

# CaseMed-Pregnancy Resource Newsletter

## October 2008

### MEDICAL STUDIES

***SAGE Publications UK; Monitoring outcomes of suicide attempts in pregnancy can better assess drug dangers***

***No authors listed***

***OBGYN & Reproduction Week, 2008; September 29: 14***

Monitoring the health of children born to women who attempted suicide while pregnant can shed light on which medicines and what doses are particularly dangerous to developing fetuses, according to researchers from Hungary who publish their findings in a series of reports in a special issue of Toxicology and Industrial Health, published this week by SAGE. "Many drugs are subject to contraindications or special warnings because their effects have not been sufficiently studied during pregnancy or non-clinical studies revealed adverse teratogenic or fetotoxic effects," explain the authors. "Data from self-poisoned pregnant women provide an appropriate source of information for use in better estimating the potential human risks of exposure to drugs during pregnancy." In designing their study, the Hungarian researchers reasoned that if no congenital abnormalities occur in children born to women who ingest very large doses of a drug during critical developmental periods, then this information supports the notion that the ingested drug is not a human teratogen. What is more, they report, self-poisoned women present the opportunity to gather data on dose-response relationships, which are difficult to ascertain from animal models, because they are hospitalized and undergo extensive pharmacological tests. To test their hypothesis that self-poisoned pregnant women could give useful drug-safety data, the researchers studied outcomes of all such admissions to the Department of Toxicological Internal Medicine, Koranyi Hospital, Budapest. During the study period of 1960-1993, 1044 pregnant women were admitted and 1021 of these attempted suicide with drugs (the other 23 pregnant women had accidental intoxication due to poisonous mushroom ingestion or carbon monoxide). Among them, these women had 411 live-born infants, and 367 exposed children were evaluated with cognitive and behavioural tests as they grew up. Although the authors acknowledge there are limitations to their method - including the fact that pregnant women who attempt suicide are younger and with lower average socioeconomic status than the general population, and they tend to combine excess medications with large amounts of alcohol, tobacco, or other drugs – they conclude that using the self-poisoning model for estimating human teratogenic risks of drugs is feasible and potentially beneficial. They suggest that an international registry of self-poisoned pregnant women should be set up to enable more in-depth study of the effects of various doses of medication in pregnancy.

***Myocardial lysis in a fetus induced by maternal paraphenylenediamine poisoning following an intentional ingestion to induce abortion***

***Abidi K, Himdi B, Cherradi N, et al***

***Hum Exp Toxicol, 2008; 27(5): 435-8***

The acute toxicity of paraphenylenediamine (PPD) has been associated with several histopathological changes. In humans, acute PPD poisoning is known to cause rhabdomyolysis

and particularly myocardial lysis. However, its toxicity for the fetus has never been reported in the literature. In this study, Abidi and colleagues report a case of myocardial lysis in a fetus expelled by a 22-year-old mother after apparent ingestion of an unknown amount of PPD. As the histopathology of the myocardium showed lysis of the cardiac muscle, the authors conclude that the PPD was most likely responsible for the myocardial injury in the fetus.

***ACOG guidelines on psychiatric medication use during pregnancy and lactation***  
***Armstrong C; American College of Obstetricians and Gynecologists***  
***Am Fam Physician, 2008; 78(6): 772, 774, 776***

No abstract available.

***Low-dose sublingual misoprostol versus methylergometrine for active management of the third stage of labor***  
***Chhabra S, Tickoo C, et al***  
***J Obstet Gynaecol Res, 2008; 34(5): 820-3***

The objective of this study was to compare the efficacy and side-effects of low-dose sublingual misoprostol and i.v. methylergometrine for active management of the third stage of labor. Chhabra and colleagues conclude that a low dose of sublingual misoprostol appears to be as effective as a low dose of i.v. methylergometrine in the prevention of post-partum hemorrhage in low-risk cases. Given the advantages of its stability at room temperature, low cost and easy route of administration, misoprostol appears to be a better choice, and a low dose is enough. However, larger studies in low-risk as well as high-risk cases are needed to advocate routine use of a low dose at the primary level.

***Azathioprine treatment during lactation***  
***Christensen LA, Dahlerup JF, Nielsen MJ, et al***  
***Aliment Pharmacol Ther, 2008; Aug 30 [Epub ahead of print]***

Thiopurines are widely used to maintain remission in inflammatory bowel disease. Treatment during pregnancy is generally recommended to improve the chance of a normal birth outcome, but advice concerning breastfeeding is conflicting. The aim of this study was to estimate the exposure of breastfed infants to 6-Mercaptopurine from maternal milk. Christensen and colleagues conclude that the major part of 6-Mercaptopurine in breast milk is excreted within the first four hours after drug intake. Based on the maximum concentration measured, the infant ingests Mercaptopurine of less than 0.008mg/kg bodyweight/24h. The findings confirm that breastfeeding during treatment with Azathioprine seems safe, and should be recommended, considering the extensive beneficial effects.

***Sirolimus used during pregnancy in a living related renal transplant recipient: a case report***  
***Chu SH, Liu KL, Chiang YJ, et al***  
***Transplant Proc, 2008; 40(7): 2446-8***

The majority of pregnancies after transplantation reported in the literature occurred in patients treated with a combination of calcineurin inhibitors, prednisolone, and azathioprine. There is little experience with newer drugs. In this study, a successful pregnancy in a kidney recipient with exposure to sirolimus-based immunosuppression is reported. The authors describe a case of successful delivery in a 30-year-old woman who became pregnant 1 year and 8 months after a living related renal transplantation. She received sirolimus, cyclosporine, and prednisolone before conception and during the first and second trimesters of gestation. The female recipient received

sirolimus in combination with cyclosporine and prednisolone. During follow-up, her serum creatinine values were stable with pregnancy occurring at 1 year and 8 months after transplantation. At 27 gestational weeks, sirolimus was discontinued and she was maintained on cyclosporine and prednisolone. There were no signs or symptoms of graft rejection. A Cesarean section was performed at 39 weeks of gestation to deliver a healthy, 2994-g, Apgar 10, male infant. The renal function of the female recipient continued to be stable after delivery.

***Pregnancy exposure registries for assessing antimalarial drug safety in pregnancy in malaria-endemic countries***

***Dellicour S, Ter Kuile FO, Stergachis A***

***PLoS Med, 2008; 5(9): e187 [Epub ahead of print]***

No abstract available.

***Interventions for heartburn in pregnancy***

***Dowswell T, Neilson JP***

***Cochrane Database Syst Rev, 2008; (4): CD007065***

Heartburn is a common symptom in pregnancy affecting up to 80% of women in the third trimester. Ranges of interventions have been used to relieve symptoms including advice on diet and lifestyle, antacids, antihistamines, and proton pump inhibitors. The safety and effectiveness of these interventions to relieve heartburn in pregnancy have not been established. The objective of this study was to assess the effect of interventions to relieve heartburn in pregnancy. Dowswell and Neilson conclude that there was little information to draw conclusions on the overall effectiveness of interventions to relieve heartburn in pregnancy.

***A comparison of the inhibitory effects of bupivacaine and levobupivacaine on isolated human pregnant myometrium contractility***

***Fanning RA, Champion DP, Collins CB, et al***

***Anesth Analg, 2008; 107(4): 1303-7***

Epidural analgesia with levobupivacaine and bupivacaine is a common and effective method of labor pain relief. However, its use is associated with an increased instrumental delivery rate. One of the mechanisms postulated to account for this unwanted effect is the direct effect of local anesthetics on myometrial contractility. In this study, Fanning and colleagues determined the effects of bupivacaine and levobupivacaine on the amplitude and frequency of contractions of human term myometrium. The researchers conclude that the concentrations required for the effects on amplitude are much higher (33 fold) than the clinically relevant plasma concentrations of these drugs after epidural administration, and are unlikely to be significant in the setting of low-dose epidural analgesia in labor.

***Rheumatoid arthritis and pregnancy***

***[Article in French]***

***Florea A, Job-Deslandre C***

***Presse Med, 2008; Sep 24 [Epub ahead of print]***

In this article, Florea and Job-Deslandre make reference to pregnancy and the use of various medications to treat rheumatoid arthritis. Methotrexate and biotherapies have demonstrated no effect on fertility; however these drugs must be stopped before conception for a period equal to seven fold of the half live of the molecule. No teratogenic effects are known for sulfasalazine and hydroxychloroquine; these drugs could be used during pregnancy. It is also the same for

ciclosporine, which used is quite infrequently in RA. Methotrexate is teratogenic in animal models and is forbidden during pregnancy. For leflunomide which is metabolised in A771726, highly teratogenic, a washout period of 3,5 months is necessary. Commercially available TNFalpha inhibitors are all classified by the FDA as pregnancy risk category B (no adverse pregnancy adverse effects have been observed in animal studies, but there have been insufficient controlled human studies). According to the authors, the published experiences with TNFalpha inhibition in pregnancy are limited to some case reports and ongoing registry. More recently some cases of Vater syndromes (polymalformations) were possibly related to TNFalpha blocking agents. Such treatment must be avoided during pregnancy. Only few case reports are published concerning rituximab use during pregnancy. No data have been found for abatacept.

***Antipsychotic therapy during early and late pregnancy. A systematic review***

***Gentile S***

***Schizophr Bull, 2008; Sep 11 [Epub ahead of print]***

Both first- (FGAs) and second-generation antipsychotics (SGAs) are routinely used in treating severe and persistent psychiatric disorders. In this study, Gentile analyzed systematically the safety of both classes of psychotropics during pregnancy. Gentile found that the reviewed information was too limited to draw definite conclusions on structural teratogenicity of FGAs and SGAs. Both classes of drugs seem to be associated with an increased risk of neonatal complications. However, most SGAs appear to increase risk of gestational metabolic complications and babies large for gestational age and with mean birth weight significantly heavier as compared with those exposed to FGAs. These risks have been reported rarely with FGAs. Hence, the choice of the less harmful option in pregnancy should be limited to FGAs in drug-naive patients. When pregnancy occurs during antipsychotic treatment, the choice to continue the previous therapy should be preferred.

***Treatment of pregnant women with a betamimetic and verapamil increases the micronuclei frequency in umbilical cord blood lymphocytes***

***Grujicić D, Milosević-Djordjević O, Arsenijević S, et al***

***Tohoku J Exp Med, 2008; 215(4): 363–71***

In prevention of preterm labor, betamimetics are used in gynecological practice mostly combined with antiarrhythmic verapamil because of their therapeutic cardiovascular side effects. The aim of this study was to investigate the influence of a betamimetic (ritodrine hydrochloride, fenoterol or hexoprenaline) and verapamil (administered to mothers) on the frequency of micronuclei (MN) in umbilical cord blood lymphocytes of neonates, using cytokinesis–block micronucleus test. The authors conclude that the treatment of pregnant women with a betamimetic and verapamil significantly increases the MN frequency in umbilical cord blood lymphocytes of neonates, regardless to therapeutic doses.

***Long-term follow-up of prenatally treated children at risk for congenital adrenal hyperplasia: does dexamethasone cause behavioural problems?***

***Hirvikoski T, Nordenström A, Lindholm T, et al***

***Eur J Endocrinol, 2008; 159(3): 309-16***

The objective of this study was to investigate the long-term effects of prenatal treatment of congenital adrenal hyperplasia (CAH) with emphasis on behavioural problems and temperament. The researchers conducted a population-based long-term follow-up study of Swedish children at risk for virilising CAH, who had received treatment prenatally with dexamethasone (DEX). A questionnaire-based follow-up was performed when the children had reached school age. Results

showed that the DEX-treated children showed good overall adjustment. The parent-child agreement with respect to social anxiety was modest, highlighting the importance of multiple information sources and assessment methods. The clinical significance of the observed difference in sociability cannot be determined within the frameworks of this study. Additional studies of larger cohorts are essential to make more decisive conclusions on the safety of the treatment. Until then, it is important that parents are thoroughly informed about the benefits and potential risks and uncertainties of this controversial treatment.

***Methadone maintenance vs. methadone taper during pregnancy: maternal and neonatal outcomes***

***Jones HE, O'Grady KE, Malfi D, et al  
Am J Addict, 2008; 17(5): 372-86***

This study compared five groups of participants: those receiving either three-day methadone-assisted withdrawal (MAW) alone, three-day MAW followed by methadone maintenance (MM), seven-day MAW alone, seven-day MAW followed by MM, or a continuous MM sample enrolled between 1995-2001 in an urban drug treatment center. Jones and colleagues found that on average, patients in the three MM groups remained in treatment longer, attended more obstetrical visits, and more often delivered at the program hospital than patients in the two MAW alone groups. The authors conclude that given the poor maternal MAW outcomes, methadone maintenance should be considered as the primary treatment approach for opioid-dependent pregnant women.

***Buprenorphine and methadone treatment of opiate dependence during pregnancy: comparison of fetal growth and neonatal outcomes in two consecutive case series***

***Kakko J, Heilig M, Sarman I  
Drug Alcohol Depend, 2008; 96(1-2): 69-78***

The aim of this study was to compare the effects of fetal buprenorphine and methadone exposure during maintenance treatment of pregnant heroin dependent subjects. Kakko and colleagues conclude that data from this non-randomized comparison suggest that buprenorphine may offer advantages for treatment of opiate dependence during pregnancy.

***Patient page. Epilepsy and pregnancy: are seizure medications safe?***

***Karceski S  
Neurology, 2008; 71(14): e32-3***

No abstract available.

***Placental production and maternal serum and urine levels of inhibin A and activin A are modified by antihypertensive therapy in hypertensive disorders of pregnancy***

***Khalil A, Jauniaux E, Harrington K, et al  
Clin Endocrinol, 2008 Sep 17 [Epub ahead of print]***

The aim of this study was to investigate the effect of the antihypertensive drug alpha-methyldopa on serum, urine and placental concentrations of inhibin A and activin A in women presenting with hypertensive disorders of pregnancy. Khalil and colleagues conclude that antihypertensive therapy with alpha-methyldopa may have an effect on the synthesis and/or release of placental proteins in pregnancies complicated by PE and that this effect may be independent of its known antihypertensive action.

***The role of antioxidant vitamins in hypertensive disorders of pregnancy***

***Kotic-Vucinic O, Terzic M, Radunovic N***

***J Perinat Med, 2008; 36(4): 282-90***

Preeclampsia (PE) is an important and a leading cause of both maternal morbidity and adverse perinatal outcomes. Despite progress in perinatal medicine for patients with an established diagnosis of PE, a therapeutic approach other than termination of pregnancy was unsuccessful. In this review, the role of vitamin antioxidants in prevention and treatment of PE is discussed. According to the authors, despite the logic behind using antioxidant vitamins, the data, thus far, are at best conflicting.

***Changes in enoxaparin pharmacokinetics during pregnancy and implications for antithrombotic therapeutic strategy***

***Lebaudy C, Hulot JS, Amoura Z, et al***

***Clin Pharmacol Ther, 2008; 84(3): 370-7***

Enoxaparin is frequently prescribed for pregnant women who are at high risk for thromboembolic complications. The researchers conducted a population pharmacokinetics study with 75 pregnant women and 38 nonpregnant women as controls to evaluate enoxaparin pharmacokinetics during pregnancy and the postpartum period. Lebaudy and colleagues recommend the administration of doses normalized for body weight changes so as to counteract enoxaparin pharmacokinetic changes that accompany various stages of pregnancy.

***Heparin-induced osteoporosis and pregnancy***

***Le Templier G, Rodger MA***

***Curr Opin Pulm Med, 2008; 14(5): 403-7***

Le Templier and Rodger recently completed an a-priori planned substudy to assess the effect of low-molecular-weight heparin on bone mineral density in an ongoing multicenter multinational randomized trial designed to compare the effect of low-molecular-weight heparin prophylaxis on pregnancy outcomes in thrombophilic pregnant women. The results revealed that there is no significant difference in mean bone mineral density between a low-molecular-weight heparin prophylaxis group and a no prophylaxis group. The authors conclude that overall, women should be reassured regarding the risk of osteoporosis associated with the use of prophylactic dose of low-molecular-weight heparin during their pregnancy.

***Twin pregnancy in a patient of chronic myeloid leukemia on imatinib therapy***

***Meera V, Jijina F, Shrikande M, et al***

***Leuk Res, 2008; 32(10): 1620-2***

Imatinib is a tyrosine kinase inhibitor and is now used regularly in chronic myeloid leukaemia therapy in chronic phase with great success. This drug, due its very nature of action, is suspected to be teratogenic hence the patients are counselled not to get pregnant while on this drug. However in world literature few normal pregnancies have been reported in patients on Imatinib therapy, though no twin pregnancy has been reported on this medication. In this study, Meer and colleagues report the birth of normal mono-ovular mono-chorionic twin while the patient is on imatinib during conception and early pregnancy for chronic myeloid leukaemia.

***Does continuous use of metformin throughout pregnancy improve pregnancy outcomes in women with polycystic ovarian syndrome?***

***Nawaz FH, Khalid R, Naru T, et al  
J Obstet Gynaecol Res, 2008; 34(5): 832-7***

This study aimed to evaluate pregnancy outcomes in women with polycystic ovarian syndrome (PCOS) who conceived while on metformin treatment, and continued the medication for a variable length of time during pregnancy. Nawaz and colleagues found that in women with PCOS, continuous use of metformin during pregnancy significantly reduced the rate of miscarriage, gestational diabetes requiring insulin treatment and fetal growth restriction. No congenital anomaly, intrauterine death or stillbirth was reported in this study.

***A randomized double-blinded comparison of phenylephrine and ephedrine infusion combinations to maintain blood pressure during spinal anesthesia for cesarean delivery: the effects on fetal acid-base status and hemodynamic control***

***Ngan Kee WD, Lee A, Khaw KS, et al  
Anesth Analg, 2008; 107(4): 1295-302***

Phenylephrine and ephedrine are both used to maintain arterial blood pressure during spinal anesthesia for cesarean delivery. Usually, either drug is given alone but several previous studies have described combining the drugs. However, the effect of varying the proportion of vasopressors in such combinations has not been reported. Results showed that when varying combinations of phenylephrine and ephedrine were given by infusion to maintain arterial blood pressure during spinal anesthesia for cesarean delivery, as the proportion of phenylephrine decreased and the proportion of ephedrine increased, hemodynamic control was reduced and fetal acid-base status was less favorable. Ngan and colleagues conclude that combinations of phenylephrine and ephedrine appear to have no advantage compared with phenylephrine alone when administered by infusion for the prevention of hypotension associated with spinal anesthesia for cesarean delivery.

***Drugs for treating uncomplicated malaria in pregnant women***

***Orton LC, Omari AA  
Cochrane Database Syst Rev, 2008; (4): CD004912***

The objective of this study was to compare the effects of drug regimens for treating uncomplicated falciparum malaria in pregnant women. Orton and Omari found that data are scant. Some combination treatments appear to be effective at treating malaria in pregnancy; however, safety data are limited.

***Pregnancy and vasculitides***

***[Article in French]***

***Pagnoux C***

***Presse Med, 2008; Sep 24 [Epub ahead of print]***

Systemic vasculitides, like Takayasu's arteritis, polyarteritis nodosa, Wegener's granulomatosis, Churg - Strauss syndrome, Henoch - Schönlein purpura, or Behçet's disease can affect women of childbearing years. The rarity of these vasculitides, their frequent fatal outcomes until recent years, and the use of toxic immunosuppressants to treat patients, contra-indicating pregnancy and/or potentially inducing hypofertility or sterility, explain the few pregnancies reported in the literature so far. According to Pagnoux, in case of vasculitis' flare during pregnancy, potential treatments include corticosteroids, intravenous immunoglobulins, azathioprine, plasma

exchanges, and, for limited skin manifestations or Behçet's disease, hydroxychloroquine or colchicine. Importantly, when the disease is severe, a delay in the prescription of a stronger, immunosuppressant, chiefly intravenous cyclophosphamide, can be more detrimental, although being potentially toxic, for both the mother and the foetus than an ineffective and/or inappropriate regimen with less active drugs. Pagnoux found that safety data on biologics, like rituximab, for pregnant women to be very sparse to date and their use is therefore not recommended, unless confronted with a severe and refractory disease, and after referring to a specialized center for vasculitides.

***Acoustic cry characteristics of infants exposed to methadone during pregnancy***

***Quick ZL, Robb MP, Woodward LJ***

***Acta Paediatr, 2008; Sep 30 [Epub ahead of print]***

Infant cry characteristics reflect the neurological and medical status of the infant. This study compared the acoustic cry characteristics of infants born to mothers maintained on methadone during pregnancy with those of infants not exposed to methadone during pregnancy. Quick and colleagues conclude that the crying behaviour of infants exposed prenatally to the synthetic opiate, methadone, is characterized by higher levels of vocal fold vibratory perturbation than NE infants. These findings suggest the possibility of early, subtle neurological vulnerability in this high-risk group of infants.

***Using observational cohort data for studying drug effects on pregnancy outcome-methodological considerations***

***Schaefer C, Ornoy A, Clementi M, et al.***

***Reprod Toxicol, 2008; 26(1): 36-41***

Clinical data are urgently needed to specify the risk and safety of drug use during pregnancy. For several reasons pregnant women are usually excluded from clinical studies. Therefore, observational data are the main source of knowledge, cohort studies as well as case-control studies. Disadvantages of cohort studies based on observational data have been repeatedly discussed. However, being involved in individual risk characterisation of pregnant women it is the experience of clinical teratologists that even reports on small cohorts should not be disregarded if no other data are available. The recently published "Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement" underlines the value of observational data and provides a checklist regarding the most important inherent methodological problems. This article describes the Teratology Information Services (TIS) document and evaluates their observations on pregnant women exposed to various drugs and discusses methodological problems and - considering the STROBE statement - how these could be addressed.

***Diagnosis, treatment, observation and outcome of fetal supraventricular tachycardia in at twin pregnancy***

***Schiermeier S, van Leeuwen P, Reinhard J, et al***

***Fetal Diagn Ther, 2008; 24(4): 327-330***

Schiermeier and colleagues describe the case of a patient who was admitted to hospital with preterm contractions and cervical insufficiency at 28 weeks of gestation. After treatment with a beta-sympathomimetic drug (Partusisten(R)) one fetus developed supraventricular tachycardia. After terminating the Partusisten medication, there was no effect on the fetal arrhythmia and flecainide therapy was initiated. Maintenance dosages controlled the condition thereafter. Cardiac time intervals of a fetus in labor can be presented, which did not change significantly throughout

the first stage of labor. The researchers conclude that flecainide is an effective therapy for supraventricular tachycardias in a twin pregnancy and that analyzing the cardiac time intervals during pregnancy can improve perinatal outcome.

***Arrhythmias during pregnancy***

***[Article in German]***

***Trappe HJ***

***Dtsch Med Wochenschr, 2008; 133(36): 1799-804***

Cardiovascular emergencies are rare during pregnancy with an incidence of 0.2-4.0%. Emergencies include arrhythmias, acute coronary syndrome, peripartum cardiomyopathy and hypertensive disorders. According to Trappe, in stable supraventricular tachycardia intravenous adenosine is the first choice drug and may safely terminate the arrhythmia. Ventricular premature beats are frequently present during pregnancy and benign in most patients. However, life-threatening ventricular tachyarrhythmias (sustained ventricular tachycardia [VT], ventricular flutter [VFlt], ventricular fibrillation [VF]) were observed less frequently. Electrical DC-cardioversion is necessary in all pregnant women who are in a hemodynamically unstable state and have life-threatening ventricular tachyarrhythmias. Lastly, in hemodynamically stable pregnant women the initial therapy with ajmaline, procainamide or lidocaine is indicated. Implantation of a cardioverter-defibrillator is indicated in patients with syncope caused by VT, VF, VFlt or aborted sudden death.

***Breastfeeding and drug management in connective tissue and rheumatic diseases***

***[Article in French]***

***Weber JC, Kuhnert C***

***Rev Med Interne, 2008; Sep 15 [Epub ahead of print]***

Breastfeeding is often contraindicated when drugs are prescribed for a chronic maternal disease. Many of the restrictions are based on theoretical concerns only and may be excessively cautious. In this article, Weber and Kuhnert review the use of various drugs and their effect on breastfeeding. According to the authors, many antirheumatic drugs can be safely used during lactation: nonsteroidal anti-inflammatory drugs, corticosteroids, sulfasalazine, antimalarial agents. Doubt remains regarding the safety of cochlincine or dapson. Expert opinions still diverge but move on in favor the use of azathioprine, ciclosporin, and even methotrexate. Leflunomide, mycophenolate mofetil and cyclophosphamide are contraindicated. No conclusion can be reached regarding anti-TNF-alpha and rituximab. Current knowledge about drug transfer in breast-milk and cumulative empirical data have expanded the possibilities to allow breastfeeding when the mother is treated with antirheumatic medications. Weber and Kuhnert conclude that the data provided by pharmaceutical industry should not be the only source of the physician's information in the risk assessment.

***The safety of cetirizine during pregnancy. A prospective observational cohort study***

***Weber-Schoendorfer C, Schaefer C***

***Reprod Toxicol, 2008; 26(1): 19-23***

The objective of this study was to assess the safety of cetirizine during pregnancy. The authors conclude that this prospective observational study on cetirizine in pregnancy suggests that the use of cetirizine is relatively safe during the first trimester.

***Treating pregnant women dependent on opioids is not the same as treating pregnancy and opioid dependence: a knowledge synthesis for better treatment for women and neonates***  
***Winklbaaur B, Kopf N, Ebner N, et al***  
***Addiction, 2008; 103(9): 1429-40***

Through a novel synthesis of the literature and the researchers' own clinical experience, the aim of this study was to derive a set of evidence-based recommendations for consideration as guidance in the management of opioid-dependent pregnant women and infants. PubMed literature searches were conducted to identify recent key publications in the areas of pregnancy and opioid dependence, neonatal abstinence syndrome (NAS) prevention and treatment, multiple substance abuse and psychiatric comorbidity. Winklbaaur and colleagues conclude that opioid maintenance therapy is the recommended treatment approach during pregnancy. Treatment decisions must encompass the full clinical picture, with respect to frequent complications arising from psychiatric comorbidities and the concomitant consumption of other drugs. In addition to standardized approaches to pregnancy, equivalent attention must be given to the treatment of NAS, which occurs frequently after opioid medication. In sum, the researchers found that methodological flaws and inconsistencies confound the interpretation of today's literature. Based on this synthesis of available evidence and their clinical experience, they propose recommendations for further discussion.

## LAY PRESS NEWS

***Anesthesia during childbirth seen very safe***  
***Rauscher, Megan***  
***Reuters Health, 2008; October 20***

The odds of a woman dying from the anesthesia she may be given during childbirth have fallen to about one in a million, according to a study described at the American Society of Anesthesiologists annual meeting in Orlando, Florida. An analysis of data from the Centers for Disease Control and Prevention's ongoing Pregnancy Mortality Surveillance project for 1997 through 2002 suggest that anesthetic deaths hover around 1.1 maternal deaths per million live births, lead researcher Dr. Joy L. Hawkins, professor of anaesthesiology at the University of Colorado Denver School of Medicine, told the conference. Over the 6-year study period, a total of 49 pregnancy-related deaths due to anesthesia were reported. Thirty-one were associated with live births or stillbirths and 16 were associated with abortion; one was an ectopic pregnancy and one had missing information. Eighty percent of the anesthesia-related deaths during childbirth were associated with caesarean delivery. Six of the anesthesia-related deaths occurred during general anesthesia and 18 during local or regional anesthesia - for example, an epidural or spinal block. In seven cases, the type of anesthesia was unknown. While past studies had indicated that general anesthesia was riskier than regional anesthetics for women during childbirth, the new data suggests that the safety of general anesthesia has improved, the study team notes.

***Duke University Medical Center; An ethical argument: Include pregnant women in research***  
***OBGYN & Reproduction Week, 2008; October 13***

Why aren't pregnant women included in most clinical trials? That's the question posed by leading bioethicists at Duke University Medical Center, Johns Hopkins and Georgetown Universities, who say it's time to confront the challenges that have led to the exclusion of pregnant women from important research that could positively impact maternal and fetal health. "Only in the last two decades did people recognize that women were being excluded not just from the risks, but

from the benefits of research - primarily because of their potential to become pregnant or because of concerns that female physiology - such as menstrual cycles - might complicate study results," says Anne Drapkin Lyerly, MD, an obstetrician/gynecologist and medical ethicist at Duke. She is the lead author of a paper appearing online and then in print in the November 2008 edition of the *International Journal of Feminist Approaches to Bioethics* detailing the justifications for responsibly including pregnant women in research. "While we've made significant progress in correcting the gender imbalance, we have a long way to go in protecting the health and safety of pregnant women and the fetuses they carry." The Institute of Medicine has recommended that pregnant women be "presumed eligible" for participation in research since 1994. However, the authors say the "delicate condition" continues to be grounds for near-automatic exclusion from research, despite the need for more effective treatment for women during pregnancy. More than four million women give birth in the U.S. each year, and many face medical conditions during their pregnancies that require clinical treatment. In fact, Lyerly says chronic diseases occurring during pregnancy are common: chronic hypertension and diabetes complicate nearly four percent of pregnancies each year; and an estimated 500,000 pregnant women experience psychiatric illness, cancers, autoimmune diseases and other conditions that require treatment. But in the absence of research on how medications work in pregnant women, doctors are often left guessing about how to safely and effectively treat patients through pregnancy. "Our best predictions when it comes to dosing medications can be disastrously wrong," says Lyerly. "This conservative stance doesn't help anybody. Without adequate research on how drugs are metabolized during pregnancy, how they are absorbed, distributed in and excreted by the body, whether they cross the placenta or affect the fetus, we have little to no evidence on how to optimize the health of pregnant women or the fetuses they carry." Lyerly and her colleagues at Johns Hopkins University's Berman Institute of Bioethics and Georgetown University clearly recognize the many challenges that need to be addressed in order to safely include pregnant women in clinical research. In fact, they are convening a meeting with officials from the FDA, NIH and leading experts in obstetrics, gynecology and maternal/fetal medicine next year to address these issues and come up with practical, public policy and moral solutions. "It's not simply a matter of including pregnant women in studies," Lyerly explains. "We need to address what we need to do to ensure maternal and fetal safety, which diseases we should study first, and what we should do when pharmaceutical companies or institutions say no."

***Doing Beautifully // Murrieta woman cancer-free after diagnosis during pregnancy***

***Burge, Sarah***

***The Press-Enterprise, 2008; October 7: C01***

Peggy Noval was 39 years old and in her ninth month of pregnancy when she was diagnosed this year with advanced breast cancer. The tumor was the size of a plum and had spread to her lymph nodes. When her doctor told her she had cancer, Peggy said, "My first thought is - 'Who's going to raise my kids?'" Back home in Murrieta, still in shock from the news, Noval went outside with her 3-year-old son, Maxwell, to look at the clouds. "I'm lying there with tears in my eyes and I thought, 'This is what life is about,'" Noval said. "I knew then - whatever it took." With her husband, Keith, and an army of family and friends rallied to help, Noval fought through a grueling series of cancer treatments. After eight months of treatment, she appears to be cancer-free. Cancer during pregnancy is not common, occurring in about 1 out of 1,000 pregnancies, according to the American Society of Clinical Oncology. But doctors expect the rate to increase as more women wait until their thirties and beyond to begin having children. Body changes during pregnancy can mask the symptoms of cancer, delaying diagnosis an average of five to 15 months, according to the National Cancer Institute. As a result, cancers in pregnant women are typically diagnosed at a more advanced stage, which carries a more grim prognosis. A cancer diagnosis during pregnancy sets off a chain of heart-wrenching decisions. In the past, women

were faced with the choice of terminating their pregnancies or going without treatment. Today, pregnant women undergo not only surgery but chemotherapy. At least after the first trimester, some chemotherapy drugs do not appear to harm the fetus. In a sense, Noval was lucky. She did not have to make those choices. On Feb. 3, less than a week after her diagnosis, she gave birth by C-section to Quinn, a 7-pound, 15-ounce girl.

***New class of drugs might cause congenital heart defects***

***Edelson E***

***HealthDay Reporter, 2008; October 2***

An animal study raises a warning sign that a new class of drugs that shows promise against a variety of ailments ranging from cancer to Alzheimer's disease might cause congenital heart defects, researchers report. "We have no idea if there will be any risk, but the study suggests we should be aware of the possibility," said Dr. Thomas Force, a professor of medicine at Thomas Jefferson University in Philadelphia and lead author of an online report in the October issue of the *Journal of Clinical Investigation*. The drugs are aimed at a gene that produces a protein called glycogen synthase kinase-3 (GSK-3). The only drug now on the market that targets GSK-3 is lithium, given to treat bipolar disorder. It is a relatively weak GSK-3 inhibitor. Because of the wide range of GSK-3 protein activity, there is active research on molecules that inhibit that activity. The study was done on mice bred to lack two forms of the gene, GSK-3-alpha and GSK-3-beta. Mice lacking GSK-3-alpha were born with normal hearts, but those lacking GSK-3-beta all died before birth. Some died halfway through gestation of severe liver degeneration. Most died at a later stage of development, with numerous heart defects, including abnormally thick heart muscle caused by overgrowth of the muscle cells. "It has been suggested in the past that lithium might cause birth defects," Force said. "It is not clear whether that is the case. The data from our paper suggest that newer agents with much more potent GSK-3 inhibitory action could raise the level of danger." It is difficult to get detailed information on the development of new GSK-3 inhibitors, because drug companies try to keep that information to themselves, Force said. "These are proprietary compounds, so they are not talking about what they are doing," he explained. But there appears to be time to investigate the danger of birth defects, because none of the new agents seem to be in human trials yet, Force said. "I have checked on clinical trials, and I did not see anything there yet," he said. The kind of animal study that his group has done can help determine whether there is danger, Force said. "Probably more work needs to be done on the basic level with these agents and their effect on embryonic development before we start giving them to women of childbearing age," he said. "Before they are given to women of childbearing age, they should be tested in animal models."

***For moms struggling to breast-feed, bad advice abounds, science lags, support is meager***

***Johnson, Carla K***

***Associated Press Newswires, 2008; September 20***

Bente White was willing to try almost anything to breast-feed her infant son. She used fenugreek, blessed thistle, alfalfa, nettle, fennel, goat's rue, bitter lettuce, brewer's yeast, hops, oatmeal and two pharmaceutical drugs to increase her milk production. Nothing worked very well. "You name it and I tried it," said White, 32, a physical therapist from Suffolk, Va., who was forced to supplement baby Austin's diet with formula. "I never thought breast-feeding would be this complicated and challenging." Almost 75 percent of U.S. babies now begin life breast-feeding, a practice that helps give them disease immunity and other benefits. Nobody knows how many women have trouble breast-feeding, but those who do run into a common frustration: Women who need help often are on their own to sort fact from folklore. Many doctors aren't educated about breast-feeding problems, and there is little rigorous research to help. Health insurers,

including Medicaid, generally don't pay for lactation consultants - who are not licensed in any state. And some consultants recommend unproven, even risky herbal remedies and drugs. A review of research on drugs used to enhance milk production, published last year in the journal *Breastfeeding Medicine*, concluded that such products "appear to have little or no added benefit" over good advice on breast-feeding techniques. The review found commonly cited research on two drugs - metoclopramide and domperidone - to be seriously flawed. As for the drugs' safety, many studies relied on casual observation of babies for side effects, or failed to mention infant safety at all. There's even less research on the usefulness or long-term safety of herbs, which have been used for generations and across many cultures to increase milk supply. What's more, herbal supplements can be sold without government approval, dosing isn't standard and some products have been known to contain toxic substances, according to the Academy of Breastfeeding Medicine. "I'm not a big fan of herbals," said Dr. Ruth Lawrence of the University of Rochester School of Medicine and the author of the primary medical text on breast-feeding. "They can put anything they want in that bottle. There's no quality control." White didn't notice any side effects in herself or her baby from the herbal remedies she tried. But she said she did get depressed while taking metoclopramide, or Reglan, an anti-nausea medicine that has been used "off label" to treat low milk supply. Depression is listed as a possible side effect on the package insert. "I remember feeling like I was out of control. I couldn't control my emotions," said White. What helped White most was a supplemental nursing system - a device that allows a baby to receive both formula and mother's milk, by delivering formula through a tube attached at the mother's nipple. Most milk-supply problems can be solved by increasing the frequency of breast-feeding or by using a breast pump. These supply-and-demand methods should be tried first, according to the Academy of Breastfeeding Medicine. Very few women have biological reasons for low milk supply, experts said. Breast surgery or endocrine problems can inhibit production, though more often the problem begins when something interferes with frequent and thorough feedings in the days after a baby's birth.

***Antibiotics link to cerebral palsy one in 400 born with cerebral palsy***  
***Rouse, Beverley***  
***Press Association National Newswire, 2008; September 17***

Giving antibiotics to some pregnant women in premature labour may increase their chance of having a child with cerebral palsy, according to a study out today. The seven-year study found babies had a greater risk of developing the disability if their mothers' waters had not broken and they were given antibiotics despite showing no signs of infection. The Medical Research Council (MRC) report found the risk was not greater where mothers had gone into premature labour and their waters had broken. The new study followed up the Oracle trial completed seven years ago to see how children developed if their mothers had been given antibiotics during premature labour. Women who showed obvious signs of infection were not included in the study as the risk to mother and child was considered too great for antibiotics not to be administered. But some women who showed no obvious symptoms were given antibiotics in case an underlying infection had caused them to go into premature labour. Today's report said parents reported a "small but statistically significant increase in the condition cerebral palsy" in their children if they had been given antibiotics during premature labour but their waters had not broken. Sara Kenyon, of the University of Leicester who led the Oracle Children Study, said: "It is unclear why the follow-up showed this unexpected increase in the number of cases of cerebral palsy in babies born to the group of women whose waters had not broken and not in the other group. "Before the Oracle trial, there was some evidence of short-term benefits of antibiotics in premature labour, but we did not know what the long-term outcomes would be, which is why we conducted the follow-up." Dr Catherine Elliott, head of clinical research support and ethics at the MRC, said today's study highlighted the importance of long-term follow-ups. "The results were unexpected and the MRC

is considering what further research could shed more light on these findings. "We will be convening an expert group to look at what potential research avenues could be explored to understand what mechanisms may be involved." The study, published in medical journal *The Lancet*, found the risk of cerebral palsy was increased by the antibiotics erythromycin and co-amoxiclav but "the overall risk of this condition was low". Children had a 3.3% chance of developing cerebral palsy if their mothers had been given the antibiotic erythromycin, compared with 1.7% if they had not received the drug. There was a 3.2% chance of developing cerebral palsy for children whose mothers received the antibiotic co-amoxiclav, compared with a 1.9% chance for those who had not taken it. Pregnant women who were given both drugs had an even bigger chance of having a child who developed cerebral palsy, almost three times that for those who took only a placebo, although the risk was still low. Richard Parnell, research and evidence manager at the charity Scope, said: "This study raises some interesting findings although the causes of cerebral palsy are complex and still not well understood." A spokesman for The Royal College of Obstetricians and Gynaecologists said: "These findings do not mean that antibiotics are unsafe for use in pregnancy. "Pregnant women showing signs of infection should be treated promptly with antibiotics."