Principles of Teratology; Treating The Mother-Protecting the Unborn

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Motherisk Program
and Ivey Chair in Molecular Toxicology
Motherisk: 1985-2010

- 65 trainees from 35 countries
- Motherisk Services initiated by our trainees:
  - Australia
  - Israel
  - Brazil
  - Italy
  - Canada
  - Japan
  - South Korea

Soon to start:
- Hong Kong
- India
- Sweden
Motherisk Sponsors

- **National Sponsor**: Shoppers Drug Mart
- **NVP Line Sponsor**: Duchesnay Inc.
- **Alcohol-Drug Helpline Sponsor**: Brewers Association of Canada
Motherisk- Knowledge Transfer

- 900 peer review papers
- 15 medical books
- Website visits: 200,000/mo
  (www.motherisk.org)

Monthly columns:
- Canadian Family Physician
Motherisk-Selected Faculty

- **Shinya Ito** MD, FRCPC: Drugs in breastfeeding
- **Irena Nulman** MD, FRCPC: Long term neurodevelopment
- **Joanne Rovet** PhD: FASD
- **Tom Einarson** PhD: Meta analysis
- **Buhshah Kapur** PhD: Toxicology analysis
Drugs in Pregnancy-The issues

- Only half of all pregnancies are planned
- Many women need medications for pregnancy induced conditions (e.g. Morning Sickness), chronic conditions (e.g. Epilepsy), intercurrent conditions (Allergies)
- Women work with chemicals, exposed to radiation and use illicit drugs
- During embryogenesis-drugs & chemicals may adversely affect development
Situational Analysis

- A) Anxiety of birth defects:
  - Leads women not to take medications during pregnancy & lactation.
  - Leads pharmaceutical companies not to develop drugs for pregnant & lactating women.

- B) Women are not treated appropriately even after first trimester, or for life threatening conditions
Perception of Teratogenic Risk(1)

- Even when exposed to non-teratogenic drugs—women assign 25% teratogenic risk (Am J Obstet Gynecol 1989)

- Evidence-based counseling can prevent unnecessary pregnancy terminations (Teratology 1990)
Perception of Teratogenic Risk (2)

- Following the Chernobyl disaster-half of all pregnancies in Athens were terminated (Trichopoulos, BMJ, 1987)
- Women exposed to diagnostic radiation assign major teratogenic risk (Bentur, Teratology, 1991)
Misperception and Pregnancy Terminations

9/200 women on quinolones terminated pregnancy vs. 2/200 controls [RR 4.5 (95% CI .98-20.6)]

Bar Oz et al (In Press):
First trimester MMR vaccine
7/94 vs 0/95 terminations (p=.007)

Cohen Kerem et al (2004): 7/198 diagnostic radiation terminated vs. 0/198 controls (p<.04)
Shepard’s Principles of Teratology

- The agent must be present during the critical periods of development
- Experimental models corroborating the findings (i.e., biological plausibility)
- Acts directly on the embryo-fetus or on the placenta
Case 1

- 25 y.o. aboriginal woman, northern reserve
- Diagnosed with Gestational Diabetes at 24 wk gestation
- Instructed to start insulin therapy
- 2 d later the nurse finds out she is reluctant to start insulin injections
- ???????????????/
Gestational Diabetes

- Affects up to 10% of pregnant women
- Glucose intolerance in third trimester
- Strong predictor of later Type 2 diabetes
- Results in higher rates of pre-eclampsia, fetal distress, macrosomia, neonatal hypoglycemia
- Managed by diet-insulin (if needed)
Glyburide

- **Fear**: oral hypoglycemics cross placenta—neonatal hypoglycemia
- Langer et al (NEJM 2001): Glyburide as effective and safe as insulin
  Undetectable umbilical cord levels with therapeutic maternal levels (50-150 ng/ml)
- **Mechanisms**: high protein binding (99.8%), short T1/2 (2-6 hr), BCRP transporter substrate.
Perfusion System

- Maternal Artery
- Maternal Vein
- Fetal Artery
- Fetal Vein
- Maternal Pump
- Fetal Pump
- Maternal Perfusate
- Fetal Perfusate

- 95% O2
- 5% CO2
- 95% N2
- 5% CO2

= Sampling Port
Fetal Safety of Glyburide

- Meta analysis (Motherisk 2006)- glyburide vs insulin
- Macrosomia - OR 1.04 (.74-1.45)
- Birth weight: WMD 17g (-44-80)
- Gestational age: WMD 0 (-.28-.27)
- Neonatal hypoglycemia OR 1.33 (.99-1.79)
- In Langer’s study: 18/201 vs. 12/203
  (OR 1.57 (.73-3.34)
Case 2

- 11 days full term baby
- Appeared not to feed well, dusky color
- At 10d- pediatric assessment “gained his birth weight”
- Day 11- not feeding, sleeping
- Found dead
- PM: negative
- Morphine in blood: 80ng/ml
- Mom prescribed codeine as Tylenol 3 for episiotomy
- Took the drug throughout
Case 2-cont’d

- Mother and grandmother: Ultra rapid metabolizers of P450 2D6
- Stored milk: 80ng/ml of morphine
- Levels described in literature: up to 5ng/ml

Lancet, Aug 18, 2005
Codeine Use During Breastfeeding in Canada

~ 129,000 Canadian breastfeeding mothers per year are prescribed codeine post-partum

- 340,000 births per year
- 73% breastfed
- 52% caesarian sections
Codeine is compatible with breastfeeding

Last updated in 2001

Based on three reports in which breast milk levels were measured and found to be low
Codeine Metabolism

- Codeine
- CYP2D6
- UGT2B7
- Codeine 6-glucuronide
- Norcodeine

- Morphine
- CYP3A4
- UGT2B7
- Morphine 3-glucuronide
- Norcodeine 6-glucuronide

- Morphine 6-glucuronide

Opioid activity in brain

Liver

Kidney
171 mothers interviewed

99 mothers excluded
did not take codeine, cough syrup, other CNS meds

Symptomatic
17
CNS Depression in infant

Asymptomatic
55
No CNS Depression

Results

Maternal DNA

Genotype CYP2D6
Genotype UGT2B7
Results

- 17 (24%) infants exhibited CNS depression
  - Major decrease in alertness during codeine compared to period without codeine

- Good concordance between maternal and infant CNS depression
  - 71% infant and mother CNS depressed
  - 10% mother only CNS depressed
# Codeine dosing

<table>
<thead>
<tr>
<th></th>
<th>Mothers of symptomatics (n = 17)</th>
<th>Mothers of asymptomatics (n = 55)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total codeine dose (mg/kg/d)</td>
<td>1.62 (0.79)</td>
<td>1.02 (0.54)</td>
<td>0.004</td>
</tr>
<tr>
<td></td>
<td>mean (SD)</td>
<td>range: *0.63-3.64</td>
<td></td>
</tr>
<tr>
<td>Codeine duration (d)</td>
<td>7 (1-180)</td>
<td>4 (1-180)</td>
<td>0.49</td>
</tr>
<tr>
<td></td>
<td>median (min-max)</td>
<td>range: 0.18-2.7</td>
<td></td>
</tr>
</tbody>
</table>

* 0.63 mg/kg/d = 44 mg in a 70 kg woman
  = 1.5 tab Tylenol 3
  = 3 tab Tylenol 2

Statistically significant p<0.05
## Genotype Results

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Symptomatic</th>
<th>Asymptomatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>2D6 UM and UGT2B7*2/*2</td>
<td>2/17</td>
<td>0/55 (0%)</td>
</tr>
<tr>
<td></td>
<td>(11.8%)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Symptomatic</th>
<th>Population</th>
<th>P-value</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>2D6 UM and UGT2B7*2/*2</td>
<td>11.8%</td>
<td>1-2%</td>
<td>&lt;0.001</td>
<td>7.84</td>
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</tbody>
</table>
FDA Public Health Advisory
Use of Codeine By Some Breastfeeding Mothers May Lead To Life-Threatening Side Effects in Nursing Babies

August 17, 2007
Case 3
Codeine Pharmacogenetics in Toddlers

- A 2 yr male toddler with Obstructive Sleep Apnea
- Otherwise healthy
- Underwent tonsillectomy as outpatient
- Was released home in the afternoon
- Received syrup codeine 10-12.5mg po q4-q6 prn
- Was found dead next morning
Case 3-cont’d

- Femoral blood-32ng/ml morphine
- CYP2D6 genotyping:
- Functional duplications of 2D6 alleles
- UM phenotype
- Presently; No genetic testing is done
- In 15-20% cases-no reversal of sleep apnea after surgery

*NEJM 2009*
Case 4

- A 29y.o. G2P1 woman, 4 wk gestation
- Very severe morning sickness in previous pregnancy (dehydration, repeated hospitalizations)
- Very concerned now about a repeat of a similar experience
Nausea and Vomiting of Pregnancy (NVP)

* NVP affects 80% of pregnant women
* Bendectin (doxylamine-pyridoxine) was used by 40% pregnant American women in 1978
* Due to litigations-drug removed in 1983 despite scientific/FDA support
* 2-3 fold increase in hospitalization rates for NVP in USA

In Canada: Diclectin use is increasing-
Temporal decrease in hospitalizations
U.S.A. Temporal Trends for Limb Reduction Deformities, Bendectin Sales, and Hospitalizations for NVP
Rate of Hospitalization in Canada

Case 5

- 32y.o woman with depression
- Well balanced on venlafaxin (effexor)
- At 4 wk gestation: told by her pharmacist that the drug may not be safe for the baby in pregnancy, and post partum
- She d/c her medication and her depression symptoms re appear
Depression in Pregnancy

* Affects up to 20% of pregnant women
* SSRI appear safe (both dysmorphology & neurobehavior) (Nulman et al 1996, 2002)
  - Neonatal Discontinuation Syndrome
  - Women commonly D/C therapy; high morbidity (Einarson et al 2001)
* Those treated—very low average doses (Nulman 2003)
Antidepressants-Malformation Rates (1)

- After 15 yrs of reassuring data-recent reports of excess cardiac malformations, mostly with paroxetine
- Led FDA & Health Canada to add warnings to label
- The studies are contradictory
- Recent meta analysis-no increased risk
Antidepressants-Malformations (2)

- Motherisk (2008): over 1000 prospectively collected paroxetine cases - 0.7% cardiac malformations, similar to the control group, and to literature (Am J Psychiatr)

- Admin database studies: chance of detection bias - depressed women more likely to see physicians and having children examined
“Cold Turkey Syndrome”

- Many women discontinue SSRI/SNRI in pregnancy due to concerns and misinformation
- Many women receive small, ineffective doses
- D/C treatment: increased risk of morbidity, depression, hospitalization, drug abuse
- Discontinuation syndrome in adults—well characterized
- Depression in late pregnancy—the strongest predictor for postpartum depression
Poor Neonatal Adaptation Syndrome

- 10-30% of exposed babies - jittery, unconsolable, tremor, diarrhea, respiratory distress - resolved spontaneously within 3-5 days
- Mostly discontinuation syndrome
- Rarely - dopaminergic syndrome (Knoppert, TDM 2006)
- Treatment with an SSRI?
- Indication for neonatal TDM
Persistent Pulmonary Hypertension of the Newborn

- Increased OR of SSRIs in cases of PPHN
- No case of SSRI-PPHN death in series
- Attributable risk: less than 1% of SSRI exposure (Chambers, NEJM, 2006)
- Produced in rats with fluoxetine (Bialek, 2008)
- This may be a mechanism for the respiratory distress
Antidepressants-Neurobehavioral Effects

Nulman (1996): IQ, language, behaviors-similar among prozac, tricyclic-exposed and controls (NEJM)

Nulman (2001): Maternal depressive syndromes, and not medications, affect adversely child achievements

Corroborated by recent studies with other SSRIs

- New Motherisk study with Venlafaxine
Antidepressants-Breastfeeding

- Normalized dose (per Kg) of SSRIs-SNRIs in milk: <5% of maternal dose
- Suggestion of lower postnatal growth rate- probably correlate with maternal depressive symptoms
- SSRIs in milk may partially mitigate neonatal withdrawal
Case 6

- A neonate born with Apgar 2 (1 min) after Placental Abruption
- Tremolous, seizures, intracranial bleeding
- Mother denies any illness or drug use
- Neonatal urine – negative for drugs of abuse
- Neonatal hair – highly positive for cocaine and benzoyleggonine
Physiology of the Hair Shaft

- Cuticle
- Trapped Detectable Toxins
- Cortex
- Skin
- Artery
- Vein
Prevalence of In Utero Exposure to Cocaine in Toronto (1990-1)
a random study of 600 cases

- 37/600 babies positive for cocaine
- 34 in hair test
- 9 urine test
- 7 maternal interviews
- Without hair test - 75% of cases would have been missed
- Neonatal hair - last 3 mo. of pregnancy = evidence of maternal addiction
Major Medicinal Teratogens (1)

- **Antiepileptics**
  - Carbamazepine-NTD(1%)
  - Valproate-NTD(2%); other malformations (Holmes 2003)
  - Phenytoin: Fetal Hydantoin Syndrome(10-15%?)

- **ACE inhibitors**: renal insufficiency, hypocalvaria

- **Lithium**: Ebstein’s anomaly(1/5000)

- **Coumadin**: Fetal Warfarin Syndrome
Actually FHS, as it was delineated was described some 7 years earlier by McLean. Cases had severe harelip and cleft palate features, including congenital heart lesions. The infants had unusual facies and skeletal anomalies.
Major Human Teratogens

- **Isotretinoin**: 50% malformation rate
- **SMART program to prevent fetal exposure** - fetuses still exposed
- **Leflunamide**: Human levels teratogenic in animals; prospective study (n=40) still negative
- **Thalidomide**: for leprosy, HIV, Drug vs Host
- **Misoprostol**: Moebius sequence; high attributable risk, very low overall risk.
Prozac product monograph (2004): “Safe use in pregnancy has not been established. Therefore, it should not be administered to women of childbearing age unless, in the opinion of the treating physician, the expected benefits to the patient markedly outweigh the possible hazards to the child or fetus.”
Labeling(2)

Scientific reality:
Till Dec. 2003:

- 6 dysmorphology studies
- 3 neurodevelopmental studies
- One meta analysis
- All showing apparent safety
Conclusions

- Pregnant and lactating women are commonly orphaned from the benefits of drug therapy, even when solid data on safety/effectiveness exist.
- Change labeling system
- Allow evidence-based counseling
- Always consider the risk of untreated maternal condition
Case 5

- A 39 y.o G1P0 woman has hypertension treated successfully with an ACE inhibitor
- She sees her doctor at 4 wks gestation
- He refers her to Motherisk
- We recommend to d/c ACE inhibitor due to potential risk of fetal renal damage and hypocalvaria
Fetal Safety of Antihypertensive Drugs (1)

- Hypertensive disorders in 5% of all pregnancies
- Many of these women require medications
- **ACE Inhibitors**: fetal/neonatal renal insufficiency, hypocalvaria; inconclusive evidence of first trimester embryopathy
Antihypertensive Drugs (2)

- **Ca++ channel blockers**: incomplete but reassuring data
- **Beta blockers**: a trend toward IUGR (atenolol more than the other?)
- **Diuretics**: theoretical concerns around decreased uterine blood flow - not proven by a meta analysis
Drugs of Choice in Pregnancy

- **Methyl Dopa**: no apparent risk of adverse perinatal outcomes
- One neurodevelopmental study to 7.5 yr of age: children developed similar to controls
- **Labetalol**: no evidence of IUGR
- No study on neurodevelopment
Motherisk study (1)

- Prospective cohort, controlled
- Children born 1996-2001
- Labetalol (n=32)
- Methyldopa (n=25)
- Controls (n=53)
Motherisk study

- **Outcome measures:**
  - Child verbal, performance, and full scale IQ
  - Attention
  - Executive processing
  - Language
  - Memory
  - Learning
  - Maternal IQ-confounder
  - SES-confounder
Results(1)

- Mothers with hypertension-older
- No differences in alcohol, cigarettes, SES
- Mothers in methyldopa treated for longer periods in pregnancy (27.6+/-12.7 vs. 198.8+/-14.2 wk)
- Methyldopa: trends toward lower maternal IQ
Results(2)

- Prematurity rates:
  - LBT-28%
  - Met-20%
  - Controls-4%
<table>
<thead>
<tr>
<th></th>
<th>LBT</th>
<th>NTC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verbal IQ</td>
<td>110+/-8</td>
<td>112+/-11</td>
</tr>
<tr>
<td>Perfor. IQ</td>
<td>105+/-8</td>
<td>109+/-12</td>
</tr>
<tr>
<td>FSIQ</td>
<td>112+/-11</td>
<td>105+/-11</td>
</tr>
</tbody>
</table>
Methyldopa scores
lower than controls for FSIQ (105 +/- 12) vs 112 +/- 11) and
Perf.IQ (109 +/- 12 VS 99 +/- 16)
Multivariate analysis:
Groups, maternal FIQ, age at testing, maternal age:
MET-significant predictor of lower child FIQ
No differences in other achievements
Conclusions

- Labetalol is not associated with neuro developmental deficits
- Methyldopa may be associated with lower FIQ
Late Pregnancy; Pharmacokinetic Changes

- Dempsy & Benowitz (2002): Increased nicotine clearance rate
- Heikkinen (2003): Increased fluoxetine apparent clearance rate
- Increased clearance rate of digoxin, lithium
- Increased hepatic blood flow, GFR, lower protein binding, lower compliance rate
- NEED FOR HIGHER DOSES
Critical Care-Issues (1)

- **Diagnostic Radiation** - use lead apron for non abdominal procedures
- Essential abdominal procedures - should go ahead
- **Average Fetal Exposure:**
  - Lumbosacral spine: 150-500mR
  - Upper GI: 245mR
  - Barium Enema: 700-1500mR
  - IVP: 800-1400mR
  - Abdominal CT: 640mR
  - Lumbar Spine: 2500mR
Critical Care- Issues (2)

- Main Antimicrobials - not teratogenic
- Penicillins
- Cephalosporins
- Aminoglycosides
- Sulfonamides - anti folates - NTD
- Quinolones - safe in humans
Critical Care-Issues (3)

- Sympatomimetics- not teratogenic in humans
- Bronchodilators-non teratogenic
- **Maternal –Fetal Conflict:** maternal well being must prevail
- Ensure the family is well informed
- Ensure a perinatologist is on the team
HOSPITALIZATION SEPARATIONS VERSUS BENDECTIN/DICLECTIN DRUG SALES

Separation/1,000 births

Prescriptions (1000s)

Hospitalization for vomiting

Bendectin

Diclectin

Year of hospitalization
Fetal Safety of Metformin

- Motherisk meta analysis
- 1% malformation rate in metformin
- 7% among disease matched controls (p<0.01)

Potential protective effect
Possibly because of improvement in insulin resistance and in androgen status

Use of metformin throughout pregnancy for maternal diabetes- appears safe (NEJM 2009)
Fetal Safety of Oral Hypoglycemics

- 10 studies
- 471 exposed; 1,344 controls
- Major malformations: OR 1.05 (0.65-1.7)
- Neonatal death: OR 1.16 (0.67-2)
Preemptive use of antinauseants can mitigate the risk of reoccurrence (J Obst Gynaecol 2006)

G.E. Reflux increases the severity of NVP

Treatment of reflux symptoms improves NVP symptoms (Motherisk, 2008)