 20% of women experience migraines, it has been difficult to determine the actual incidence of migraine during pregnancy (Silberstein, 1997). Migraine headaches can be influenced by the hormonal changes of pregnancy, and may result in improvement or worsening of headache symptoms. Additionally, some women report experiencing a migraine for the first time during pregnancy, and as such, there is no consensus about how migraine symptoms will be experienced by a particular woman during pregnancy (Silberstein, 1997). Given the unpredictable nature of migraine symptoms, management during pregnancy must begin by ruling out underlying pathology of new onset headaches, and then selecting a treatment to maximize benefit to the women while minimizing risk to the fetus.

Migraine treatments can be symptomatic, abortive or prophylactic, and are frequently given in conjunction with antiemetics. Although many medications are available to treat migraine, this RISK//NEWSLETTER will only examine those which are most commonly used.

#### **Symptomatic Relief:**

Migraine symptoms can be alleviated by non-pharmacologic means or by using a medication specifically designed to treat migraines. Non-pharmacologic treatments include rest, biofeedback, ice, massage, and the avoidance of recognizable trigger factors (Paulson, 1995). If these remedies do not alleviate migraine symptoms, various medications may provide relief. The most common of these include analgesic preparations, abortive agents such as serotonin agonists or ergot, and migraine prophylaxis.

#### **ANALGESIC TREATMENTS**

Many migraine preparations consist of a combination of a barbiturate, an analgesic and caffeine, with or without a narcotic such as codeine. Examples include Fioricet, Fiorinal, Mygracet, Axocet, Phrenellin and Esgic.

Butalbital exposure during pregnancy has been examined in two retrospective studies. The Collaborative Perinatal Project and the Michigan Medicaid Study reported 112 and 1124 pregnancies exposed during the first trimester, respectively (Heinonen et al., 1977; Briggs, 1994). Neither found an association with first trimester exposure to the medication and an increased risk of birth defects. No prospective human study has addressed the use of butalbital during pregnancy. Transient neonatal withdrawal symptoms, however, have been reported in association with butalbital use near term

(Ostrea, 1982).

Some migraine medications (e.g., Fiorinal) include aspirin, whose use during pregnancy is controversial. While some retrospective studies have noted a small increase in birth defects seen in infants exposed to aspirin during the first trimester, most studies have not supported this association (Slone et al., 1976; Werler et al., 1989; Briggs, 1994). Maternal aspirin use during the third trimester, however, has been associated with adverse effects, including uterine contraction inhibition, increased maternal and newborn bleeding and premature narrowing of the fetal ductus arteriosus. Therefore, aspirin-containing medications (as well as non-steroidal anti-inflammatories) should be avoided, especially during the third trimester of pregnancy (Briggs, 1994).

Other formulations such as Fioricet, Esgic, and Mygracet contain acetaminophen as the analgesic component. Acetaminophen has been well studied in pregnancy and does not appear to increase the risk for birth defects or other adverse outcomes (Niederhoff, 1983).

Caffeine consumption during pregnancy is relatively common, but is often difficult to quantify. Many studies have attempted to correlate caffeine consumption with pregnancy outcome. In general, exposures of less than 300mg per day during pregnancy do not appear to increase the risk for birth defects or other adverse outcomes (Mills et al., 1993). However, exposures greater than 300mg/day may increase the risk for spontaneous abortion and low birth weight infants (Mills et al., 1993). Typical migraine preparations contain 40-50 mg of caffeine. Women taking such migraine medications should be aware of other dietary sources of caffeine and minimize these exposures to maintain levels less than 300 mg per day.

Codeine is present in many migraine treatments. Case control studies and case reports have suggested that defects such as cardiac and respiratory system defects, inguinal hernia, clefting and dislocated hips occur more frequently in babies born to mothers who consumed codeine during pregnancy (Saxen, 1975; Rothman et al., 1979; Bracken et al., 1981). However, since there is no pattern to these birth defects and these findings have not been observed consistently in larger studies, the association is probably not causal. A number of retrospective studies, including the Collaborative Perinatal Project and Michigan Medicaid study, examined exposure to codeine in 565 and 7640 exposed pregnancies, respectively, and did not find an increased risk of birth defects (Heinonen et al., 1977; Briggs, 1994). Based on all of these findings, it is unlikely that codeine significantly increases the risk for malformations. Codeine exposure in third trimester has been associated with an increased risk for transient neonatal withdrawal symptoms (Van Leeuwen, 1965).

### **Isometheptene Preparations**

Midrin contains isometheptene, dichloralphenazone and acetaminophen. There are no human studies examining the first two components during pregnancy, and therefore the risks of this medication is undetermined. Due to the lack of information about the risk of Midrin exposure during pregnancy, clinicians may want to help their patients select a medication whose effects during pregnancy have been studied more extensively.

## **ABORTIVE AGENTS**

### **Serotonin Receptor Agonists**

Imitrex (sumatriptan) is the most popular serotonin receptor agonist. The manufacturer's prospective registry followed 208 pregnancies exposed during the first trimester; there was no association with an increased risk for birth defects and no pattern of specific defects was noted (Eldridge et al., 1997; Glaxo Wellcome, July 1998). A retrospective study by the manufacturer supported these findings. In addition, a prospective cohort study followed 86 women that were exposed during their first trimester and found no association with an increased risk for birth defects (Shuhaiber et al., 1997). These

findings make it unlikely that sumatriptan significantly increases the risk for birth defects.

Naramig (naratriptan) is a newer serotonin agonist, closely related to sumatriptan. The manufacturer's prospective registry describes only 7 women exposed to naratriptan in the first trimester; all of the infants were healthy (Glaxo Wellcome, July 1998). However, because of the paucity of data available on naratriptan, its risk during pregnancy remains undetermined.

### **Ergot Derivatives**

Ergot derivatives (e.g., Cafergot, Wigraine) are frequently used to treat migraine, often in conjunction with caffeine. The oxytocic properties of ergot have been known for many centuries, but few studies have assessed the potential risk for malformations. Several small studies have examined the use of ergotamine during pregnancy and have found an increased risk for birth defects. A retrospective study found that 9/59 (15.3%) pregnancies that were exposed to ergotamine in the first trimester had major birth defects (Briggs, 1994). While the total number of defects is slightly higher than would be expected, the association may be due to other uncontrolled factors such as maternal disease, concurrent drug use or chance (Briggs, 1994). The Collaborative Perinatal Project found 2/25 exposed pregnancies (8%) with birth defects, but again, this sample size was too small to deduce causal association (Heinonen et al., 1977). In a large case control study, 13 out of 9460 malformed infants were born to mothers exposed to ergotamine during pregnancy; this was similar to the proportion of exposed women among non-malformed controls (Czeizel, 1989). Eight case reports of ergotamine use in pregnancy have been associated with infants born with birth defects consistent with ischemic injuries (reviewed in Raymond, 1995). Because of the reported increased risk for birth defects and the theoretical vasoconstrictive and labor-inducing properties, ergotamine and its derivatives should be avoided during pregnancy, if possible.

### **PREVENTATIVE THERAPY**

Many medications are given as migraine prophylaxis. These include beta-adrenergic blocking agents, calcium channel blockers, antidepressants, and anticonvulsants. Only beta-blockers will be discussed, as several of these other treatments have been reviewed in previous RISK//NEWSLETTERS.

#### **Beta-Blockers**

Propranolol (Inderal) is a beta-blocker that has been well studied in pregnancy, mostly in women with hypertension. Retrospective studies of 274 women exposed to propranolol in the first trimester did not find an increased risk for birth defects (Briggs, 1994). However, some studies found an association with intrauterine growth restriction (IUGR), primarily in mothers who used propranolol to treat their hypertension (Redmond, 1982). It is difficult to separate the medication's effects from the effects of the maternal hypertension or concordant medication use. There appears to be a dose dependant relationship, with higher doses of propranolol resulting in more serious complications including IUGR (Redmond, 1982), hypoglycemia (Frishman et al., 1988), bradycardia (Mitrani et al., 1975; Jensen, 1984) and respiratory depression. (Tunstall, 1969). Due to the controversial findings associated with this medication, the risks and benefits of its use during pregnancy should be carefully examined before selecting it as a preventative therapy, particularly near term and while breast-feeding.

### **Summary**

It is difficult to select a migraine treatment that provides the maximum benefit to the pregnant women experiencing migraine, while presenting the least risk to her fetus. While most of the common medications do not appear to significantly increase the risk of birth defects, we must always be aware of the uncertain effects of concordant drug use when selecting treatments and the possible neonatal effects of medication used near term. Ergot derivatives in particular should be avoided because of their vasoconstrictive and oxytocic properties.

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