

Principles of Human Teratology: Drug, Chemical, and Infectious Exposure

This consensus has been reviewed by the Genetics Committee and the Maternal Fetal Medicine Committee and approved by the Executive of the Society of Obstetricians and Gynaecologists of Canada.

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Abstract

Objective: To provide a teratology update for prescription and non-prescription drugs and infections during pregnancy.

Options: Limited to teratology principles and possible common exposures during pregnancy.

Evidence: A search of Medline and textbooks was conducted for information published to June 2006 on teratology exposure risks. This document represents an abstraction of the information.

Benefits, Harms, and Costs: This consensus provides practitioners with a summary of information regarding teratology risks for drug, chemical, and infection exposures during pregnancy.

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INTRODUCTION

Teratology is the study of anomalous fetal development. The categories of teratogenic exposures during pregnancy include drug and chemical agents, infectious agents, physical agents (e.g., ionizing radiation, mechanical factors, and heat), and maternal or metabolic factors (e.g., diabetes and phenylketonuria). This consensus summarizes fetal and maternal factors relating to common drug/chemical (Table 1) and infectious agent (Table 2) exposure during pregnancy; it is not designed to be exhaustive, but it aims to be a rapid resource for clinical use and education.

Approximately 50% of all pregnancies in North America are unplanned,¹ and women whose pregnancies are unintended and unexpected are more likely to be exposed to a wide range of potential teratogens.^{2,3} A recent survey of pregnant women showed that unintended pregnancies are associated with a higher risk for teratogenic exposures during pregnancy than planned pregnancies (alcohol RR 1.9; 95% CI 1.5–2.5; medications RR 3.0; 95% CI 2.0–4.5; cigarette smoking RR 1.5; 95% CI 1.0–2.3; X-rays 2.9; 95% CI 1.1–7.2; any exposure RR 2.0; 95% CI 1.6–2.4).⁴

Rubella, rubeola, and mumps susceptibility in pregnant women was shown to be 9.4%, 16.5%, and 16.3%,

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respectively. Susceptibility to at least one virus was 32.6%, but only 1.7% were at risk for all three viruses.⁵ The background risk of major fetal anomalies identified at birth is estimated at 3%. At five years of age, the risk of major anomalies increases to 4.5%. The etiology of these birth defects is unknown in greater than 50% of anomalous cases. It is not uncommon for a pregnancy to be exposed to multiple teratogenic risk agents, and therefore precise risk advice becomes complicated. This consensus focuses on fetal structural effects/anomalies and does not consider the complications of infectious etiologies or obstetrical outcomes such as premature rupture of membranes and preterm labour or delivery.

PRINCIPLES OF HUMAN TERATOLOGY

1. Characterization of teratogenic exposures involves the specific agent, the dose of the agent, the gestational age, and other factors such as genetic susceptibility (Table 3).⁶
2. Characterization of teratogenic effects includes general effects such as alterations of morphogenesis or CNS function, death, prenatal onset growth deficiency, specific effects like carcinogenesis and recognizable syndromes, magnitude of risk (absolute, relative), and prenatal diagnosis (invasive and non-invasive techniques) (Table 4).⁶
3. Five categories of maternal benefit to fetal risk with respect to drug exposures have been developed by the USFDA. (A, B, C, D, X).⁷ The manufacturer's literature

for some drugs in all categories contains warnings with respect to fetal exposure; this is indicated by "m" in Table 1.

- **Category A:** Controlled studies in women failed to demonstrate a risk to the fetus in the first trimester, and the possibility of fetal harm appeared remote.
 - **Category B:** Either animal reproductive studies have not demonstrated fetal risks but no controlled studies in pregnant women have been reported, or animal reproductive studies have shown an adverse effect that was not confirmed in controlled studies in women in the first trimester.
 - **Category C:** Either studies in animals have revealed adverse effects in the fetus but no controlled studies have been reported, or studies in women and animals are not available. Drugs should be given only if potential benefit justifies the potential risk to the fetus.
 - **Category D:** Positive evidence of human fetal risk exists but the benefits for use in pregnant women may be acceptable despite the risk.
 - **Category X:** Contraindicated in pregnancies: studies in animals or human beings have demonstrated fetal anomalies or evidence exists of fetal risks based on human experience or both, and the fetal risk clearly outweighs any possible benefit.
4. Any drug or chemical given to the mother will cross the placenta to some extent unless it is destroyed or altered during placental passage or its molecular size or lipid solubility limits transplacental transfer. The onset of this placental transfer starts at the fifth embryonic week or seventh gestational week. For drugs or chemicals with low molecular weight, the transmission from placenta to fetus is based on the concentration gradient.⁸
 5. Fetal anatomical anomalies may represent malformations or disruptions when obvious physical changes are identified, but functional or behavioural changes in the fetus, newborn, or child will be more difficult to link to the teratogenic risks.⁶
 6. Recreational, non-prescription, and prescription drug use in pregnancy is common. A WHO survey found that 86% of women took medications during their pregnancy, with an average of 2.9 (range 1–15) prescriptions.⁹ Andrade et al.¹⁰ found that 64% of pregnant women received a drug prescription, not including vitamins or minerals, within 270 days of delivery. Approximately 50% of these prescriptions were in the risk categories C, D, or X. (A: 2.4%, B: 50%, C: 37.8%, D: 4.8%, X: 4.6%) Over-the-counter medications commonly used in pregnancy include acetaminophen (65%), ibuprofen (10%), and pseudoephedrine (15%).¹¹

ABBREVIATIONS

| | |
|-------|--|
| CHD | congenital heart disease |
| CI | confidence interval |
| CL±CP | cleft lip plus/minus cleft palate |
| CMV | cytomegalovirus |
| CNS | central nervous system |
| DES | diethylstilbestrol |
| FAES | fetal alcohol effect spectrum |
| GI | gastrointestinal |
| GU | genitourinary |
| IUGR | Intrauterine growth restriction (birth weight <5th percentile) |
| MR | mental retardation |
| NTD | neural tube defect |
| PCB | polychlorinated biphenyls |
| RR | relative risk |
| SSRI | selective serotonin reuptake inhibitor |
| TORCH | toxoplasmosis, rubella, cytomegalovirus, herpes simplex |
| USFDA | United States Food and Drug Administration |
| WHO | World Health Organization |

Table 1. Drugs/chemicals

| Agent/Drug/Chemical | Risk category | Fetal effects | Fetal risks | Maternal risks |
|--|---------------|--|--|---|
| Prescribed or street drugs | | | | |
| Ethanol ^{6,8,18-20} | D/X | FAES:IUGR, MR, microcephaly, characteristic facies, CHD, joint, skeletal, dermal | 40% risk of FAES 6 drinks/day | — |
| Cocaine ^{6,8,18} | C/X | IUGR, cerebral infarction, bowel atresia, heart, limb, facial, GU tract, vascular disruption | Fetal death | Abruption placenta |
| Toluene ⁶ | X | Toluene embryopathy similar to FAS | Maternal inhalation 10–100 times occupational exposure | — |
| Antimicrobial | | | | |
| Tetracycline ^{6,8,18} | D | Tooth enamel hypoplasia, discoloration of deciduous teeth | Risk in 2nd and 3rd trimester | — |
| Amnioglycoside ^{6,8,18} | | | | |
| Streptomycin | Dm | Hearing loss-in rare cases with prolonged high dose exposure | Risk is mainly in 2nd and 3rd trimester | — |
| Kanamycin | D | | | |
| Gentamycin | C | | | |
| Vancomycin | Bm | | | |
| Fluconazole ^{6,8,21} | Cm | Brachycephaly, cleft palate, arthrogryposis, CHD | Risk in 1st trimester | Treatment of cocecidodomycosis, high dose |
| Efavirenz ^{6,8} | Cm/D | Anencephaly, spina bifida | Risk in 1st trimester | — |
| Metronidazole ⁸ | | No evidence for anomalies | — | — |
| Fluoroquinolones ⁸ | | Impaired cartilage formation in animal studies | Throughout pregnancy | — |
| Trimethoprim-sulam ethoxazole ⁸ | | Impaired bilirubin conjugation | 3rd trimester | — |
| Anticancer | | | | |
| Folic Acid Antagonist ^{6,7,18} | Xm | Increased spontaneous abortion, craniofacial anomalies, skeletal anomalies, limb reduction defects, ectrodactyly, IUGR, stillbirth, neonatal death | 30% risk with 1st trimester exposure (methotrexate) probable increased risk with 1st trimester exposure | — |
| Methotrexate | X | | | — |
| Aminopterin | Dm | | | |
| Alkylating agents ^{6,8} | Dm | IUGR, microphthalmia, cleft palate, GU anomalies, limb reduction defects | | |
| Busulfan | Dm | | | |
| Chlorambucil | | | | |
| Cyclophosphamide | | | | |
| Anticonvulsants | | | | |
| Phenytoin (hydantoin) ^{6,8,18,22} | D | IUGR, mental retardation, microcephaly, facial, heart, hypoplastic nails/distal phalanges, neuroblastoma (increased risk) | 10% syndrome 30% exposure effect | Genetic predis position affects metabolism. |
| Carbamazepine ^{6,8,18,22} | Dm | Lumbo-sacral NTD (1%), facial, fingernail hypoplasia, microcephaly, IUGR, developmental delay | 1st trimester exposure | — |
| Valproic acid ^{6,8,18,22} | Dm | Lumbo-sacral NTD (1%) possible fetal valproate syndrome | 1st trimester exposure | Maternal drug metabolism modifies risk |
| Trimethadione ^{6,8,18} | D | IUGR, CL±CP, microcephaly, facial, mental retardation, ophthalmologic, limb, GU | 60–80% risk with 1st trimester exposure | — |
| Paramethadione | Dm | | | |
| Antihypertensive | | | | |
| ACE inhibitors ^{6,8,18,23} (enalapril, captopril, lisinopril) | Cm/Dm | IUGR, renal tubular dysplasia, oligohydramnios, fetal morbidity, 30% joint contractures, pulmonary hypoplasia | Increased risk with 2nd and 3rd trimester exposure | — |

Table 1 continued

Table 1. Drugs/chemicals (continued)

| Agent/Drug/Chemical | Risk category | Fetal effects | Fetal risks | Maternal risks |
|--|---------------|--|---|--|
| Endocrine | | | | |
| Danazol ^{6,8,18} | Xm | Female virilization | Dose and gestational age dependent | — |
| DES ^{6,8,18} | Xm | Female vaginal, cervical, uterine effects, clear-cell adenocarcinoma | — | — |
| Letrozole ²⁴ | D | Bone, cardiac, and gastrointestinal malformation (abstract: limited information) | — | — |
| Antithyroid ^{6,8} (propylthiouracil, methimazole, carbimazole) | D | Hypothyroidism, cutis aplasia, methimazole embryopathy (choanal atresia, esophageal atresia, hypoplastic nipples, scalp defect, developmental delay) | — | — |
| Oral contraceptives ^{6,8} | Xm | Female masculinization, neonatal hyperbilirubin | Risk 0.3% | — |
| Psychiatric | | | | |
| Lithium ^{6,8,18,25} | D | Congenital heart disease (Ebstein anomaly), neonatal CNS, and neuromuscular complications are increased | — | — |
| SSRI ^{6,8,18,26-31} (Paroxetine) | Cm | no associated birth anomalies reported | Risk/benefit with cautionary recommendation | — |
| Tricyclic antidepressants ^{8,32} | D | (Paxil: cardiac malformations 2%) inconsistent fetal effects small studies show no risk | Risk/benefit with cautionary recommendation | — |
| Bupropion ^{8,22} | Bm | | — | — |
| Heavy metals/ environmental | | | | |
| Lead ^{6,8,18,33} | — | Reduced fetal growth | — | Increased spontaneous abortion and stillbirth |
| Organic mercury ^{6,8,18} | — | Cerebral atrophy, microcephaly, mental retardation, seizures, blindness, spasticity | Exposure in any trimester | Maternal neurotoxicity with fish and grain contamination |
| PCB ⁶ | — | Intrauterine growth restriction, dermal pigmentation, developmental delay | — | — |
| Miscellaneous | | | | |
| Statin (HMG-CoA reductase inhibitors) ^{6,34} | Xm | No associated birth anomalies established (hypothetical risk) | — | — |
| Methyl blue ⁶ | Cm/D | Intra-amniotic exposure associated with possible bowel atresia | Dose dependent | — |
| misoprostol ^{6,8,35} | Xm | Moebius syndrome, terminal transverse limb defects, arthrogyposis, CNS | — | — |
| Penicillamine ^{6,8} | D | Cutis laxa/connective tissue anomaly | — | — |
| Thalidomide ^{6,8} | X | Bilateral limb deficiency, anotia, microtia, cardiac, GI | 20% risk with exposure at 35–50 gestational days. | — |
| Vitamin A ^{6,8,18} (retinol, Vitamin A ₁) | Cm | Microtia, craniofacial, microphthalmia, CL ± CP | Vitamin A risk may require > 30 000 IU/day | — |
| Isotretinoin ^{6,8,18,36} (Accutane) | Xm | microtia, microphthalmia, craniofacial, cardiac, CL ± CP | topical use appears to have no risk | — |
| Warfarin ^{6,8,18,37,38} (Coumadin) | D/X | nasal hypoplasia, stippled bone epiphyses, IUGR, ophthalmologic, CNS, developmental delay | 5–25% risk with 1st trimester exposure | — |

Table 2. Infections

| Agent | Fetal effects | Fetal Risk | Maternal Risks |
|---|--|--|---|
| Bacteria ^{6,18,39} Syphilis | Severe: hydrops, fetal death mild: skin, teeth, or bone anomalies neonatal: rhinitis, rash, liver dysfunction, thrombocytopenia, pneumonia | penicillin treatment given early in pregnancy will prevent congenital infection | complex diagnosis and treatment—refer to appropriate references and an expert |
| Parasite ^{6,18,40–44} Toxoplasmosis | Microcephaly, ventriculomegaly, cerebral calcification, chorioretinitis | Primary infection 9% 1st trimester 60% 2nd trimester can be prevented with early diagnosis and therapy | — |
| Viral | | | |
| Rubella ^{6,18,45–47} | Microcephaly, cataracts, deafness, mental retardation, congenital heart disease, certain deficits may not be apparent in the neonatal period | Primary infection 50% 1st trimester 6% 2nd trimester congenital: | — |
| CMV ^{6,18,48–51} | | 40% primary exposure | — |
| Parvo virus B19 ^{6,52–58} | Microcephaly, ventriculomegaly, cerebral calcifications, mental retardation, IUGR, deafness, ocular, hepatitis, thrombocytopenia, late diagnosis in 10–15% but 90% of infected infants are asymptomatic at birth. | 20% secondary exposure infected/affected: 20% primary exposure 8% secondary exposure | — |
| Varicella ^{6,18,59,60} | | | — |
| Herpes simplex ^{6,61–65} | Severe anemia, hydrops which can result in death, cardiomyopathy Microcephaly, cataracts, chorioretinitis, skin scarring, hypoplasia hands/feet, muscle atrophy, IUGR transplacental transmission is rare, CNS, ophthalmologic, IUGR, skin lesions | — 1–2% with < 20 week exposure — | — |

7. Lo et al.¹² found that teratogenic risks were undetermined for 91.2% of drug treatments approved in the United States from 1980 to 2000. There was inadequate information to determine whether the benefits exceed the teratogenic risks for most drug treatments introduced in the past 20 years. Marcus and Snodgrass¹³ recommend that obstetricians advise women not to expose their fetuses to the risks of herbal medications. The quality control is variable and there is inadequate information regarding toxicity. Friedman¹⁴ emphasizes that dietary supplements cannot be assumed to be safe for the embryo or fetus. Dietary supplements should not be labelled for use in pregnancy unless they have been shown to be safe by standard scientific methods.
8. Recognized effects of certain fetal infections include death, intrauterine growth restriction, congenital defects, and mental retardation. The pathogenesis of these anomalies can generally be ascribed to direct fetal infection, which may be associated with inflammation of fetal tissues and cellular death.⁶
9. Serological studies in the mother and infant may be helpful, but TORCH screening alone is usually insufficient in newborns with suspected congenital infection, since diagnosis of in utero infection requires time-sensitive serologic studies, evaluation of seroconversion, and, potentially, identification of the infectious agent.¹⁵

Table 3. Characterization of teratogenic exposures*

| | |
|---------------------------|---|
| Agent | Nature of the chemical, physical or infectious agent Inherent developmental toxicity Capacity to produce other kinds of toxicity in the mother |
| Dosage to embryo or fetus | Single, repeated, or chronic exposure Duration of exposure Maternal dose Maternal route of exposure Maternal absorption Maternal metabolism and clearance Placental transfer |
| Period of pregnancy | Between conception and onset of embryogenesis Embryogenesis Fetal period |
| Other factors | Genetic susceptibility of mother Genetic susceptibility of the fetus Other concurrent exposures Maternal illness or other condition associated with exposure Availability of tests to quantify the magnitude of maternal exposure |

*adapted from Friedman and Hanson⁶

Table 4. Characterization of teratogenic effects*

| |
|--|
| General effects |
| Alterations of morphogenesis |
| Alterations of CNS function |
| Other functional impairments |
| Death of the conceptus, embryo, or fetus |
| Prenatal-onset growth deficiency |
| Carcinogenesis |
| Specific effects |
| Recognizable syndrome |
| Other distinctive features |
| Magnitude of risk |
| Absolute |
| Relative |
| Prenatal diagnosis |
| Detailed ultrasound examination |
| Amniocentesis or other invasive method |
| Availability |
| Reliability |
| Utility |

*adapted from Friedman and Hanson⁶

Additional perinatal consultations with an infectious disease specialist may be required.

- There is no specific constellation of fetal/neonatal signs and symptoms that is pathognomonic of infection. Each infectious agent, depending on time of exposure and viral host interactions, can result in a diverse range of manifestations.⁶
- Routine screening for teratogenic risk from infectious agents is currently limited to rubella, syphilis, hepatitis B, human immunodeficiency virus, and varicella (history or serology). Additional screening should be individualized.¹⁶⁻¹⁸

REFERENCES

- Henshaw SK. Unintended pregnancy in the United States. *Fam Plann Perspect* 1998;30:24-9, 46.
- Daniel KL, Honein MA, Moore CA. Sharing prescription medication among teenage girls: potential danger to unplanned/undiagnosed pregnancies. *Pediatrics* 2003;111:1167-70.
- Naimi TS, Lipscomb LE, Brewer RD, Gilbert BC. Binge drinking in the preconception period and the risk of unintended pregnancy: implication for women and their children. *Pediatrics* 2003;111:1136-41.
- Han JY, Nava-Ocampo AA, Koren G. Unintended pregnancies and exposure to potential human teratogens. *Birth Defects Res A Clin Mol Teratol* 2005;73:245-8.
- Haas DM, Flowers CA, Congdon CL. Rubella, rubeola, and mumps in pregnant women. Susceptibilities and strategies for testing and vaccinating. *Obstet Gynecol* 2005;106(2):295-300.

- Friedman JM, Hanson JW. Clinical Teratology. In Rimoin DL, Connor JM, Pyeritz RE, Korf BR, eds. *Emery and Rimoin's principles and practice of medical genetics* 4th ed. New York: Churchill Livingstone; 2002:1011-45.
- Food and Drug Administration (Federal Register 1980;44:37434-67).
- Briggs GG, Freeman RK, Yaffe SJ. *Drugs in pregnancy and lactation*. 7th ed. Philadelphia: Lippincott Williams and Wilkins; 2005.
- Collaborative Group on Drug Use in Pregnancy. An international survey on drug utilization during pregnancy. *International Journal of Risk and Safety in Medicine* 1991;1:1.
- Andrade SE, Gurwitz, JH, Davis RL, Chan KA, et al. Prescription drug use in pregnancy. *Am J Obstet Gynecol* 2004;191:398-407.
- Werler MM, Mitchell AA, Hernandez-Diaz S, Honein MA. National Birth Defects Prevention Study. *Am J Obstet Gynecol* 2005;193:771-7.
- Lo WY, Friedman JM. Teratogenicity of recently introduced medications in human pregnancy. *Obstet Gynecol* 2002;100(3):465-73
- Marcus DM, Snodgrass WR. Do no harm: avoidance of herbal medicines during pregnancy. *Obstet Gynecol* 2005;105(5) part 1:1119-22.
- Friedman JM. Teratology society: presentation to the FDA public meeting on safety issues associated with the use of dietary supplements during pregnancy. *Teratology* 2000;62:134-7.
- Remington JS, Klein JO. *Infectious diseases of the fetus and newborn Infant*. 4th ed. Philadelphia: WB Saunders; 2005:140-267.
- Schrag SJ, Arnold KE, Mohle-Boetani JC, Lynfield R, Zell ER, Stefonek K, et al. Prenatal screening for infectious diseases and opportunities for prevention. *Obstet Gynecol* 2003;100(3):465-73.
- Reddy UM, Baschat AA, Zlatnik MG, Towbin JA, Harman CR, Weiner CP. Detection of viral deoxyribonucleic acid in amniotic fluid: association with fetal malformation and pregnancy abnormalities. *Fetal Diagn Ther* 2005;20:203-7.
- American College of Obstetrician and Gynecologists. *Ultrasonography in pregnancy*. ACOG Technical Bulletin 236. Washington, DC: ACOG, April 1997.
- Loock C, Conry J, Cook J. Identifying fetal alcohol spectrum disorder in primary care. *CMAJ* 2005;172(5):628-30.
- Chudley AE, Conry J, Cook, JL, Loock C, Rosales T, LeBlanc N; Public Health Agency of Canada's National Advisory Committee on Fetal Alcohol Spectrum Disorder. Fetal alcohol spectrum disorder: Canadian guidelines for diagnosis. *CMAJ* 2005;172(5):S1-S21.
- Lopez-Rangel E, Van Allen MI. Prenatal exposure to fluconazole: an identifiable dysmorphic phenotype. *Birth Defects Res A Clin Mol Teratol* 2005;73:919-23.
- Artama M, Auvinen A, Raudaskoski T, Isojärvi I, Isojärvi J. Antiepileptic drug use of women with epilepsy and congenital malformations in offspring. *Neurology* 2005; 64:1874-8.
- Alwan S, Polifka JE, Friedman JM. Angiotensin II Receptor antagonist treatment during pregnancy. *Birth Defects Research (Part A): Clinical and Molecular Teratology* 2005;73:123-30.
- Biljan MM, Tkalec DD, Lachgar H. The outcome of 150 babies following the treatment with letrozole or letrozole and gonadotropins. *Fertil Steril* 2005;84(supp 1):S95.
- Newport DF, Viguera AC, Beach AJ, Ritchie JC, Cohen LS, Stowe ZN. Lithium placental passage and obstetrical outcome: implications for clinical management during late pregnancy. *Am J Psychiatry* 2005;162:2162-70.
- Wen SW, Walker M. The use of selective serotonin reuptake inhibitors in pregnancy. *J Obstet Gynaecol Can* 2004;26:819-22.
- Koren G, Matsui D, Einarson A, Knoppert D, Steiner M. Is maternal use of selective serotonin reuptake inhibitors in the third trimester of pregnancy harmful to neonates? *CMAJ* 2005;172(11):1457-9.

28. Peck P. manufacturer warns of potential birth defects with Paxil. 2004–5 MedPage Today.
29. Sanz EJ, De-las-Cuevas C, Kiuru A, Bate A, Edwards R. Pregnancy paroxetine use linked to neonatal withdrawal. *Lancet* 2005;365:482–7, 451–453.
30. Malm H, Klaukka T, Neuvonen. Risks associated with selective serotonin reuptake inhibitors in pregnancy. *Obstet Gynecol* 2005;106(6):1289–96.
31. Chambers CD, Hernandez-Diaz S, Van Marter LJ, Werler MM, Louik C, Jones KL, et al. Selective Serotonin-reuptake inhibitors and risk of persistent pulmonary hypertension of the newborn. *N Engl J Med* 2006;354(6):579–87.
32. Wen SW, Walker M. Risk of fetal exposure to tricyclic antidepressants. *J Obstet Gynaecol Can* 2004;26(10):887–92.
33. Beller DC. Teratogen update: lead and pregnancy. *Birth Defects Research (Part A)* 2005;73:409–20.
34. Pollack PS, Shields KE, Burnett DM, Osborne MJ, Cunningham ML, Stepanavage ME. Pregnancy outcomes after maternal exposure to simvastatin and lovastatin. *Birth Defects Res A Clin Mol Teratol* 2005;73:888–96.
35. Yedlinsky NT, Morgan FG, Whitecar PW. Anomalies associated with failed methotrexate and misoprostol termination. *Obstet Gynecol* 2005;105(5:2):1203–5.
36. Robertson J, Polifka JE, Avner M, Chambers C, Delevan G, Koren G, et al. A survey of pregnant women using isotretinoin. *Birth Defects Res A Clin Mol Teratol* 2005;173:881–7.
37. van Driel D, Wesseling J, Sauer PJ, van der Veer E, Touwen B.C., Smrkovsky M. In utero exposure to coumarins and cognition at 8 to 14 years old. *Pediatrics* 2001;107:123–9.
38. Finkelstein Y, Chitayat D, Schechter T, Keating S, Toi A, Koren G. Warfarin embryopathy following low-dose maternal exposure. *J Obstet Gynaecol Can* 2005;27:702–6.
39. Jones H, Taylor D, Montgomery CA, Patrick DM, Money D, Vipond JC, et al. Prenatal and congenital syphilis in British Columbia. *J Obstet Gynaecol Can* 2005;5:467–72.
40. Foulon W, Villena I, Stray-Pedersen B, Decoster A, Lappalainen M, Pinon JM, et al. Treatment of toxoplasmosis during pregnancy: A multicenter study of impact on fetal transmission and children's sequelae at age 1 year. *Am J Obstet Gynecol* 1999;180(2;1):410–5.
41. Antsaklis A, Daskalakis G, Papanioniou N, Mentis A, Michalis S. Prenatal diagnosis of congenital toxoplasmosis. *Prenat Diagn* 2002; 22:1107–11.
42. Montoya JG, Liesenfeld O. Toxoplasmosis. *Lancet* 2004;363:1965–76.
43. Boyer KM, Holfels E, Roizen N, Swisher C, Mack D, Remington J, et al. Risk factors for *Toxoplasma gondii* infection in mothers of infants with congenital toxoplasmosis: implications for prenatal management and screening. *Am J Obstet Gynecol* 2005;192:564–71.
44. Chen KT, Eskild A, Bresnahan M, Stray-Pedersen B, Sher A, Jenum PA. Previous maternal infection with *Toxoplasma gondii* and the risk of fetal death. *Am J Obstet Gynecol* 2005;193:443–9.
45. Gyorkos TW, Tannenbaum TN, Abrahamowicz M, Delage G, Carsley J, Marchand S. Evaluation of rubella screening in pregnant women. *CMAJ* 1998;159(9):1091–97.
46. Banatvala JE, Brown DWG. Rubella. *Lancet* 2004;363:1127–37.
47. Rittler M, Lopez-Camelo J, Castilla EE. Monitoring congenital rubella embryopathy. *Birth Defects Res A Clin Mol Teratol* 2004;70:939–43.
48. Guibaud L, Attia-Sobol J, Buenerd A, Foray P, Jacquet C. Focal sonographic periventricular pattern associated with mild ventriculomegaly in foetal cytomegalic infection revealing cytomegalic encephalitis in the third trimester of pregnancy. *Prenat Diagn* 2004;24:727–32.
49. Picone O, Costa JM, Dejean A, Ville Y. Is fetal gender a risk factor for severe congenital cytomegalovirus infection? *Prenat Diagn* 2005; 25: 34–8.
50. Nigro G, Adler SP, LaTorre R, Best AM, for the Congenital Cytomegalovirus Collaborating Group. Passive immunization during pregnancy for congenital cytomegalovirus infection. *N Engl J Med* 2005;353(13):1350–62.
51. Duff P. Immunotherapy for congenital cytomegalovirus infection. *N Engl J Med* 2005;353(13):1402–4.
52. Dieck D, Schild RL, Hansmann M, Eis-Hübinger AM. Prenatal diagnosis of congenital parvovirus B19 infection: value of serological and PCR techniques in maternal and fetal serum. *Prenat Diagn* 1999;19:1119–23.
53. Von Kaisenberg CS, Jonat W. Fetal parvovirus B19 infection. *Ultrasound Obstet Gynecol* 2001;18:280–8.
54. Crane J, Boucher M. Parovirus B19 infection in pregnancy. SOGC Clinical Practice Guideline, No. 119, September 2002. *J Obstet Gynaecol Can* 2002;24:727–34.
55. Nyman M, Tolfvenstam T, Petersson K, Krassny C, Skjöldebrand-Sparre L, Broliden K. Detection of human parvovirus B19 infection in first-trimester fetal loss. *Obstet Gynecol* 2002;99(5:1):795–98.
56. Mostello D, Holcomb WL, Talsky JM, Winn HN. Fetal parvovirus B19 infection. Doppler studies allow noninvasive treatment of Ascites. *J Ultrasound Med* 2004;23:557–60.
57. Enders M, Weidner A, Zoellner I, Searle K, Enders G. Fetal morbidity and mortality after acute human parvovirus B19 infection in pregnancy: prospective evaluation of 1018 cases. *Prenat Diagn* 2004;24:513–8.
58. Weir E. Parvovirus B19 infection: fifth disease and more. *CMAJ* 2005;172(6):743.
59. Harger JH, Earnest JM, Thurnau GR, Moawad A, Thom E. Frequency of congenital varicella syndrome in a prospective cohort of 347 pregnant women. *Obstet Gynecol* 2002;100(2):260–5.
60. Verstraelen H, Vanzieleghem B, Defoort P, Vanhaesebrouck P, Temmerman M. Prenatal ultrasound and magnetic resonance imaging in fetal varicella syndrome: correlation with pathology findings. *Prenat Diagn* 2003;23:705–9.
61. Brown ZA, Wald A, Morrow RA, Selke S, Zeh J, Corey L. Effect of serologic status and cesarean delivery on transmission rates of herpes simplex virus from mother to infant. *JAMA* 2003;289(2):203–9.
62. Watts DH, Brown ZA, Money D, Selke S, Huang ML, Sacks SL, et al. A double-blind, randomized, placebo-controlled trial of acyclovir in late pregnancy for the reduction of herpes simplex virus shedding and cesarean delivery. *Am J Obstet Gynecol* 2003;188:836–43.
63. Sheffield JS, Hollier LM, Hill JB, Stuart GS, Wendel GD Jr. Acyclovir prophylaxis to prevent herpes simplex virus recurrence at delivery: a systematic review. *Obstet Gynecol* 2003;102(6):1396–403.
64. Frenkel LM. Challenges in the diagnosis and management of neonatal herpes simplex virus encephalitis. *Pediatrics* 2005;115(3):795–7.
65. Brown ZA, Gardella C, Wald A, Morrow RA, Corey L. Genital herpes complicating pregnancy. *Obstet Gynecol* 2005;106(4):845–56.
66. Motherisk [website]. The Hospital for Sick Children/University of Toronto. Available at: <http://www.motherisk.org>. Accessed September 19, 2007.
67. Clinical Teratology Web. A resource guide for clinicians [website]. TERIS (Teratogen Information System) Program. University of Washington. Available at: <http://depts.washington.edu/~terisweb/>. Accessed September 19, 2007.