

CaseMed-Pregnancy Resource Newsletter

October 2007

MEDICAL STUDIES

Polycystic Ovarian Syndrome; Data from D.S. Feig et al provide new insights into polycystic ovarian syndrome. OBGYN & Reproduction Week, 2007; October 1: p.192

The aim of this Canadian study was to provide information on the use of oral antidiabetic agents in pregnancy and breast-feeding. The results of the study indicate that neither glyburide nor metformin have caused developmental toxicity in humans. Metformin has been used in women with Polycystic Ovarian Syndrome who eventually became pregnant and glyburide has been used for the treatment of gestational diabetes. The researchers concluded “Metformin, glyburide, and glipizide appear to be compatible with breast-feeding.”

D.S. Feig, G. Koren and G.G. Briggs published their study in Annals of Pharmacotherapy (Oral antidiabetic agents in pregnancy and lactation: a paradigm shift? Annals of Pharmacotherapy, 2007; 41(7-8):1174-1180).

Obstetrics; Researchers test old drug with new hopes for preeclampsia cure. OBGYN & Reproduction Week, 2007; October 1: p.20

Researchers at the University of Texas Medical Branch at Galveston, Texas are trying to determine whether a drug already available to heart patients can also be used to delay delivery in expectant mothers with severe preeclampsia. The drug, Digibind, has been prescribed for over 20 years to patients who overdose on a certain heart medication. The clinical trial will test whether Digibind reverses or prevents the abnormalities that occur with preeclampsia and allows the fetus to remain in the womb longer. This would give doctors more time to administer steroids to prevent respiratory complications in premature births and reduce the need for costly and lengthy neonatal intensive care. UTMB will continue enrolling participants at least through the end of this year. The study is sponsored by Protherics and is taking place in eight states around the country.

In utero valproate exposure hits IQ. Australian Doctor, 2007; September 28: p.6

Australian experts are warning that children exposed to valproate in utero are at risk of adverse IQ outcomes. Recent U.S. research found children exposed to the drug in utero had IQ scores at two years that were 4-8 points lower than children exposed to other common anti-epileptic drugs. According to Melbourne neurologist Professor Frank Vajda, professor of neuropharmacology at Monash University and director of the Australian Register of Pregnancy for Women with Epilepsy, “The neurocognitive effects of valproate use in pregnancy may be even more disturbing than the physical malformation effects.” Several international studies have suggested verbal IQ scores that measure semantic knowledge, attention skills and abstract reasoning were particularly affected by valproate exposure, however, the exact nature and mechanism of the cognitive effects were not known. Dr Vajda and Dr. Amanda Wood have commenced research to elucidate the cognitive effects of anti-epileptic drug use in pregnancy and expect to have cross-sectional data next year and longitudinal data within five years.

Antiepileptic medication during pregnancy: does fetal genotype affect outcome?

Atkinson DE, Brice-Bennett S, D'Souza SW

Pediatr Res, 2007; 62(2): 120-7

Congenital abnormalities and impaired development in childhood are attributable to fetal exposure to antiepileptic drugs (AEDs). Pregnancy registries set up to obtain information about the potential risks of fetal exposure to AEDs, in particular major congenital malformations, suggest that valproate exposure increases the frequency of congenital malformations more than other AEDs. Cognitive impairments in later childhood after prenatal exposure to valproate have also been highlighted in recent follow-up studies. In this study, the authors surmise that fetal exposure to AEDs may be influenced by drug transporting proteins in the placenta, including P-glycoprotein (P-gp), multidrug resistance protein (MRP) 1, and breast cancer resistance protein (BCRP). Their location in the syncytiotrophoblast plasma membrane, at the interface of the maternal and fetal circulations, allow these transport proteins to efflux xenobiotics back to the mother and offers the fetus protection from medications taken during pregnancy. Genetic variations in the expression and activity of these transport proteins may influence fetal exposure to AEDs and thus the risk of teratogenicity. Atkinson, Brice-Bennett and D'Souza conclude that identification of a hierarchy of haplotypes ranging from susceptible to protective of congenital abnormalities could assist genetic counseling, in assessing fetal risks from exposure to AEDs.

Exposure to amlodipine in the first trimester of pregnancy and during breastfeeding

Ahn HK, Nava OAA, Han JY, et al

Hypertens Pregnancy, 2007; 26(2): 179-87

The objective of this study was to assess the fetal outcome of three hypertensive women exposed to amlodipine, 5 mg/day, in the first trimester of pregnancy. At the conclusion of the study, the researchers stated that as reported with other calcium-channel blockers, amlodipine does not appear to be teratogenic and it appears to be compatible with breastfeeding.

Atrial and ventricular rate response and patterns of heart rate acceleration during maternal-fetal terbutaline treatment of fetal complete heart block

Cuneo BF, Zhao H, Strasburger JF, et al

Am J Cardiol, 2007; 100(4): 661-5

Terbutaline is used to treat fetal bradycardia in the setting of complete heart block; however, little is known of its effects on atrial and ventricular beat rates or patterns of heart rate acceleration. In this study, fetal atrial and ventricular beat rates were compared before and after transplacental terbutaline treatment (10 to 30 mg /day) by fetal echocardiography in 17 fetuses with complete heart block caused by immune-mediated damage to a normal conduction system (isoimmune, n = 8) or a congenitally malformed conduction system associated with left atrial isomerism (LAI, n = 9). While receiving terbutaline, 9 of the 17 fetuses underwent fetal magnetocardiography to assess maternal heart rate and rhythm, patterns of fetal heart rate acceleration, and correlation between fetal atrial and ventricular accelerations (i.e., AV correlation). The authors concluded that the pathophysiologic heterogeneity of complete heart block is reflected in the differing effect of terbutaline on the atrial and ventricular pacemaker(s) and varying patterns of heart rate acceleration. However, regardless of the cause of complete heart block, terbutaline augments heart rate but not AV correlation, suggesting that its effects are determined by the conduction system defect rather than the autonomic control of the developing heart.

Oxycodone as a component of multimodal analgesia for lactating mothers after Caesarean section: relationships between maternal plasma, breast milk and neonatal plasma levels.

Seaton S, Reeves M, McLean S

Aust N Z J Obstet Gynaecol, 2007; 47(3): 181-5

Oxycodone has become popular for post-caesarean section analgesia yet it is not currently recommended for use in breastfeeding mothers because of limited information on its excretion into breast milk. The aim of this study was to investigate the relationship between maternal ingestion of oxycodone after caesarean section and the resultant maternal plasma, breast milk and neonatal plasma drug levels up to 72-h post-partum. Samples of the blood and breast milk of fifty breast-feeding mothers taking oxycodone were analyzed for oxycodone levels at 24 h intervals after caesarean section. Blood samples from forty-one neonates were also taken at 48 h. The researchers found that oxycodone is concentrated in human breast milk up to 72-h post-partum and that breastfed infants may receive > 10% of a therapeutic infant dose. However, maternal oxycodone intake up to 72-h post-caesarean section poses only minimal risk to the breast-feeding infant as low volumes of breast milk are ingested during this period.

Breastfeeding and visual development of children

Chapman DJ

J Hum Lact, 2007; 23(3): 287-8

No abstract is available.

Microphthalmos associated with Dartmouth combination chemotherapy in pregnancy: a case report

Li RHW, Tam WH, Ng PC, et al

J Reprod Med, 2007; 52(6): 575-6

The use of Dartmouth combination chemotherapy in pregnancy is scarcely reported, with only one report of its use in the late second and third trimesters and no report of its use in the first trimester. This study examines the first reported case in which the Dartmouth combination chemotherapy regimen was inadvertently used in a pregnant woman during the first and second trimesters for treatment of metastatic melanoma. The infant was found to have isolated microphthalmos and severe hypermetropia at 1 year of age. The authors conclude that although a causal relationship cannot be established from a single case, this report does provide useful information to discourage the use of this chemotherapy regimen in the first trimester, which is the critical period for organogenesis.

Serotonin reuptake inhibitors in pregnancy and the risk of major malformations: a systematic review

Bellantuono C, Migliarese G, Gentile S

Hum Psychopharmacol, 2007; 22(3): 121-8

The purpose of this study was to review studies conducted to establish the risk of major congenital malformations in women exposed to serotonin reuptake inhibitors (SRIs) during the first trimester of pregnancy. The authors conducted literature searches within PsycINFO, EMBASE, MEDLINE and Cochrane Databases from 1966 to 2006, to identify studies assessing the risk of major malformations in infants whose mother was taking SRIs (SSRIs and SNRIs) during the first trimester of pregnancy. The reviewed studies suggest that exposure to fluoxetine, sertraline, citalopram and venlafaxine in early pregnancy is not associated with an increased risk of major congenital malformations. For paroxetine, recent data call for caution in prescribing

such a drug in early pregnancy. For the other SRIs, the risk remains substantially undetermined, as data are so far scanty. Given this background, large prospective cohort studies are urgently needed to better assess the risk/benefit ratio of SRIs-treatment during pregnancy.

Long-term outcomes after repeat doses of antenatal corticosteroids

***Wapner RJ, Sorokin Y, Mele L, et al
N Engl J Med, 2007; 357(12): 1248-50***

Previous trials have shown that repeat courses of antenatal corticosteroids improve some neonatal outcomes in preterm infants but reduce birth weight and increase the risk of intrauterine growth restriction. The purpose of this study was to report long-term follow-up results of children enrolled in a randomized trial comparing single and repeat courses of antenatal corticosteroids. In this study, women at 23 through 31 weeks of gestation who remained pregnant 7 days after an initial course of corticosteroids were randomly assigned to weekly courses of betamethasone, consisting of 12 mg given intramuscularly and repeated once at 24 hours, or an identical-appearing placebo. The authors studied 556 children who were born after these treatments when they were between 2 and 3 years of corrected age. Prespecified outcomes included scores on the Bayley Scales of Infant Development, anthropometric measurements, and the presence of cerebral palsy. Results demonstrate that children who had been exposed to repeat as compared with single courses of antenatal corticosteroids did not differ significantly in physical or neurocognitive measures. Although the difference was not statistically significant, the higher rate of cerebral palsy among children who had been exposed to repeat doses of corticosteroids is of concern and warrants further study.

Outcomes at 2 years of age after repeat doses of antenatal corticosteroids

***Crowther CA, Doyle LW, Haslam RR, et al
New Engl J Med, 2007; 357(12): 1248-50***

Previously, Crowther and colleagues had reported the results of a randomized, controlled trial showing that repeat doses of antenatal corticosteroids reduced the risk of respiratory distress syndrome and serious neonatal morbidity. In the present study, women who had received an initial course of corticosteroid treatment 7 or more days previously were randomly assigned to receive an intramuscular injection of corticosteroid (11.4 mg of betamethasone) or saline placebo; the dose was repeated weekly if the mother was still considered to be at risk for preterm delivery and the duration of gestation was less than 32 weeks. The researchers assessed survival free of major neurosensory disability and body size of the children at 2 years of corrected age. They concluded that administration of repeat doses of antenatal corticosteroids reduces neonatal morbidity without changing either survival free of major neurosensory disability or body size at 2 years of age.

Summaries for patients. Frequency of birth control services with prescriptions for unsafe drugs during pregnancy.

[No authors listed]

Ann Intern Med, 2007; 147(6): 370-6

No abstract available.

Treatment of pulmonary arterial hypertension in pregnancy

***Huang S, DeSantis ER
Am J Health Syst Pharm, 2007; 64(18): 1922-6***

This article reviews the treatment of pulmonary arterial hypertension in pregnancy. The authors conclude that targeted pulmonary vasodilators are viable treatment options for pregnant patients with pulmonary arterial hypertension and that early recognition and management of worsening symptoms are essential to improve outcomes for both the mother and infant.

Pregnancy problem yields insight into cancer drug induced high blood pressure

Beckman M

J Natl Cancer Inst, 2007; 99(17): 1288-9

No abstract available.

International recommendations on antiretroviral drugs for treatment of HIV-infected women and prevention of mother-to-child HIV transmission in resource-limited settings: 2006 update

Dao M, Mofenson LM, Ekpini R, et al

Am J Obstet Gynecol, 2007; 197(3 Suppl): S42-55

The World Health Organization recommends that countries adopt more effective antiretroviral regimens to increase the effectiveness of the prevention of mother-to-child human immunodeficiency virus (HIV) transmission programs. The 2006 guidelines recommend a tiered approach for the delivery of antiretroviral to pregnant women who are infected with HIV and include triple-drug antiretroviral treatment for those women who are eligible. Those women who are not eligible for antiretroviral treatment should receive a combination prophylaxis antiretroviral regimen, preferably zidovudine from 28 weeks of gestation; zidovudine, lamivudine, and a single dose of nevirapine during delivery; and zidovudine and lamivudine for 7 days after delivery to reduce the development of nevirapine resistance. Newborn infants should receive a single dose of nevirapine and 1-4 weeks of zidovudine, depending on the duration of the regimen received by the mother. Although steps are being taken to provide more effective regimens, the use of single-dose nevirapine alone should still be used in situations in which more effective regimens are not yet feasible or available. HIV transmission through breastfeeding remains a problem, and several interventions are under evaluation that includes maternal and/or infant antiretroviral prophylaxis during breastfeeding.

Use of enhanced perinatal human immunodeficiency virus surveillance methods to assess antiretroviral use and perinatal human immunodeficiency virus transmission in the United States, 1999-2001

Harris NS, Fowler MG, Sansom SL, et al

Am J Obstet Gynecol, 2007; 197(3 Suppl): S33-41

Harris and colleagues used data collected through the Enhanced Perinatal Surveillance system for HIV-exposed singleton births that occurred from 1999-2001 in 24 sites to examine the use of antiretrovirals and perinatal HIV transmission. Their findings support the current treatment recommendations and showed that infants were less likely to be infected when the mothers were given a prenatal antiretroviral therapy regimen that contained zidovudine with additional antiretroviral drugs with or without a protease inhibitor in addition to receiving antiretrovirals during delivery and neonatally.

Recommendations for human immunodeficiency virus screening, prophylaxis, and treatment for pregnant women in the United States

Jamieson DJ, Clark J, Kourtis AP, et al

Am J Obstet Gynecol, 2007; 197 (3 Suppl): S26-32

In the United States, current human immunodeficiency virus (HIV) testing guidelines recommend an opt-out approach for pregnant women, whereby HIV testing is incorporated routinely into the standard panel of prenatal tests with the option to decline. Current recommendations for the initiation of treatment of HIV infection in pregnant women are the same as those for nonpregnant women. However, the special circumstances of pregnancy raise additional issues that are related to potential drug toxicity to the mother and fetus, which affect the choice of antiretroviral drugs to be used. For HIV-infected pregnant women who do not require therapy for their own health, antiretroviral drugs are recommended for prevention of mother-to-child transmission. Highly active antiretroviral therapy is recommended for all women with HIV RNA levels of $>$ or $=$ 1000 copies/mL, along with consideration of elective cesarean delivery. For women with HIV RNA levels of $<$ 1000 copies/mL, a 3-part zidovudine prophylaxis regimen (prenatal, intrapartum, and neonatal) should be used alone or in combination with other antiretroviral drugs.

Comment on single-dose methotrexate regimen in the treatment of low-risk gestational trophoblastic neoplasia

Mahajan NN, Soni RN, Mahajan KN

Am J Obstet Gynecol, 2007; 197(3): 325; author reply 325

Comments regarding the Chan KK et al study from the American Journal of Obstetrics & Gynecology, 2006; 195(5): 1282-6.

Randomized, double-blind, placebo-controlled trial of transdermal nitroglycerin for preterm labor.

Nassar AH, Usta IM

Am J Obstet Gynecol, 2007; 197(3): 325-6; author reply 326

Comments regarding the Smith GN et al study from the American Journal of Obstetrics & Gynecology, 2007; 196(1): 37.e1-8.

The National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network Beneficial Effects of Antenatal Repeated Steroids study: impact of repeated doses of antenatal corticosteroids on placental growth and histologic findings

Sawady J, Mercer BM, Wapner RJ, et al

Am J Obstet Gynecol, 2007; 197(3):281.e1-8

In utero exposure to repeated doses of antenatal corticosteroids has been shown to reduce fetal growth. The objective of this study was to evaluate whether weekly betamethasone alters placental growth and histologic findings. The researchers concluded that repeated antenatal corticosteroid treatments in pregnancy are associated with decreased placental growth in a dose-dependent fashion, but not with evident differences in histologic markers of placental inflammation, ischemia, or infarction. Histologic placental abnormalities should not be attributed to repeated courses of corticosteroids.

Serious psychiatric outcomes of subjects prenatally exposed to diethylstilboestrol in the E3N cohort study

Verdoux H, Ropers J, Costagliola D, et al

Psychol Med, 2007; 37(9): 1315-22

Prenatal exposure to diethylstilboestrol (DES) may induce neurodevelopmental disturbances potentially mediating an increased risk of psychiatric disorders in exposed subjects. In this study, information on hormonal treatment during pregnancy and on offspring's medical outcome was

collected from women participating in the Etude Epidemiologique de femmes de la Mutuelle Générale de l'Education Nationale prospective cohort who completed consecutive postal questionnaires on a range of medical events since 1990. Information on hormonal treatment during pregnancy was collected in 1992 and on offspring's medical outcome in 2004. The psychiatric outcome of subjects prenatally exposed to DES was compared to that of their unexposed siblings. The findings of Verdoux and colleagues suggest the impact of prenatal DES exposure on fetal brain development, if any, is unlikely to increase the risk of serious psychiatric disorders.

Polytherapy with hERG-blocking antiepileptic drugs: increased risk for embryonic cardiac arrhythmia and teratogenicity

Danielsson C, Azarbayjani F, Sköld AC, et al

Birth Defects Res A Clin Mol Teratol, 2007; 79(8): 595-603

The antiepileptic drugs (AEDs) phenytoin, phenobarbital, dimethadione, and carbamazepine cause a similar pattern of malformations in humans, with an increased risk after polytherapy. The teratogenicity has been linked to cardiac rhythm disturbances and hypoxic damage as a consequence of their common potential to inhibit a specific potassium ion current (IKr). The IKr is of major importance for embryonic cardiac repolarization and rhythm regulation. This study investigated whether these AEDs cause irregular rhythm and if various combinations of AEDs result in higher arrhythmia risk than exposure to a single AED. The researchers' results suggest that polytherapy more than monotherapy causes substantial prolongation of the cardiac repolarization, a marker associated with high risk of developing irregular rhythm during longer exposure periods (days to months). This supports the idea that the increased risk for malformations following polytherapy is linked to an increased risk for cardiac rhythm disturbances.

The impact of autoimmune disorders and adverse pregnancy outcome

Mecacci F, Pieralli A, Bianchi B, et al

Semin Perinatol, 2007; 31(4): 223-6

This article discusses “connective tissue diseases” or CTD (such as systemic lupus erythematosus, rheumatoid arthritis, systemic sclerosis, Sjogren syndrome, and others) and the impact that these diseases and their therapies have on pregnancy and, conversely, the effect of pregnancy on these disorders, which may have long-lasting implications for mothers and neonates. According to Mecacci et al, adverse fetal outcomes, maternal disease flares, and drug potential teratogenic risk are the main reasons why women suffering from CTD and who are pregnant or intend to become pregnant are considered a high-risk population. These patients require integrated, interdisciplinary care, addressing every aspect of rheumatology, obstetrics, and neonatology to reduce maternal, fetal, and neonatal complications.

LAY PRESS NEWS

Women on drugs that can cause offspring birth defects not always warned: study

Loviglio J

CBC.ca, 2007; September 17

Doctors are not doing a very good job of warning young women to avoid getting pregnant when they're taking prescription drugs that can cause birth defects, a new study suggests. Fewer than half of the women taking the medicines did not get counseling from their doctor about using

contraceptives or other birth control measures, University of Pittsburgh Medical center researchers found in a study of nearly 500,000 women. “The message is not that women should avoid taking prescription medications that they need and that their doctors recommend,” said Dr. Eleanor Bimla Schwarz, lead author of the study in Tuesday’s *Annals of Internal Medicine*. “But women should discuss the potential pregnancy risks with their doctors before taking the drugs.” The researchers looked at data for women ages 15 to 44 enrolled in Kaiser Permanente Northern California in 2001 who filled about one million prescriptions. One in six of the women got a least one prescription for a drug with birth-defect risks. They found that women prescribed drugs that might cause birth defects were no more likely to get counseling about pregnancy prevention than women prescribed safer drugs. In both groups, fewer than half of the women received guidance from their doctors (48 per cent of the higher risk drug group, 47 per cent of the safe drug group). Internists and family doctors prescribed the highest proportion of the riskier drugs to women of childbearing years, followed far behind by psychiatrists, dermatologists and obstetricians-gynecologists. Researchers did find that women on the acne drug isotretinoin (Accutane) received the most pregnancy prevention counseling while women taking statins for cholesterol received the least counseling.

Studies find steroid use in pregnancy mostly safe

Emery G

Reuters Health E-Line, 2007; September 20

Two new studies are offering mixed signals about the long-term safety of repeatedly giving pregnant women steroid drugs intended to prevent complications once a premature delivery seems likely. While one report in *The New England Journal of Medicine* found little evidence that the widespread practice is dangerous, another study in the medical magazine offers hints that repeated injections may raise the risk of cerebral palsy in babies born to the women receiving steroids. Doctors give such drugs to help the fetus’ lungs mature quickly if they suspect premature delivery. But the baby does not always come as soon as expected, raising the question of whether steroid treatment should continue in that situation. The first study led by Caroline Crowther noted a small difference in attention problems with children in a repeat-corticosteroid group compared to a group of children whose mothers had been given placebo shots after the first steroid injection. The second study led by Ronald Wapner found that 2.9 percent of the steroid-treated pregnancies produced a baby with cerebral palsy, compared to a rate of 0.5 percent among the children of placebo recipients.

Thalidomide – it’s not over yet. When the parents of thalidomide children finally won compensation in the 1970’s, everyone thought that the case was closed. But with money running out, the now middle-aged thalidomiders are fighting on and winning.

Jack A

Financial Times Weekend Magazine, 2007; September 22: p.16

This article interviews a number of British adults whose mothers took thalidomide while it was heavily marketed for stress and morning sickness in pregnancy. The drug had never been tested on pregnant animals – let alone women – and families and supporters of thalidomide children fought high-profile battles in the late 1960s and 1970s to win compensation from the drug’s makers and licensees. In the UK, £20 million went into the Thalidomide Trust for the 458 thalidomide survivors. Now, thalidomide survivors are entering late middle age, and many find their physical condition deteriorating. Original compensation deals made in the 1970’s are no longer enough to pay all the bills and the compensation itself varies greatly from country to country. Germany’s 2,872 thalidomide survivors receive far less than British victims – a maximum of just 545 a month from the fund created by the original manufacturer of the drug,

Chemie Grunenthal, and since topped up by the German state. Those affected in Sweden, Canada and Japan also have some compensation. In Spain, where thalidomide was withdrawn more than six months later in Germany, there is no money at all. Italian thalidomide survivors only won medical recognition last year, and promised support has yet to materialize. British thalidomide campaigners are now linking with others in Europe and North America to make plans to seek compensation from Chemie Grunenthal of Germany. Sebastian Wirtz, grandson of the company's founder and now the most senior executive, stresses that the original DM100 million paid out was "gigantic"; that dealing with the tragedy cannot be reduced to a sum of money; and that there is no question of paying compensation or even seeking forgiveness in a way that suggests the company's guilt. He says the controversial television film "Eine einzige Tablette" (A Single Pill) has created a "very difficult" atmosphere in which to negotiate with the campaigners. Currently, thalidomide is marketed by Celgene to treat ENL (a complication of leprosy) and multiple myeloma. Last year, thalidomide generated 433 million in sales for Celgene.