

CaseMed-Pregnancy Resource Newsletter

January 2008

MEDICAL STUDIES

Follow-up of children exposed in utero to 17 alpha-hydroxyprogesterone caproate compared with placebo

***Northen AT, Norman GS, Anderson K, et al
Obstet Gynecol, 2007; 110(4): 865-72***

The aim of this study was to assess whether there are evident adverse effects of 17 alpha-hydroxyprogesterone caproate after in utero exposure. The researchers conclude that 17 alpha-hydroxyprogesterone caproate seems to be safe for the fetus when administered in the second and third trimesters of pregnancy.

The effects of fish oil supplementation in pregnancy on breast milk fatty acid composition over the course of lactation: a randomized controlled trial

***Dunstan JA, Mitoulas LR, Dixon G, et al
Pediatr Res, 2007; 62(6): 689-94***

This study evaluated the longitudinal effect of fish oil in pregnancy on breast milk fatty acid composition and infant outcomes. In a randomized, controlled trial, 98 women received 2.2 g docosahexaenoic acid (DHA) and 1.1 g eicosapentaenoic acid (EPA) or olive oil from 20 wk of gestation until delivery. The researchers conclude that supplementation in pregnancy was associated with increased n-3 long-chain polyunsaturated fatty acids (LCPUFAs) in breast milk, particularly in early lactation, and this was positively associated with infant DHA status at 1 year.

Thromboembolic events in pregnancy: pharmacological prophylaxis and treatment

***Nelson SM, Greer IA
Expert Opin Pharmacother, 2007; 8(17): 2917-31***

Nelson and Greer's review describes the recent developments in pharmacological thromboprophylaxis and acute treatment of arterial and venous thromboembolism in pregnancy.

Intermittent preventive therapy with sulfadoxine-pyrimethamine during pregnancy: seeking information on optimal dosing frequency

***Ter Kuile FO, Steketee RW
J Infect Dis, 2007; 196(11): 1574-6***

No abstract available.

Inferiority of single-dose sulfadoxine-pyrimethamine intermittent preventive therapy for malaria during pregnancy among HIV-positive Zambian women

***Gill CJ, Macleod WB, Mwanakasale V, et al
J Infect Dis, 2007; 196(11): 1577-84***

The WHO advocates 2-3 doses of sulfadoxine-pyrimethamine (SP) for intermittent preventive treatment of malaria (SP IPTp). The optimal number of doses and the consequences of single-dose therapy remain unclear. The researchers collected data from a randomized, controlled study of human immunodeficiency virus-positive Zambian women comparing monthly versus 2-dose SP IPTp. They compared maternal and neonatal birth outcomes as a function of how many doses the mothers received (1 to > or =4 doses). Results showed that of 387 deliveries, 34 received 1 dose of SP. Single-dose SP was significantly associated with higher proportions of maternal anemia, peripheral and cord blood parasitemia, infant prematurity, and low birth weight. SP conferred dose-dependent benefits, particularly in the transition from 1 to 2 doses of SP. Women randomized to the standard 2-dose regimen were much more likely to receive only 1 dose than were women randomized to monthly IPT. Gill and colleagues conclude that single-dose SP was a common result of trying to implement the standard 2-dose regimen and was inferior to all other dosing regimens. At a programmatic level, this implies that monthly SP IPTp may ultimately be more effective than the standard regimen by reducing the risk of inadvertently underdosing mothers.

Two-dose versus monthly intermittent preventive treatment of malaria with sulfadoxine-pyrimethamine in HIV-seropositive pregnant Zambian women

***Hamer DH, Mwanakasale V, Macleod WB, et al
J Infect Dis, 2007; 196(11): 1585-94***

Intermittent preventive treatment of malaria during pregnancy (IPTp) reduces placental infection, maternal anemia, and low birth weight (LBW). However, the optimal dosing regimen in settings in which human immunodeficiency virus (HIV) is highly prevalent among pregnant women remains controversial. Hamer and colleagues conducted a randomized, double-blind, placebo-controlled study of IPTp comparing the standard 2-dose sulfadoxine-pyrimethamine (SP) regimen with monthly IPTp among a cohort of HIV-positive pregnant Zambian women. Primary outcomes included placental malaria (by smear and histology) and maternal peripheral parasitemia at delivery. The authors conclude that in an area of mesoendemicity in Zambia, monthly SP IPTp was not more efficacious than the standard 2-dose regimen for the prevention of placental malaria or adverse birth outcomes. IPTp policy recommendations need to take into account local malaria transmission patterns and the prevalence of HIV.

Risk factors for in utero or intrapartum mother-to-child transmission of human immunodeficiency virus type 1 in Thailand

***Jourdain G, Mary JY, Coeur SL
J Infect Dis, 2007; 196(11): 1629-36***

The identification of risk factors for in utero and intrapartum transmission of human immunodeficiency virus type 1 (HIV-1) is crucial to the design and understanding of preventive interventions. The randomized Perinatal HIV Prevention Trial-1 enrolled 1437 pregnant women and their non-breast-fed infants, to compare the efficacy of various durations of zidovudine prophylaxis. Using univariate and multivariate logistic regression analyses, the researchers studied the role that factors known or occurring at various times during gestation or delivery play in in utero and intrapartum transmission. Results show that with the exception of very high HIV-1 load, risk factors for in utero transmission were different from those for intrapartum transmission. Jourdain and colleagues conclude that optimal prophylactic interventions must address each of the major risk factors, with appropriate timing.

Extended release epidural morphine, far from ideal for postcesarean delivery pain control
Roboubi B
Anesth Analg, 2007; 105(6): 1864; author reply 1864-5

No abstract available.

Maternal corticosteroid use and orofacial clefts
Carmichael SL, Shaw GM, Ma C, et al
Am J Obstet Gynecol, 2007; 197(6): 585.e1-7; discussion 683-4, e1-7

The purpose of this study was to examine whether maternal corticosteroid use during pregnancy is associated with delivering an infant with an orofacial cleft. The authors' results suggest a moderately increased risk of cleft palate among women who use corticosteroids during early pregnancy.

Importance of monotherapy in women across the reproductive cycle
Montouris G
Neurology, 2007; 69(24 Suppl 3): S10-6

Special treatment considerations are warranted in women with epilepsy, particularly those of childbearing age. Treatment guidelines generally recommend the use of antiepileptic drug (AED) monotherapy at the lowest dose possible during pregnancy. The UK Epilepsy and Pregnancy Register reported that the risk for major congenital malformations is higher with AED polytherapy than with monotherapy (6.0% vs 3.7%, respectively) and that valproate carries the highest individual risk. The AEDs that induce hepatic cytochrome CYP450 enzymes carry particular concern both before and after pregnancy. Hepatic enzyme inducers alter steroid metabolism in women receiving oral contraceptives, increase the risk for contraceptive failure, and interfere with calcium absorption and vitamin D metabolism, thus increasing the risk for osteoporosis and fractures. Vitamin K deficiency is another potential consequence of treatment with a hepatic enzyme-inducing AED, increasing the risk for coagulopathy and neonatal intraparenchymal and intracerebral hemorrhage during the first 24 hours of life. Supplemental vitamin K therapy during the last month of pregnancy is warranted. Preconceptional and gestational folate supplementation may also be warranted to prevent neural tube malformation related to AED treatment. Because AED pharmacokinetics may be altered during pregnancy, plasma AED concentrations should be measured before conception and monthly during pregnancy to prevent seizure breakthrough.

Dandy-Walker variant in an infant prenatally exposed to antiretroviral medication
Urban MF, Chersich MF
S Afr Med J, 2007; 97(10): 947-8

No abstract available.

Immune system development in infants born to mothers with autoimmune disease, exposed in utero to immunosuppressive agents
Motta M, Ciardelli L, Marconi M, et al
Am J Perinatol, 2007; 24(8): 441-7

Exposure to immunosuppressant agents during gestation can affect the fetal immune system. The objective of this study was to evaluate the immune function of infants whose mother were administered immunosuppressants during pregnancy for the treatment of autoimmune disorders.

The researchers assessed circulating lymphocyte subsets and in vitro immunoglobulin production at birth and months 1, 6, and 12 of life in 19 infants exposed in utero to glucocorticoid alone or in combination with azathioprine, cyclosporine A, or hydroxychloroquine. The results were compared with those obtained in 15 age-matched infants from mothers with autoimmune diseases not exposed to immunosuppressants. The authors found no immune system dysfunction in the two studied groups, suggesting a lack of interference between immunosuppressive treatment and the immune systems of the infants.

The emerging importance of transporter proteins in the psychopharmacological treatment of the pregnant patient

***Wang JS, Newport DJ, Stowe ZN, et al
Drug Metab Rev, 2007; 39(4): 723-46***

This review summarizes the current data on drug transporters in the placental passage of medications, with a focus on medications used in clinical psychopharmacology.

Point: Oral hypoglycemic agents should not be used to treat diabetic pregnant women

***Jovanovic L
Diabetes Care, 2007; 30(11): 2976-9***

No abstract available.

Infant serotonin transporter (SLC6A4) promoter genotype is associated with adverse neonatal outcomes after prenatal exposure to serotonin reuptake inhibitor medications.

***Oberlander TF, Bonaguro RJ, Misri S, et al
Mol Psychiatry, 2008; 13(1): 65-73***

Reduced Apgar scores and birth weight, increased risk of respiratory distress, jitteriness and increased tone have been reported in up to 30% of neonates with prenatal exposure to serotonin reuptake inhibitor (SRI) antidepressant medications. In adults, the effects of these medications may be related to the genotype for the serotonin transporter (SLC6A4) promoter. In this study, Oberlander and colleagues investigated whether SLC6A4 genotype influences the risk for adverse outcomes in neonates with prenatal SRI exposure. Results showed that prenatal SRI exposure was associated with adverse neonatal outcomes and these effects were moderated by infant SLC6A4 genotype. The authors conclude that relationships between polymorphisms and specific outcomes varied during the neonatal period, suggesting that beyond apparent gene-medication interactions, multiple mechanisms contribute to adverse neonatal outcomes following prenatal SRI exposure.

Psychotropic medication during pregnancy and lactation

***Menon SJ
Arch Gynecol Obstet, 2008; 277(1): 1-13***

In this article, Menon discusses the importance of providing pregnant or breastfeeding women with individualized risk-benefit analyses with regard to the commencement or continuance of psychotropic medication. The pregnant or breastfeeding woman should be educated with regard to early detection of signs of drug toxicity in both herself and her baby. Menon maintains that the ultimate decision with regard to reasonable risk and what constitutes it rests with the informed patient. In sum, close psychiatric monitoring and coordinated multidisciplinary care with the obstetrician and pediatrician combined with informed patient choices comprise a holistic model of care, targeted at optimizing the complex management of women with psychiatric illness during pregnancy.

Exposure to mercury during the first six months via human milk and vaccines: modifying risk factors

Dórea JG

Am J Perinatol, 2007; 24(7): 387-400

Maternal exposure to environmental Hg during pregnancy can predispose nursing children to neurodevelopmental disorders. Despite the World Health Organization's assurance that thimerosal-preserved vaccines are safe to use in infants, the United States, the European Union, and dozens of other countries have eliminated thimerosal as a vaccine preservative and stopped the immunization of children with such vaccines. According to the author, there is a need to address the uncertainty of vaccine-ethylmercury risk of toxicity and Hg exposure during breastfeeding due of the increase in environmental pollution and the need to produce cheap and safe vaccines.

The safety of amodiaquine use in pregnant women

Tagbor HK, Chandramohan D, Greenwood B

Expert Opin Drug Saf, 2007; 6(6): 631-5

Few antimalarial drugs have been evaluated extensively in pregnancy due to fears over toxicity. However, increasing Plasmodium falciparum resistance to chloroquine and sulfadoxine-pyrimethamine makes finding alternative antimalarials that are safe and effective in pregnancy a priority. There is a renewed interest in amodiaquine as a potential candidate, particularly as a partner drug in artemisinin-based combination therapy. The available data suggest that, at standard dosages, amodiaquine is not teratogenic and that the adverse events associated with taking amodiaquine in pregnancy are not greater than those associated with falciparum malaria in pregnancy. Thus, amodiaquine in combination with other antimalarial drugs may be useful for malaria treatment in pregnancy; however, inadequate data on its safety and pharmacokinetics in pregnancy limits its deployment for intermittent preventive treatment in pregnancy.

Nevirapine-associated toxicity in HIV-infected Thai men and women, including pregnant women

Phanuphak N, Apornpong T, Teeratakulpisarn S, et al

HIV Med, 2007; 8(6): 357-66

The aim of this study was to determine the incidence of, and risk factors for, nevirapine (NVP)-associated hepatotoxicity and rash in HIV-infected Thai men and women, including pregnant women, receiving NVP-containing highly active retroviral therapy (HAART). The authors conclude that incidence of (NVP)-associated hepatotoxicity and rash in Thai adults is similar to incidences reported for other populations. While larger studies are needed, their data supports the continued use of NVP-containing regimens as first-line treatment in developing countries for HIV-infected patients, including pregnant women. Phanuphak and colleagues state that pregnant women with high CD4 cell counts may experience higher rates of symptomatic hepatotoxicity and thus require careful clinical and laboratory monitoring.

Review article: Reproduction in the patient with inflammatory bowel disease

Heetun ZS, Byrnes C, Neary P, et al

Aliment Pharmacol Ther, 2007; 26(4): 513-33

The aim of this study was to review the best management of IBD in the reproductive and pregnant population. Results from Medline and Embase searches found that the risk of

pregnancy-related complication and the disease behaviour during pregnancy depends mainly on disease activity at the time of conception. Proactive treatment for maintenance of disease remission during gestation is recommended. Aside from methotrexate, the drugs used in IBD appeared safe in pregnancy. Breastfeeding should also be encouraged. Heetun and colleagues conclude that the management of IBD in the young and pregnant population remains controversial because the literature is from mainly retrospective studies. They recommend conducting further studies – particularly large prospective trials – to guide clinicians in decision making.

Marked improvement of Churg-Strauss vasculitis with intravenous gamma globulins during pregnancy

***Hot A, Perard L, Coppers B, et al
Clin Rheumatol, 2007; 26(12): 2149-51***

Churg-Strauss syndrome (CSS) is an extremely rare disease, and even less common in women of childbearing age. Patients with severe disease or those who are unresponsive to corticosteroids are usually treated with cytotoxic drugs, especially cyclophosphamide. Intravenous immunoglobulin (IVIg) has become a promising, but not completely accepted, form of treatment for systemic vasculitis that is un-responsive to standard therapy. Hot and colleagues report the case of a woman who presented with a CSS flare during pregnancy. Because of mononeuritis, treatment with IVIg was instituted with successful results. The authors conclude that their case not only supports the beneficial effect of IVIg in CSS, but it also illustrates its successful and safe use in a patient who was pregnant. The indication of IVIg during the course of anti-neutrophil cytoplasm antigen (ANCA) vasculitis during the pregnancy is also discussed.

Arrhythmias in the pregnant patient: current concepts in evaluation and management

***Kron J, Conti JB
J Inter Card Electrophysiol, 2007; 19(2): 95-107***

Maternal arrhythmias during pregnancy may jeopardize the health of both mother and fetus. Kron and colleagues believe that treatment should be reserved for arrhythmias that are hemodynamically unstable or that cause debilitating symptoms. When medications are deemed necessary, the physician should use as few drugs as possible at the lowest effective doses and choose drugs with a history of safe use in pregnancy.

Pregnancy outcome of women exposed to azathioprine during pregnancy

***Goldstein LH, Dolinsky G, Greenberg R, et al
Birth Defects Res A Clin Mol Teratol, 2007; 79(10): 696-701***

The aim of this study was to determine whether exposure to azathioprine (AZP) during pregnancy increases the risk for major malformations and to determine the effect on pregnancy outcome. Goldstein and colleagues' results suggest that AZP (50-100 mg/day) does not triple the rate of birth defects; however, it is associated with lower birth weight, gestational age, and prematurity. They conclude that larger studies are needed to confirm their observations.

Randomized trial to improve prescribing safety during pregnancy

***Raebel MA, Carroll NM, Kelleher JA, et al
J Am Med Inform Assoc, 2007; 14(4): 440-50***

The objective of this study was to determine whether a computerized tool that alerted pharmacists when pregnant patients were prescribed U.S.FDA pregnancy risk category D or X medications

was effective in decreasing dispensing of these medications. The authors conclude that coupling data from information systems with knowledge and skills of physicians and pharmacists resulted in improved prescribing safety. However, the project was discontinued due to system limitations. Linking ambulatory clinical, laboratory, and pharmacy information to provide safety alerts is not sufficient to ensure project success and sustainability.

Early thimerosal exposure and neuropsychological outcomes at 7 to 10 years

Thompson WW, Price C, Goodson B, et al

N Engl J Med, 2007; 357(13):1281-92

It has been hypothesized that early exposure to thimerosal, a mercury-containing preservative used in vaccines and immune globulin preparations, is associated with neuropsychological deficits in children. Thompson and colleagues enrolled 1047 children between the ages of 7 and 10 years and administered standardized tests assessing 42 neuropsychological outcomes. They assessed the association between current neuropsychological performance and exposure to mercury during the prenatal period, the neonatal period (birth to 28 days), and the first 7 months of life. Among the 42 neuropsychological outcomes, only a few significant associations with exposure to mercury from thimerosal were detected. The detected associations were small and almost equally divided between positive and negative effects. The researchers conclude that their study does not support a causal association between early exposure to mercury from thimerosal-containing vaccines and immune globulins and deficits in neuropsychological functioning at the age of 7 to 10 years.

Angiotensin-converting enzyme inhibitor fetopathy: long-term outcome

Laube GF, Kemper MJ, Schubiger G, et al

Arch Dis Child Fetal Neonatal Ed, 2007; 92(5): F402-3

Fetal exposure to angiotensin-converting enzyme inhibitors (ACEIs) is associated with increased neonatal morbidity and mortality. Long-term follow-up of three patients with fetal ACEI exposure revealed impaired renal function in two, severe hypertension and proteinuria in one and isolated polycythaemia in all three. The authors conclude that careful long-term follow-up of children with ACEI fetopathy is recommended.

Risks of statin use during pregnancy: a systematic review

Kazmin A, Garcia-Bournissen F, Koren G

J Obstet Gynaecol Can, 2007; 29(11): 906-8

While statins have been identified as potential teratogens on the basis of theoretical considerations and small case series, the available evidence is far from conclusive. The actual risk for an exposed pregnancy seems to be small and does not itself warrant the termination of a pregnancy. The authors conclude that, given the lack of available data, it is still advisable to avoid the use of these drugs in patients who are planning a pregnancy.

Drug misuse during pregnancy and fetal toxicity

Anderson M, Choonara I

Arch Dis Child Fetal Neonatal Ed, 2007; 92(5): F332-3

No abstract available.

Fetal exposure to isotretinoin - An international problem

Garcia-Bournissen F, Tsur L, Koren G, et al

Reprod Toxicol, 2008; 25(1): 124-8

The aim of this study was to compare the management of fetal risk of isotretinoin in three countries, including information given to women, implementation of contraceptive methods, and pregnancy outcomes. The authors conclude that since isotretinoin-exposed pregnancies still occur, there is a need for more effective strategies, which should take into account the cultural differences.

Prenatal supplementation with multivitamins and the incidence of pediatric cancers: clinical and methodological considerations

Goh YI, Koren G

Pediatr Blood Cancer, 2008; 50(2 Suppl): 487-9; discussion 498

This review summarizes the available knowledge associating prenatal multivitamin consumption with the prevention of pediatric cancers.

Pre-conceptional vitamin/folic acid supplementation 2007: the use of folic acid in combination with a multivitamin supplement for the prevention of neural tube defects and other congenital anomalies

Wilson RD, Johnson JA, Wyatt P, et al

J Obstet Gynaecol Can, 2007; 29(12): 1003-13

This article aims to provide information regarding the use of folic acid in combination with a multivitamin supplement for the prevention of neural tube defects and other congenital anomalies, so that physicians, midwives, nurses and other health care workers can assist in the education of women in the pre-conception phase of their health care.

LAY PRESS NEWS

Is your milk safe?

Sprinkle N

Parenting, 2008; 22(1): 78

This article warns mothers who take narcotics like codeine or Percocet while breastfeeding that the drugs can quickly metabolize into morphine causing their infant to suffer an overdose after drinking his mother's milk. According to Sprinkle, while there is no reliable test to see if you are a rapid metabolizer, this does not mean that women need to tolerate the pain or stop breastfeeding. Dr. Robin Kalish, Director of Clinical Maternal Fetal Medicine at New York-Presbyterian Hospital/Weill Cornell states, "An overdose is extremely rare, so just make sure your doctor prescribes the lowest-dose pain reliever possible for the shortest amount of time." The article also recommends that parents watch for limpness, breathing troubles, or napping that lasts longer than four hours as these are warning signs of an overdose.

Oh, baby! Don't do this. Don't do that. With all the pregnancy 'advice' out there, it's hard to know what or whom to believe. Here, experts bust the nine biggest myths about what to expect.

Friedman A

The Fort Worth Star-Telegram, 2008; January 5

According to this article, the seventh myth of pregnancy is that you will have to suffer through sickness. Many OTC meds are safe during pregnancy, but somehow women believe they need to put up with migraines and be a slave to an upset stomach. Not so. You should consult your OB/GYN before you take anything, but many experts give the following drugs the green light: Tylenol for headaches and fever; Tums or Mylanta for heartburn; Imodium for diarrhea; Robitussin for colds; and Sudafed or Benadryl for allergies. Many prescription drugs are also fine to continue with during pregnancy, but again, follow your doctor's orders.

Thalidomide must be used 'properly'
Gloucestershire Echo, 2008; January 4

Thalidomide has been approved by the U.S. FDA as a treatment for multiple myeloma and is being used by thousands of people in Europe on a named-patient basis. Pharmion, the company that distributes the drug in Europe, has applied for a licence from the European Medicines Agency (EMA). If granted, thalidomide would be accepted as a treatment and more people would be prescribed it. According to a spokeswoman for the Thalidomide Society, which has attended licensing meetings between Pharmion and the EMA, a license for the drug's use in multiple myeloma may be issued in March 2008. The article discusses the rigorous procedures patients are required to undergo that help to ensure that newborns are protected from the drug's devastating effects. Thalidomide survivor Louise Medus states, "If it's used properly and all steps are taken to prevent harm to a foetus, than I wouldn't want to prevent someone getting benefit from it."

The six-year-old for whom Christmas was so difficult
McIntyre A
Wharfedale Observer, 2008; January 3

This article discusses Fetal Anti-Convulsant Syndrome which is caused by an epilepsy drug taken by women during their pregnancies. Nationwide group litigation is being organized by The Organisation for Anti-Convulsant Syndrome, which is a support group for the sufferers and families of those affected. On its website the group says FAC is caused by medication used to control epilepsy. Primarily during the first three months, the anti-convulsant medication can cross the placenta and affect the developing foetus. The drugs can affect the child in a number of ways, ranging from developmental delay, learning delay, dysmorphic facial features, physical disabilities as well as speech and language delays. The group says it is well documented that congenital abnormalities can be caused by many anti-convulsants - with neural tube defects estimated to occur at around ten times the normal incidence in foetuses exposed to sodium valproate or Epilim. Many families are still unaware their child has this condition as it has been frequently misdiagnosed as an Autistic Spectrum Disorder.