

CaseMed-Pregnancy Resource Newsletter

November 2008

MEDICAL STUDIES

Hospital for Special Surgery; Statins may prevent miscarriages

Author unknown

OBGYN & Reproduction Week, 2008; October 27

Hospital for Special Surgery researchers have found that statins may be able to prevent miscarriages in women who are suffering from pregnancy complications caused by antiphospholipid syndrome (APS), according to a study in mice. In this autoimmune syndrome, the body produces antibodies directed at phospholipids, the main components of cell membranes. This news comes from a study published in the October issue of the Journal of Clinical Investigation that is currently online in advance of print. In low risk pregnancies, APS is associated with a nine-fold increase in miscarriage. In high-risk pregnancies (women who have had at least three prior losses), APS is associated with a 90 percent risk of miscarriage. "Statins may work as a treatment for women with APS-induced pregnancy complications," said Guillermina Girardi, Ph.D., associate scientist at Hospital for Special Surgery in New York, who is lead author of the study. "They are drugs that have been shown to be very safe. There are a lot of women who continue to take statins through pregnancy and the drugs have not been shown to produce birth defects." Statins do not increase the risk of bleeding like anticoagulants, the current treatment for patients with APS. In previous studies, Dr. Girardi and colleagues showed that antiphospholipid (aPL) antibodies in female mice caused inflammation that injured the placentas and induced abortions. These antibodies activate a protein, C5a, that activates another protein, tissue factor, that is expressed on the surface of certain white blood cells called neutrophils. This spurs the neutrophils into action, they attack the placenta, and the fetus dies. While investigators had unveiled this basic chain of events, they didn't know any further details about the mechanism. Women are advised to discontinue most medications, including statins, during pregnancy, but Dr. Girardi says that no fetal defects have been reported in women who have continued to use statins while pregnant. The researchers say that careful studies should be conducted to confirm the safety of statins in pregnancy in humans. "Women that are antiphospholipid antibody positive and have a history of previous miscarriages are a good group to perform a clinical trial," Dr. Girardi said.

University of Montreal; Pregnant women consuming flaxseed oil have high risk of premature birth

Author unknown

OBGYN & Reproduction Week, 2008; November 10

A study has found that the risks of a premature birth quadruple if flaxseed oil is consumed in the last two trimesters of pregnancy. The research was conducted by Professor Anick Berard of the Universite de Montreal's Faculty of Pharmacy and the Sainte-Justine Hospital Research Center and Master's student Krystel Moussally. In Canada, 50 percent of pregnant women take prescription medication. Yet many of them prefer to use natural health products during the pregnancy. "We believe these products to be safe because they are natural. But in reality, they are

chemical products and we don't know many of the risks and benefits of these products contrarily to medication," says Berard. Berard and Moussally set out to conduct one of the largest studies ever undertaken on by analyzing data from 3354 Quebec women. The first part of the research established that close to 10 percent of women between 1998 and 2003 used natural health products during their pregnancy. Before and after pregnancy they were respectively 15 and 14 percent to use these products. The increase means that about one third of women consuming natural health products stopped during the pregnancy. The most consumed natural health products by pregnant women are chamomile (19 percent), green tea (17 percent), peppered mint (12 percent), and flaxseed oil (12 percent). Berard and Moussally correlated these products to premature births and only one product had a very strong correlation: flaxseed oil. "In the general population, the average rate of premature births is 2 to 3 percent. But for women consuming flaxseed oil in their last two trimesters that number jumps up to 12 percent," says Berard. "It's an enormous risk."The correlation existed only with flaxseed oil, yet women consuming the actual seed were unaffected. Even if more studies must be undertaken to verify these results, Berard recommends caution when it comes to consuming flaxseed oil.

Mycophenolate mofetil embryopathy may be dose and timing dependent

Ang GS, Simpson SA, Reddy AR

Am J Med Genet A, 2008; 146A(15): 1963-6

Mycophenolate mofetil (MMF) is an immunosuppressive agent that has now been recognized as teratogenic in humans. A pattern of malformations from in utero exposure to MMF has recently been described, and includes cleft lip and palate, microtia and atresia of the external auditory canal. In this study, the authors present a nulliparous mother who had taken MMF for recurrent erythema multiforme for the first 5 weeks of her pregnancy, and developed a spontaneous miscarriage during the seventh week of pregnancy. For her second pregnancy, she took MMF on her own accord for four days in the seventh week after her last menstrual period. The newborn had bilateral microtia, absence of the external auditory canals, and right iris and chorioretinal coloboma, consistent with the pattern recognized as part of the MMF embryopathy phenotype. As the newborn was not exposed to other immunosuppressive agents in utero, the authors believe that the phenotype described to be the result of the teratogenic effect of MMF. The spontaneous miscarriage in the first pregnancy may be due to the higher dose and longer duration of MMF exposure. The second pregnancy, with MMF exposure of 4 days, proceeded to term with the resultant phenotype. Ang and colleagues conclude that the effect and severity of the embryopathy may be dependent on the dose, timing, and duration of MMF exposure. The manufacturer and the United States Food and Drug Administration have now disseminated information regarding the teratogenic risk of MMF. Women should be fully counselled and advised about contraception during the course of treatment with MMF.

Fetal and neonatal effects of maternal drug treatment for depression

Belik J

Semin Perinatol, 2008; 32(5): 350-4

Depression has a female sex predilection with 2% to 3% of the pregnant women population presently requiring treatment with selective serotonin reuptake inhibitors (SSRI). Exposure to SSRIs in late gestation leads to clinical manifestations in as much as 30% of the neonates. These include neurobehavioral, respiratory, gastrointestinal, and somatic symptoms. This review discusses the pharmacological effects of SSRI on the fetus and newborn, available treatment, and prevention strategies.

Effects of vitamin B12 and folate deficiency on brain development in children
Black MM
Food Nutr Bull, 2008; 29(2 Suppl): S126-31

According to the author, folate deficiency in the periconceptional period contributes to neural tube defects; deficits in vitamin B12 (cobalamin) have negative consequences on the developing brain during infancy; and deficits of both vitamins are associated with a greater risk of depression during adulthood. This review examines two mechanisms linking folate and vitamin B12 deficiency to abnormal behavior and development in infants, disruptions to myelination, and inflammatory processes.

Safety and efficacy of initiating highly active antiretroviral therapy in an integrated antenatal and HIV clinic in Johannesburg, South Africa
Black V, Hoffman RM, Sugar CA, et al
J Acquir Immune Defic Synd, 2008; 49(3): 276-81

The objective of this study was to describe the safety and efficacy of highly active antiretroviral therapy (HAART) in pregnant women treated in an integrated antiretroviral antenatal clinic (ANC ARV). Black and colleagues found that within the ANC ARV program, initiating pregnant women on HAART was feasible, safe, and effective. Results also showed that advanced gestational age at treatment initiation and loss to follow-up emerged as important challenges in this population.

Management of malignant gliomas during pregnancy: a case series
Blumenthal DT, Parreño MG, Batten J, et al
Cancer, 2008; Nov 5 [Epub ahead of print]

As limited data are available on the management of glioma in pregnant women, the aim of the current article was to describe the outcome of women with malignant gliomas who were exposed to chemotherapy early in the gestation period of their pregnancies. The authors present a case series of six women with malignant gliomas who during glioma-directed treatment were discovered to have an unplanned pregnancy. All patients elected to discontinue chemotherapy and carry their pregnancy to term. All women had uneventful pregnancies with no glioma-related complications. All women delivered healthy newborns without evidence of congenital malformations despite exposure to cytotoxic chemotherapy and anticonvulsant medications. Blumenthal and colleagues conclude that the management of malignant glioma during pregnancy is challenging; however, normal delivery and healthy live birth is possible

Individual and interdisciplinary treatment of rheumatic diseases in pregnancy
[Article in German]
Bolz M
Dtsch Med Wochenschr, 2008; 133(46): 2415

No abstract available.

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 occur in patients treated with a combination of calcineurin inhibitors, prednisolone, and azathioprine. There is little experience with newer drugs. In this study, Chu and colleagues 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. 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.

Highly active antiretroviral therapy versus zidovudine/nevirapine effects on early breast milk HIV type-1 Rna: a phase II randomized clinical trial

***Chung MH, Kiarie JN, Richardson BA, et al
Antivir Ther Lond, 2008, 13(6): 799-807***

Defining the effect of antiretroviral regimens on breast milk HIV type-1 (HIV-1) levels is useful to inform the rational design of strategies to decrease perinatal HIV-1 transmission. In this study pregnant HIV-1 seropositive women (CD4+ T-cell count >250 and <500 cells/mm³) electing to breastfeed in Nairobi, Kenya were randomized to highly active antiretroviral therapy (HAART; zidovudine (ZDV), lamivudine and nevirapine (NVP)) during pregnancy and 6 months post-partum or to short-course ZDV plus single-dose NVP (ZDV/NVP). Breast milk samples were collected two to three times per week in the first month post-partum. Chang and colleagues conclude that HAART resulted in lower breast milk HIV-1 RNA than ZDV/NVP; however, ZDV/NVP yielded comparable breast milk HIV-1 RNA levels in the first 2 weeks post-partum. Breast milk HIV-1 RNA remained suppressed in the ZDV/NVP arm despite increased plasma HIV-1 levels, which might reflect local drug effects or compartmentalization

Rosacea fulminans in the early course of a pregnancy by in vitro fertilization with embryo transfer

[Article in French]

***Cisse M, Maruani A, Bré C, et al
Ann Dermatol Venereol, 2008; 135(10): 675-8***

Rosacea fulminans is a rare and severe form of rosacea, with acute onset in women between 20 and 40 years. Although the aetiology remains unknown, pregnancy has been reported to be a triggering factor. This article reports the case of a 32-year-old woman with no previous history of dermatological disease consulted for rosacea fulminans appearing within the first three weeks of her first pregnancy, which required hormonal stimulation with recombinant FSH (follitropin alpha, Gonal F) and an LHRH inhibitor (cetorelix, Cetrotide). She did not use topical corticosteroids or any other medication and had no other abnormalities at clinical examination. The skin disease lasted throughout pregnancy despite different treatments. After delivery, moderate improvement was observed within two weeks. Treatment with isotretinoin 0.5 mg/kg/day was started three months after delivery and led to the disappearance of the papular and pustular lesions within three weeks, with persistence of the erythema for six months. Ciss and colleagues discuss a possible triggering role of endocrine factors, as well as therapeutic options.

Teratogenicity of antibacterial agents

Erić M, Sabo A

Coll Antropol, 2008; 32(3): 919-25

The aim of this study was to examine the possible correlation between use of antibacterial drugs in pregnancy and occurrence of congenital malformations. The results of this study show possible teratogenic potential even with those antibacterials which are considered safe, but as those are usually minor malformations, they often pass undetected. Because of that and because of frequent use of antibacterials during pregnancy, the authors conclude that detailed examinations concerning their safety should be made.

Selective serotonin reuptake inhibitors (SSRIs) in pregnancy: a review

Fleschler R, Peskin MF

MCN Am J Matern Child Nurs, 2008; 33(6): 355-61

Major affective disorders including depression and anxiety occur commonly in women of childbearing age and their incidence can increase during and after pregnancy. There is a critical clinical demand for treatment of these disorders, but the balance between treating affective disorders without harming the developing fetus is a difficult one. This has created concern both among women planning pregnancies, and those women who are pregnant already, as well as among families and healthcare providers. Currently, selective serotonin reuptake inhibitors (SSRIs) are the drugs of choice for the treatment of these disorders in pregnant women because of their documented efficacy and mild side effect profile. There is some research concerning SSRI use and pregnancy, which is the focus of this article.

Maternal glucose levels after dexamethasone for fetal lung development in twin vs singleton pregnancies

Foglia LM, Deering SH, Lim E, et al

Am J Obstet Gynecol, 2008; 199(4): 380.e1-4

Betamethasone administration in singleton pregnancies causes maternal hyperglycemia. With the increased risk of glucose intolerance in twin pregnancies, the researchers sought to determine whether maternal hyperglycemia after dexamethasone administration is different in twin vs singleton pregnancies. Foglia and colleagues conclude that twin pregnancies had higher mean glucose values than singleton pregnancies in the first 24 hours after dexamethasone administration.

Prescription drug use during pregnancy: a population-based study in Regione Emilia-Romagna, Italy

Gagne JJ, Maio V, Berghella V, et al

Eur J Clin Pharmacol, 2008; 64(11): 1125-32

Drug utilization studies in pregnant women are crucial to inform pharmacovigilance efforts in human teratogenicity. The purpose of this study was to estimate the prevalence of prescription drug use among pregnant women in Regione Emilia-Romagna (RER), Italy. Results showed that a large proportion of women who gave birth in RER in 2004 were exposed to prescription medications. Approximately 1 in 100 women were exposed to contraindicated drugs. Gagne and colleagues conclude that the most commonly identified drug exposures can help focus pharmacoepidemiologic efforts in drug-induced birth defects.

Anticoagulant prophylaxis in women affected by thrombophilia and previous obstetric complications

***Grandone E, Colaizzo D, Vergura P, et al
Minerva Ginecol, 2008; 60(5): 431-436***

Pregnancy is a condition of excessive clotting due to a decrease of some coagulation factors and a reduction of anticoagulant proteins, such as protein S. It is known that the causes of congenital or acquired thrombophilia may be associated with an increased risk of venous thromboembolism during pregnancy and/or obstetric complications, such as early or late fetal loss, intrauterine fetal deaths, pre-eclampsia, fetal growth restriction. During pregnancy, the use of a prophylaxis with antithrombotic drugs is considered at present a promising opportunity to significantly reduce the prevalence of thromboembolic complications, improving maternal and fetal outcomes. This article is a review of the most recent evidence of pregnant anticoagulant prophylaxis in women with previous thromboembolic events.

Drugs during pregnancy and lactation: treatment options and risk assessment, 2nd edition

***Gross GA
J Am Coll Surg, 2008; 207(4): e1-2***

No abstract available.

Epileptic disorders in pregnancy: an overview

***Harden CL, Sethi NK
Curr Opin Obstet Gynecol, 2008; 20(6): 557-62***

This article discusses new information that has now become available regarding outcomes of women with epilepsy (WWE) and pregnancy. According to the authors, the use of valproate and polytherapy with any antiepileptic drug (AED) combinations should be avoided, if clinically appropriate, during pregnancy. Seizure freedom in 9-12 months before pregnancy should be a goal. AED levels should be maintained at or near the therapeutic level known for that individual patient, with frequent monitoring during pregnancy as appropriate for the patient and the AED.

Do women with Caesarean section have to choose between pain relief and breastfeeding?

***[Article in Norwegian]
Hestenes S, Høymork SC, Løland BF, et al
Tidsskr Nor Laegeforen, 2008; 128(19): 2190-2***

The Caesarean section is a unique surgical procedure in that physicians postoperatively not only have to cater to the mothers' need for analgesics, but must also take into account the impact of this medication on the infant. Too cautious prescription of strong analgesics postoperatively may have untoward consequences, such as immobilisation and delayed onset of breastfeeding. The authors sent a questionnaire on procedures for standard postoperative analgesics after Caesarean section to the 46 Norwegian hospitals with anaesthesiology departments organized in conjunction with delivery units. Results revealed that most of these hospitals routinely prescribe both Paracetamol (95%) and NSAID (90%) in postoperative care immediately after Caesarean section. However, only 61% routinely prescribed an opioid. Hestenes and colleagues conclude that when the mother is most in need of opioid analgesics, lactation is barely established. Therefore, even if traces of opioids are absorbed into the mother's milk, the doses will be very small and the infant's oral bioavailability at this time is likely to be low. Consequently, there is little evidence to support a policy of overly restrictive use of opioids.

Peripartum cardiomyopathy - a new treatment option by inhibition of prolactin secretion
Jahns BG, Stein W, Hilfiker-Kleiner D, et al
Am J Obstet Gynecol, 2008; 199(4): e5-6

Peripartum cardiomyopathy (PPCM) is a rare disease of unclear etiology with a frequent poor outcome, despite optimal medical therapy. Recent experimental data implicate a causal role of prolactin. In this study, Jahns and colleagues report a patient with PPCM who responded well to treatment with Bromocriptine in addition to standard therapy of heart failure.

Study on the correlation of serum folate and red blood cell folate level with birth defects and unexplained recurrent pregnancy loss
Jiang Y, Sun N, Xiang Y, et al
[Article in Chinese]
Zhonghua Fu Chan Ke Za Zhi, 2007; 42(7): 448-52

The objective of this study was to understand the correlation of lower serum folate, and red blood cell (RBC) folate level with birth defects including unexplained recurrent pregnancy loss, and to evaluate the role of RBC folate level as a suitable marker for folate supplement. The authors conclude that RBC folate level is more closely correlated than serum folate level with the incidence of main birth defect.

Patient page. Epilepsy and pregnancy: are seizure medications safe?
Karceski S
Neurology, 2008; 71(14): e32-3

No abstract available.

Pregnancy and rheumatic disease: "by the book" or "by the doc"
Keeling SO, Oswald AE
Clin Rheumatol, 2008; Nov 6 [Epub ahead of print]

This article reviews the general state of pregnancy and how prototypical rheumatic diseases including rheumatoid arthritis and systemic lupus erythematosus affect it. In addition, Keeling and Oswald present the most commonly used disease-modifying antirheumatic drugs and immunosuppressants and explain the difference between the FDA category and clinical practice among rheumatologists. Finally, the authors provide some general recommendations on how to manage a rheumatic disease during pregnancy including: (a) preconception planning to ensure no teratogenic medications on board, (b) early disclosure of pregnancy to all caregivers including the rheumatologist, family physician, obstetrician, and maternal-fetal medicine specialist, and (c) planning of safe medication use for acute flare-ups and disease suppression peripartum and postpartum.

Childhood outcomes after prescription of antibiotics to pregnant women with spontaneous preterm labour: 7-year follow-up of the ORACLE II trial
Kenyon S, Pike K, Jones DR, et al
Lancet, 2008; 372(9646): 1319-27

The ORACLE II trial compared the use of erythromycin and/or amoxicillin-clavulanate (co-amoxiclav) with that of placebo for women in spontaneous preterm labour and intact membranes, without overt signs of clinical infection, by use of a factorial randomised design. The aim of the present study--the ORACLE Children Study II--was to determine the long-term effects on

children after exposure to antibiotics in this clinical situation. Kenyon and colleagues conclude that the prescription of erythromycin for women in spontaneous preterm labour with intact membranes was associated with an increase in functional impairment among their children at 7 years of age. Either antibiotic increased the risk of cerebral palsy, although the overall risk of this condition was low.

Childhood outcomes after prescription of antibiotics to pregnant women with preterm rupture of the membranes: 7-year follow-up of the ORACLE I trial
Kenyon S, Pike K, Jones DR, et al
Lancet, 2008; 372(9646): 1310-8

The ORACLE I trial compared the use of erythromycin and/or amoxicillin-clavulanate (co-amoxiclav) with that of placebo for women with preterm rupture of the membranes without overt signs of clinical infection, by use of a factorial randomised design. The aim of the present study--the ORACLE Children Study I--was to determine the long-term effects on children of these interventions. The researchers conclude that the prescription of antibiotics for women with preterm rupture of the membranes seems to have little effect on the health of children at 7 years of age.

Estimation of embryotoxic effect of fluoxetine using embryonic stem cell differentiation system
Kusakawa S, Yamauchi J, Miyamoto Y, et al
Life Sci, 2008; Oct 28 [Epub ahead of print]

Fluoxetine is an antidepressant drug of the selective serotonin reuptake inhibitor (SSRI) class, which is commonly prescribed to treat a wide spectrum of mood disorders including depression during pregnancy and lactation. Recent studies have proposed a possible association between an increase in major malformations and the maternal use of SSRI drugs during pregnancy. The aim of this study was to assess the effects of fluoxetine using a mouse ES cell differentiation system to clarify the possible association. Kusakawa and colleagues conclude that these results using the in vitro ES cell assay system suggest a possible relationship between the teratogenicity of fluoxetine and its molecular mechanism.

Management of Graves hyperthyroidism in pregnancy. Focus on both maternal and foetal thyroid function, and caution against surgical thyroidectomy in pregnancy
Laurberg P, Bournaud C, Karmisholt J, et al
Eur J Endocrinol, 2008; Oct 10 [Epub ahead of print]

Graves disease is a common autoimmune disorder in women in fertile ages. The hyperthyroidism is caused by generation of TSH- receptor activating antibodies. In pregnancy, both the antibodies and the antithyroid medication given to the mother pass the placenta and affect the foetal thyroid gland. Thyroid function should be controlled not only in the mother with Graves hyperthyroidism but also in her foetus. This review includes two cases illustrating some of the problems in managing Graves disease in pregnancy. The authors conclude that antithyroid drug therapy of pregnant women with Graves hyperthyroidism should be balanced to control both maternal and foetal thyroid function. Surgical thyroidectomy of a pregnant woman with active disease may lead to isolated foetal hyperthyroidism.

Pregnancy outcome in HIV-1 infected women receiving combination antiretroviral therapy prior versus after conception.

***Machado ES, Hofer CB, Costa TT, et al
Sex Transm Infect, 2008; Nov 5 [Epub ahead of print]***

Results regarding potential adverse effects of antiretroviral drugs during pregnancy are discrepant and few studies, most from Europe, have provided information about pregnancy outcomes of those already on treatment at conception. The aim of this study was to investigate the impact of antiretrovirals on pregnancy outcome according to the timing of treatment initiation in relation to pregnancy in a cohort of Brazilian HIV-infected pregnant women. In conclusion, Machado and colleagues identified an increased risk for low birth weight and preterm delivery in patients in receipt of HAART prior to pregnancy.

Drugs during lactation accenting boron exposure. Case Report

***Manakova E, Hubickova-Heringova L, Novakova L
Neuro Endocrinol Lett, 2008; 29(5): 631-634***

This article discusses the counselling experiences of the Czech Teratology Information Service regarding the risk of drug exposure during pregnancy and breastfeeding. In their counselling they consider the factors which are involved in drug transfer in the milk and mechanisms and the steps of transfer. They follow the classification of drugs during lactation by their effect on infants: absolutely contraindicated, temporary cessation of breastfeeding, drugs of special concern and drugs compatible with breastfeeding.

Rheumatic diseases in pregnancy

***[Article in German]
Märker-Hermann E, Bauer H, Gromnica-Ihle E
Dtsch Med Wochenschr, 2008; 133(46): 2410-4***

Rheumatic diseases can influence the reproduction, the course of pregnancy and the development of the fetus. The inflammatory rheumatic disease itself can be modulated in its activity in terms of amelioration or exacerbation of the rheumatic symptoms. In this article, the associations between rheumatic diseases and pregnancy are illustrated using rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and systemic lupus erythematosus as examples. The authors also state that antirheumatic drug therapy during pregnancy and the breast feeding period has to be adapted critically.

Pregnancy outcomes in women with epilepsy: a systematic review and meta-analysis of published pregnancy registries and cohorts

***Meador K, Reynolds MW, Crean S, et al
Epilepsy Res, 2008; 81(1): 1-13***

The purpose of this study was to conduct a systematic review and meta-analysis to quantify the incidence of congenital malformations (CMs) and other pregnancy outcomes as a function of in utero anti-epileptic drug (AED) exposure. Meador and colleagues found that results of this systematic literature review suggested that the overall incidence of CMs in children born of WWE is approximately threefold that of healthy women. The risk is elevated for all AED monotherapy and further elevated for AED polytherapy compared to women without epilepsy. The risk was significantly higher for children exposed to valproate monotherapy and to polytherapy of 2 or more drugs when the polytherapy combination included phenobarbital, phenytoin, or valproate. The authors conclude that further research is needed to delineate the

specific risk for each individual AED and to determine underlying mechanisms including genetic risk factors.

Potential significance of physiological and pharmacological glucocorticoids in early pregnancy

Michael AE, Papageorghiou AT

Hum Reprod Update, 2008; 14(5): 497–517

Despite extensive studies of the developmental consequences of increased glucocorticoid exposure in mid- to late pregnancy, relatively little is known regarding the significance of glucocorticoids in early pregnancy. The objective of this review was to consider potential roles for this family of corticosteroids that might relate to early pregnancy. Michael and Papageorghiou conclude that glucocorticoids exert many actions that could impact both negatively and positively on key aspects of early pregnancy. These steroids may also be implicated in obstetric complications, including intra-uterine growth restriction, pre-term labour, pre-eclampsia and chorio-aminionitis.

Antiretroviral prophylaxis to reduce breast-milk HIV-1 transmission

Mills J

N Engl J Med, 2008; 359(17): 1846; author reply 1846-7

No abstract available.

Should paroxetine be used to treat depression during pregnancy?

Mintzes B, Jureidini J

Am J Psychiatry, 2008; 165(11): 1487; author reply 1487-8

No abstract available.

Use of platinum derivatives during pregnancy

Mir O, Berveiller P, Ropert S, et al

Cancer, 2008; Nov 4 [Epub ahead of print]

The incidence of cancer during pregnancy is increasing given the trend for women to postpone childbearing. Knowledge of the potential toxicity and teratogenicity of chemotherapy agents is crucial for patient counselling. Platinum derivatives are active against various malignancies that occur more frequently during pregnancy: melanoma, cervical and ovarian cancers, and lung cancer. The authors of this article performed a systematic review of reports documenting the use of platinum derivatives during pregnancy in the English literature from 1977 through January 2008. Forty-three pregnancies were described: 36 patients received cisplatin, 6 patients received carboplatin, and 1 patient received both drugs. Two fetal malformations occurred after in utero exposure to cisplatin, but the causative link between cisplatin administration and these malformations remains speculative. However, either detectable cisplatin levels or platinum-DNA adducts were observed in neonates who were exposed to platinum derivatives during the third trimester, providing evidence for a late-onset transplacental transfer of these drugs. Mir and colleagues conclude that the administration of platinum derivatives, although feasible during the second and third trimesters of pregnancy, raises concern regarding the transplacental transfer of these drugs in late pregnancy and has unknown short- and long-term effects.

Guideline for the use of antenatal corticosteroids for fetal maturation

Miracle X, Di-Renzo GC, Stark A, et al

J Perinat Med, 2008; 36(3): 191-6

The aim of this article was to present a document, which is based on current evidence and serves as a guideline for use in clinical practice. The following questions are addressed: Is the use of antenatal corticosteroids (ACS) an effective therapy? Who are the candidates for antenatal corticosteroid therapy? Is there benefit after 34 weeks' gestation? When is the optimal time to treat? Which are the optimal steroids; what is the ideal dose and route of administration? Are there any contraindications to the administration of ACS? Are antenatal corticosteroids indicated in women with premature rupture of membranes (PROM)? Is the use of ACS recommended in pregnancies complicated by maternal diabetes mellitus? Should the treatment with corticosteroids be repeated?

Folic acid use and major congenital malformations in offspring of women with epilepsy. A prospective study from the UK Epilepsy and Pregnancy Register

Morrow JI, Hunt SJ, Russell AJ, et al

J Neurol Neurosurg Psychiatry, 2008; Oct 31 [Epub ahead of print]

In the general population folic acid supplementation during pregnancy has been demonstrated to reduce the frequency of neural tube defects and other major congenital malformations (MCMs). It is recommended that women with epilepsy contemplating pregnancy take supplemental folic acid due to the known anti-folate effect of some anti-epileptic drugs. The aim of this article was to determine effectiveness of this practice. The authors conclude that this study supports the view that extrapolation from studies carried out in the general population to groups of women with epilepsy may be questionable. It may be that the increased risk of MCM recorded in this group occurs through mechanisms other than that of folic acid metabolism.

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 KWD, 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. Ngan and colleagues conclude 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. 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.

Maternal exposure to statins and risk for birth defects: a case-series approach

Petersen EE, Mitchell AA, Carey JC, et al

Am J Med Genet A, 2008; 146A(20): 2701-5

No abstract available.

Antidepressant therapy during pregnancy: an insight on its potential healthcare costs
Ramos E, Ofori B, Oraichi D, et al
Can J Clin Pharmacol, 2008; 15(3): e398-410

Information on healthcare costs associated with poorly treated psychiatric disorders during and after pregnancy is limited. The objective of this study was to compare the direct healthcare costs, during and after pregnancy, between women who continue their antidepressant therapy during the whole gestational period and those who discontinue their treatment during the first trimester. The authors conclude that women who use antidepressants during pregnancy are likely to have disorders of greater severity compared to those who discontinue during the first trimester. They incur significantly greater healthcare costs. However, this increased cost is attributable to higher prescription costs.

Prescribing medications safely during pregnancy
Rayburn WF, Amanze AC
Med Clin North Am, 2008; 92(5): 1227-37

A large body of information about medications prescribed during pregnancy is readily available to internists and patients either on-line or through books and medical journals. Much of the evidence about many prescribed drugs is either anecdotal or presented with sufficient warnings about its use during pregnancy. This article discusses specific medications to set the risks and benefits into a more proper perspective, thereby alleviating certain fears and, when necessary, improving compliance.

Risperidone safety in pregnancy. A case report
Rodríguez-Salgado B
Actas Esp Psiquiatr, 2008; 36(6): 366-8

The use of risperidone and other antipsychotic drugs during pregnancy is sometimes essential, although it is impossible to design clinical trials to demonstrate the safety of these kinds of drugs. The common method to communicate the absence of drug-related events is through case reports, even though they might be insufficient. This case report describes a woman with a schizophreniform disorder who continued treatment with risperidone during all her pregnancy, and who gave birth to a healthy baby. The scientific evidence regarding risperidone safety during pregnancy is reviewed and the need to conduct follow-up studies evaluating the consequences of using antipsychotic drugs in pregnant women is stated.

Smoking cessation in pregnancy
Rore C, Brace V, Danielian P, et al
Expert Opin Drug Saf, 2008; 7(6): 727-37

Pregnant women who continue to smoke expose their developing fetus to a wide range of risks. Assisting these patients to stop smoking can be an important intervention for the health of the baby and the mother. The management of pregnant smokers can be challenging, due to the potential risks of pharmacotherapy. There are a number of options available to the clinician to aid smoking cessation in non pregnant women. These include nicotine replacement therapy (NRT), bupropion, varenicline, and a range of non-drug therapies. The objective of this study was to provide guidance to prescribers on the best way to manage smoking cessation in the pregnant patient, reviewing the risks and efficacy of the different approaches. Rore and colleagues conclude that NRT is the agent of choice for smoking cessation in pregnancy as the safety of

other therapies in pregnancy have not yet been proved.

Antibiotics in preterm labour--the ORACLE speaks
Russell AR, Steer PJ
Lancet, 2008; 372(9646): 1276-8

No abstract available.

Comparison of three doses of epidural fentanyl followed by bupivacaine and fentanyl for labor analgesia
Siddik-Sayyid SM, Taha SK, Azar MS, et al
Acta Anaesthesiol Scand, 2008; 52(9): 1285-90

Epidural fentanyl 100 microg after lidocaine-epinephrine test dose has been shown to provide adequate analgesia in early labor. This investigation determines the effect of three different bolus doses of epidural fentanyl on duration and quality of analgesia during early first stage of labor. The researchers found that after a test dose of lidocaine-epinephrine, the three epidural fentanyl doses produced similar effective labor analgesia. However, epidural fentanyl 75 microg followed by epidural infusion of dilute bupivacaine and fentanyl produced longer duration of analgesia than fentanyl 50 microg followed by the same infusion, with no further prolongation when the dose of fentanyl was increased up to 100 microg.

Why won't this newborn be breast-fed?
J Perinat Neonatal Nurs, 2008; 22(3): 177-8
Silbert FJ

No abstract available.

Pregnancy and liver transplantation
Surti B, Tan J, Saab S
Liver Int, 2008; 28(9): 1200-6

Since the first pregnancy in a transplant recipient in 1958, pregnancy in recipients of solid organ transplants has become increasingly common. Although previously considered a hazardous event, data collected over the last 50 years demonstrate that despite an increased risk of maternal and fetal complications, pregnancy in transplant recipients can have a successful outcome. According to Surti and colleagues, many medications used for post-transplant immunosuppression have potential effects during pregnancy and breast-feeding. The risks and benefits of each medication should be reviewed with patients contemplating pregnancy, and regimens should be tailored accordingly.

Acute voluntary intoxication with selective serotonin reuptake inhibitors during the third trimester of pregnancy: therapeutic management of mother and fetus
Tixier H, Feyeux C, Girod S, et al
Am J Obstet Gynecol, 2008; 199(5): e9-e12

Selective serotonin reuptake inhibitor (SSRI) antidepressants are preferred to tricyclics, because, for the same efficacy, they are better tolerated. The mechanisms of action are well understood and these drugs may be used during pregnancy. In this study, Tixier and colleagues present the case of a voluntary intoxication with SSRI in the third trimester of pregnancy.

A reproductive screening test of hawthorn
Yao M, Ritchie HE, Brown-Woodman PD
J Ethnopharmacol, 2008; 118(1): 127–32

Hawthorn (*Crataegus*) has a long history as a medicine. The current clinical use of hawthorn as a heart medicine dates back to the late 19th century. It is well tolerated clinically yet contraindicated in pregnancy. The aim of this study was to determine the safety of hawthorn to the developing fetus. The researchers found that hawthorn did not have an adverse effect on embryonic development in vivo or in vitro. While the results suggest that hawthorn, taken at the recommended dose would have no adverse effects on embryonic development this may be due to the low bioavailability of some hawthorn constituents when taken orally. Yao and colleagues conclude that pharmacokinetic studies are required to determine the extent of absorption of hawthorn from the small intestine in healthy adults in order to verify its safety.

LAY PRESS NEWS

FDA notes pregnancy risks with Theravance drug
Perrone M
BusinessWeek, 2008; November 17

Shares of drugmaker Theravance surged Monday on the release of a federal review of the company's experimental antibiotic, despite concerns about the product's risks to pregnant women. Rachel McMinn wrote in a research note the Food and Drug Administration's review contains "nothing shocking," despite highlighting potential safety issues for kidney-failure patients and pregnant women. San Francisco-based Theravance has asked the FDA to approve telavancin for hard-to-treat skin infections caused by gram-positive bacteria, including staph infections. Gram-positive bacteria are highly resistant to many antibiotics now on the market. The FDA delayed a decision on the injectable product last October, asking Theravance to work on manufacturing issues and submit new clinical data. The company submitted the drug for review in December 2006. On Wednesday, the agency will ask a panel of antibiotic experts to assess the safety and effectiveness of the once-a-day treatment. The FDA is not required to follow its advisers' recommendations, though it usually does. Regulators plan to ask the panel whether telavancin's risks to pregnant women outweigh its benefits. The agency notes that early stage studies of the antibiotic linked it to deformations in the offspring of pregnant rabbits, rats and other laboratory animals. McMinn wrote that the antibiotic likely would win approval, but with restrictions for certain patient groups. "We believe telavancin will get a mixed approval recommendation from the committee, but will have restrictions in renally impaired patients and receive a black box warning in pregnancy," she wrote. In briefing documents posted online Monday, the agency recommends giving the treatment a "black box" warning label - the most serious type available - and limiting prescriptions to women who can demonstrate they are not pregnant. FDA reviewers concluded telavancin is about as effective at treating severe skin infections as an older antibiotic, vancomycin, based on two patient studies. However, reviewers noted that the effectiveness of Theravance's product appeared to decline in patients with kidney problems. Overall, the company reported nine deaths among patients taking telavancin - the same as the group taking the comparison antibiotic.

Folic acid and epilepsy
Pulse, 2008; November 12

UK researchers have questioned the recommended high doses (5mg) of folic acid in women taking anti-epileptic drugs who are planning to conceive or who are in the early stages of pregnancy. In a study of 1,935 women who reported receiving preconceptual folic acid, there were 76 major congenital malformations and eight neural tube defects. This compared with 53 major congenital malformations and eight neural tube defects in 2,375 women who reported receiving the supplement later in pregnancy or not at all. The researchers warned that extrapolation from studies carried out in the general population to women with epilepsy could be questionable.

Safety concerns drive call for drug studies that involve pregnant women
Desmon S
The Baltimore Sun, 2008; November 9

Very few drugs are approved for use during pregnancy. Yet millions of pregnant women each year take prescribed medication to treat high blood pressure or depression or cancer, without meaningful data on whether the drugs are safe for them or their fetuses. Many researchers have long considered including pregnant women in their studies taboo. But a push is on to learn more, amid fears that leaving serious health problems untreated could be more dangerous for pregnant women and their babies than taking an unstudied medication. "I can't identify any other group that has been as systematically neglected" in biomedical research, said Ruth Faden, director of the Johns Hopkins Berman Institute of Bioethics. Others worry that fetuses could be hurt by clinical research and that it would be difficult, if not impossible, to recruit enough pregnant women to participate. Many haven't forgotten the horror story of the morning sickness medication Thalidomide, which caused severe limb deformities in thousands of children after their pregnant mothers took the drug in the late 1950s and early 1960s. "We can't throw [women] into studies who are pregnant just to see," said Dr. Hugh E. Mighty, an obstetrician/gynecologist at the University of Maryland Medical Center. No one is suggesting women be included in every study of every drug. But Faden - who is co-hosting a conference on the subject this spring - thinks mothers and their children can be kept safe even as researchers find creative ways to study the risks, benefits and proper dosing of medications in pregnancy. She wants to see review boards at hospitals and academic institutions, the gatekeepers to research, develop ethical guidelines for including pregnant women whenever possible. "It's really controversial," said Dr. Donald Mattison, a senior adviser at the National Institute of Child Health and Human Development. "There are some groups who believe it's completely inappropriate, and others who are outraged that more hasn't been done." In the meantime, Faden and others say, obstetricians and patients are often forced to make treatment decisions without all the facts. "Pregnant women sometimes feel like they're put in a situation where they feel they have to choose between their own well-being and what's best for their baby," said Dr. Karen Feibus, who heads the maternal health team at the Food and Drug Administration's Center for Drug Evaluation and Research. "Some women feel guilty for taking medication. That's not good for their health or the health of their baby," Feibus said. "There isn't enough well-vetted, data-based information out there to let them know ... what their decisions should be based on." Just a dozen medications have been approved for use in pregnancy, all of them for gestation- or birth-related issues such as inducing or delaying labor, regional anesthesia or nausea and vomiting. Any drug used to treat a pregnant woman's illness is used without FDA approval, though doctors prescribe medicine to pregnant women all the time to treat their illnesses. Drug companies are accumulating some information, both through complaints and through pregnancy registries where the health of medicated mothers and their babies are closely monitored. The FDA is developing labelling rules that would specify what is and is not

known about how every drug on the market affects pregnancy "The realization that a lack of data can cause harm is pulling people together to start a serious conversation about how to best obtain data that is needed," the FDA's Feibus said. Faden has been trying to start the conversation for more than 15 years, but has found that ethical concerns have outweighed the health concerns for pregnant women and their unborn children. "We are so conflicted as a nation on how to think about what we owe to very early life," she said. "Nobody wants to touch it." That, she thinks, could be changing. "There is a growing consensus that the current situation is unfair," she said. "We need to push as far as we can."

My miracle chemo baby

Clarke L

Sunday Tribune, 2008; November 9

Conceived while her mother was undergoing chemotherapy and surviving five-and-a-half months of chemotherapy bombardment while her mother was unaware of the pregnancy, 3-month-old Talia Zoe's arrival in this world is nothing short of astonishing. Worldwide, there are only 35 babies like Talia Zoe, who have survived chemotherapy while in their mother's womb, say the mother's gynaecologists. In October last year, 27-year-old Fiona Donnelly, a housewife from Glenwood in Pietermaritzburg, was diagnosed with Hodgkins Lymphoma, a cancer of the lymph system (part of the body's immune structure). While undergoing chemotherapy, Fiona discovered she was five-and-a-half-months pregnant. Doctors advised her to terminate the pregnancy. They felt there was no chance of the baby surviving or being normal. Chemotherapy in the first trimester of a pregnancy poses a risk of birth defects. Since chemotherapy drugs interfere with cell growth and division, the foetus is most vulnerable during the first trimester when many of the internal and external structures of the foetus are formed. "They told me the effects of chemotherapy are harsh. If it could make my hair and teeth fall out, imagine what it could have done to my baby. "Nonetheless, I had more tests and scans done to check on my baby's condition and from that we saw she appeared to be normal. I decided to continue with the pregnancy. My doctors supported me," said Fiona. In week 30 of her pregnancy, her gynaecologists, Dr David Swan and Dr James Parkes, noticed her baby was not growing. They put her on steroids to aid the baby's growth so they could deliver her as soon as possible. Chemotherapy had stopped. Four weeks later, on July 25, Fiona was taken to hospital. Swan found her placenta had ruptured and the cord was tangled around the baby's neck. Talia Zoe was born later that night by Caesarean section, weighing 1.5kg. Whisked off by her paediatrician, Dr Mohammed Jooma, Talia Zoe was examined and found to be in perfect condition. She spent two weeks in an incubator and was discharged weighing a thriving 1.8kg. The doctors are still baffled that the chemotherapy did not affect her. "She is a perfectly normal baby girl. The baby was given to me to give me hope, to give others hope, to show others that cancer is not the end of the world," said Fiona. Swan described Talia Zoe's birth as a medical wonder. "It's unusual to fall pregnant while receiving chemotherapy. "It is even more unusual for a baby to do well despite the mother receiving really strong medicine . . . It was a wonderful thing to happen," he said. Although in remission, Fiona continues to undergo radiation therapy for her cancer, but is fit and well and enjoying her baby.

Pregnancy and lactation labeling proposed for drugs

Food & Drug Letter, 2008; November 7

The FDA wants to overhaul the labeling system to describe the risks and benefits that drugs and biologics pose to fetuses, breastfeeding infants, lactating mothers and women who are or might become pregnant. A proposed rule issued by the agency last week would require all drug and biologic labels to contain a pregnancy subsection whereas current regulations do not require this if the product "is not absorbed systemically and is not known to have a potential for indirect harm

to the fetus," it says. The rule has been in the works since 1997, and the agency was spurred into action in part by the FDA Amendments Act of 2007, which authorized it to follow up safety issues with special populations, including pregnant women, Rear Admiral Sandra Kweder, deputy director of the FDA's Office of New Drugs, said. The agency's goal is to provide the right information to a pregnant woman when she receives a drug prescription and asks, "Will this hurt my baby?" FDA Commissioner Andrew von Eschenbach said. Studies in the U.S. and other Western countries show that pregnant women take an average of three to five prescription drugs during pregnancy, Kweder said. Pregnant women with pre-existing conditions such as asthma or who develop complications of pregnancy may have to take additional drugs, she noted. Three Elements in Pregnancy Subsection The pregnancy subsection in the proposed rule would contain three major elements: a fetal risk summary, clinical considerations and data. Pregnancy registry information also would have to be included, if applicable, along with a general statement about the background risk of fetal developmental abnormalities. Information on labor and delivery would be included under clinical considerations instead of being listed separately because, from a medical standpoint, labor and delivery constitute the final phase of pregnancy. Similarly, the labeling for breastfeeding and lactation risks would have three major elements: a risk summary, clinical considerations and data. Critical information would include the drug's presence in mother's milk, its effects on breastfeeding infants and whether its risks outweigh the known benefits of breastfeeding, Kweder said. The rule does not necessarily require manufacturers to do new studies, nor does it require setting up a pregnancy registry if one does not exist, Kweder said. Pregnancy registries provide a central repository for the effects of a drug on pregnant women. Where such registries exist, the label should contain information on how patients can access them, she added. Guidance on the definition of low, moderate and high risk for pregnancy and lactation labeling will come after the FDA holds a series of public workshops, Kweder said. Risks to be addressed include potential problems for women who do not yet know they are pregnant as approximately half of all pregnancies are unplanned.

Business Day (South Africa): Single dose of childbirth HIV drug 'can be fatal'.

Kahn T

Business Day (South Africa), 2008; November 6

Taking just a single dose of nevirapine during childbirth can make a woman resistant to the drug during subsequent treatment, raising the risk of premature death. This is according to interim results from an international study funded by the US National Institutes of Health. Nevirapine is widely used in SA and other developing countries to reduce the risk of an HIV-positive pregnant woman passing the virus on to her baby, and to treat the disease. Each year in SA, about 100000 HIV-positive pregnant women are given a single dose of nevirapine during labour. Researchers involved in the study have called for an urgent review of SA's guidelines for preventing mother-to-child transmission of HIV, saying the problem of nevirapine resistance can be easily fixed by giving mothers a cheap, seven-day course of combivir after their babies are born. "I'm not saying nevirapine should not have been given to these women it was the best we had at the time. What we can do now is protect nevirapine (to ensure it can be safely used in their subsequent treatment)", said study investigator Dr Francesca Conradie of the University of the Witwatersrand's Clinical HIV Research Unit. "Women who received nevirapine during childbirth and were now being treated with a nevirapine-based cocktail should be closely monitored to make sure the drugs were effectively suppressing HIV, and switched to a drug called kaletra if they showed signs of drug resistance", she said. "The longer you leave them on a failing regimen, the greater the risk that they will become resistant to all the drugs they are taking", she said. The optimal combination therapy after nevirapine exposure (Octane) study included 745 women in seven African countries. It compared two AIDS-drug cocktails nevirapine, emtricitabine (FTC) and tenofovir (TDF) or lopinavir-boosted ritonavir, FTC and TDF in two groups of women: those

who got nevirapine during labour, and those who did not. A routine interim review of the trial by an independent data safety monitoring board on October 6 found women who had nevirapine-resistant strains of HIV fared better if they were treated with a regimen that did not contain the drug. Five of the 13 women (38%) who had nevirapine-resistant strains of HIV and were treated with a nevirapine-based cocktail either died or failed to suppress the virus, while all 12 women who had nevirapine-resistant strains of HIV but were treated with a cocktail containing lopinavir-boosted ritonavir were alive and holding the virus at bay. The board recommended that this part of the trial stop, and researchers have begun informing trial participants of their findings. Research is continuing to compare the efficacy of nevirapine and lopinavir-boosted ritonavir in women with no prior exposure to nevirapine.

Benefits of antidepressants during pregnancy outweigh risks
The Practitioner, 2008; October 17

A case-control study has found no link between the duration of antidepressant therapy during pregnancy and the risk of major congenital abnormality. The study identified 2,329 women who were pregnant between January 1998 and December 2002. All women had a recorded diagnosis of at least one major psychiatric disorder, had taken antidepressants for at least 30 days in the year before they became pregnant and had subsequently had a live birth or stillbirth. Paroxetine, sertraline and venlafaxine were the most commonly used antidepressants, although tricyclics and other drugs were also prescribed. The mean duration of therapy during the first trimester was 55 days. Women were assigned to the case group if their infants had at least one major congenital abnormality (8.1% of the study population). The remaining women formed the control group. The most common anomaly was atrial septal defect (12.1% of cases). No link between the risk of major congenital abnormality and the class or type of antidepressant used, or duration of use, during the first trimester was found (OR 1.10, 95% CI 0.75-1.62). Case-control studies have to be interpreted cautiously. The congenital abnormality rate of 8.1% is more than double what might have been expected in the general population. However, poorer socioeconomic status and psychiatric illness, both features of this cohort, are associated with adverse neonatal outcomes. The lack of a link between the type of drug and duration of use in this higher-risk group is useful. The findings reassure me that initiation or maintenance of antidepressant therapy in pregnancy still appears safe relative to the dangers of withholding or stopping treatment.