Prescription drugs in pregnancy

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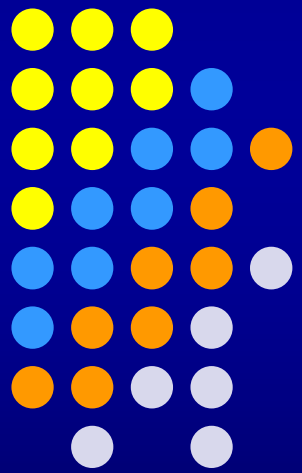
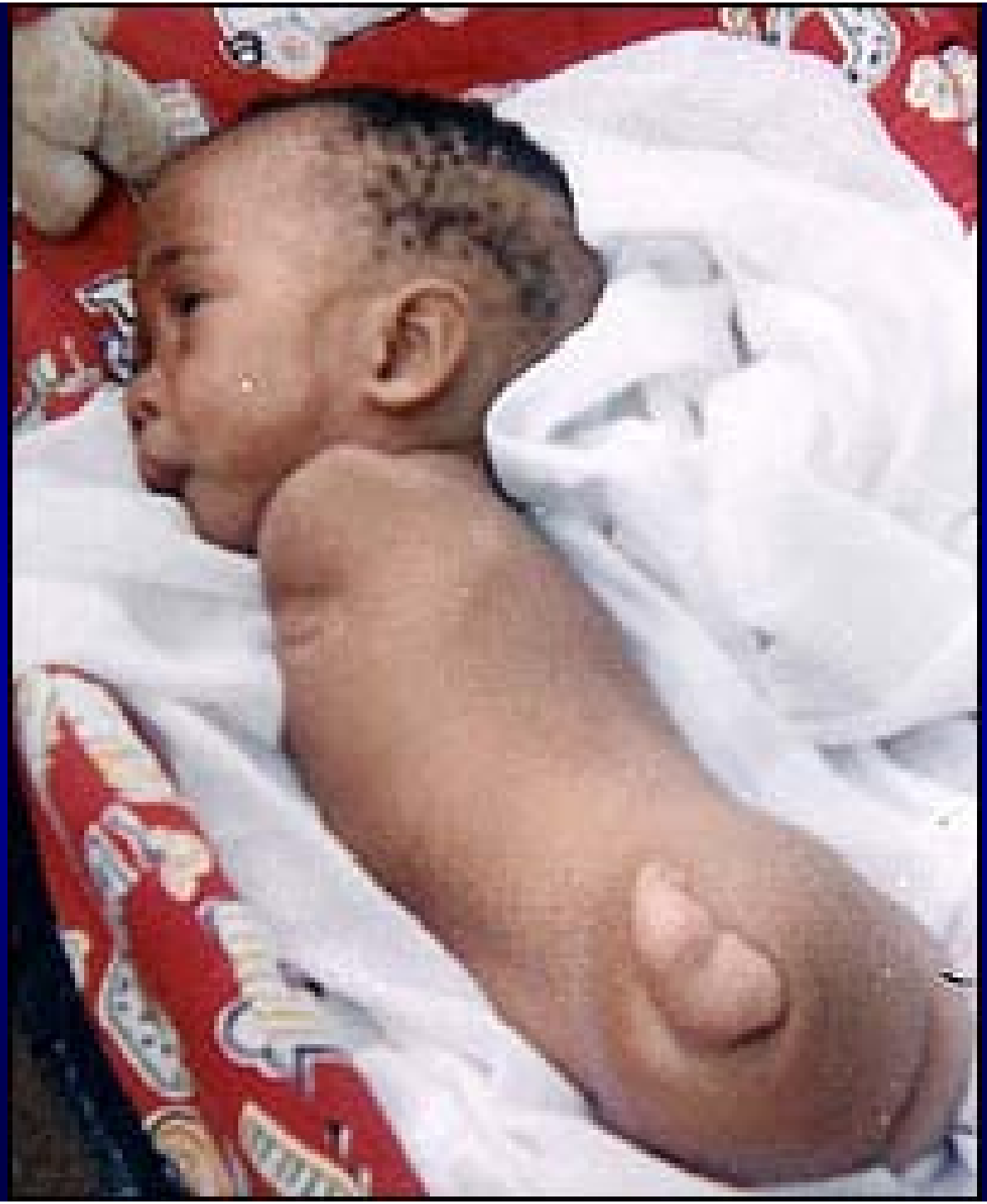
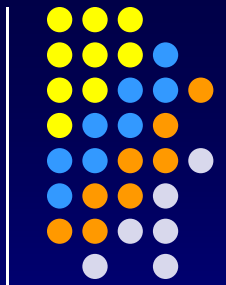


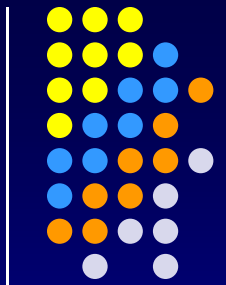


Case study



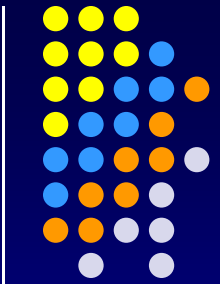
- Thalidomide is a sedative, hypnotic, and anti-inflammatory medication
- Thalidomide was chiefly sold and prescribed during the late 1950s and 1960s to pregnant women, as an antiemetic to combat morning sickness and as a sleep aid
- Unfortunately, inadequate tests were performed to assess the drug's safety; it’s use led to one of the worst man-made "fetal poisoning" tragedies in history

Objectives of the talk



- Why is there such poor evidence for the safety of so many drugs in pregnancy
- How are drugs categorized for safety in pregnancy
- What are available for drug safety in pregnancy
- What are the findings in our pharmacoepidemiologic studies using Saskatchewan databases

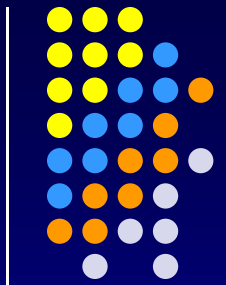
Why evidence for the safety of drugs in pregnancy is poor?



- Pregnancy is an exclusion for most, if not all, phase I, II and III studies; the pharmaceutical industry generally discourages the trial of medications in pregnancy

- Despite the paucity of information on the safety of drugs in pregnancy, prescription drug use in pregnancy is widespread

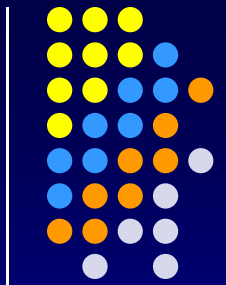
Pharmaceutical use in Pregnancy



- There are a variety of reasons to use pharmaceuticals in pregnancy:
  - Treat pre-existing medical conditions such as asthma, epilepsy
  - Treat pregnancy related conditions such as hypertension and nausea
  - Initiate therapies for new diagnosis such as depression, thyroid disease, and infection which develop during the pregnancy

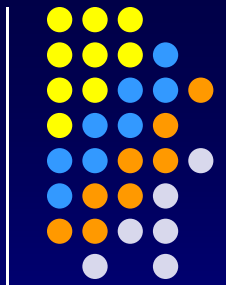
FDA Drug Classification in Pregnancy

FDA drug classifications



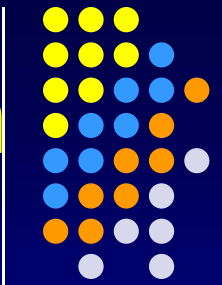
- In 1979, the United States Food and Drug Administration (FDA) introduced a classification of fetal risks due to pharmaceuticals
- The pregnancy category of a pharmaceutical agent is an assessment of the risk of fetal injury due to the pharmaceutical, if used as directed
- This system was based on a similar system that was introduced in Sweden just one year earlier

FDA drug classifications



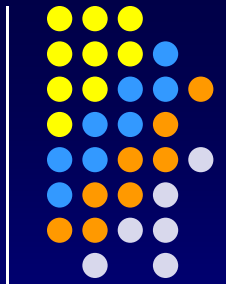
A	Adequate, well-controlled studies in pregnant women have not shown an increased risk of fetal abnormalities to the fetus in any trimester of pregnancy.
B	Animal studies have revealed no evidence of harm to the fetus, however, there are no adequate and well-controlled studies in pregnant women. OR Animal studies have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in any trimester.
C	Animal studies have shown an adverse effect and there are no adequate and well-controlled studies in pregnant women. OR No animal studies have been conducted and there are no adequate and well-controlled studies in pregnant women.
D	Animal studies have shown an adverse effect and there are no adequate and well-controlled studies in pregnant women. OR No animal studies have been conducted and there are no adequate and well-controlled studies in pregnant women.
X	Adequate well-controlled or observational studies in animals or pregnant women have demonstrated positive evidence of fetal abnormalities or risks. The use of the product is contraindicated in women who are or may become pregnant.

Notes on the FDA classification system



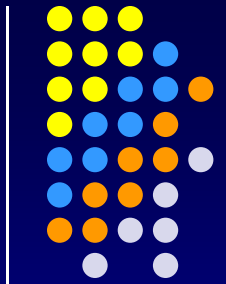
- The FDA requires a relatively large amount of high-quality data on a pharmaceutical for it to be defined as Pregnancy Category A
- Many drugs that would be considered Pregnancy Category A in other countries are allocated to Category C by the FDA as a result

Using the classification system



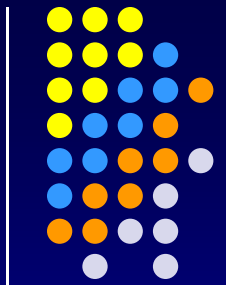
- The majority of medication safety information in pregnancy is obtained through case reports, epidemiological studies, and animal studies, all of which have limitations that make determining risks of a drug during pregnancy difficult
- Case studies in which the drug is not shown to increase risk often have a difficult time being published

Using the classification system



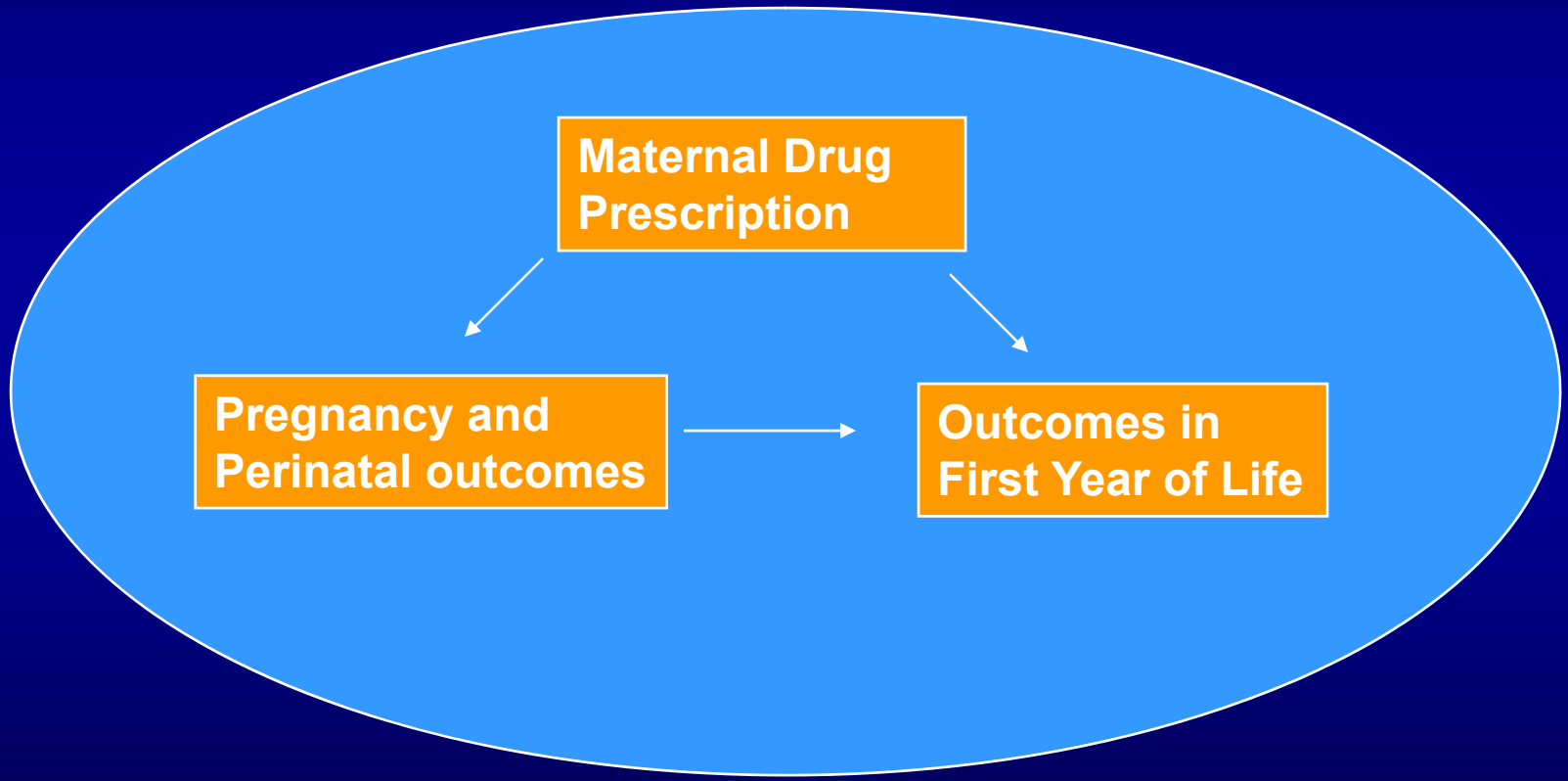
- Animal studies are very limited
  - Dosing, metabolism, and sensitivities can be profoundly different in humans
  - Thalidomide's human embryopathy was not evident through the routine animal testing that was required at the time of its marketing, causing researchers to lose confidence in the predictive ability of animal data

Using the classification system



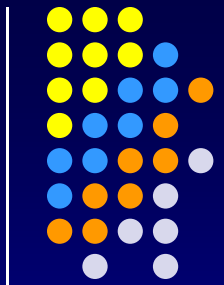
- Most human teratogens mimic those observed in animals, but not all
  - Angiotensin-converting enzyme (ACE) inhibitors, lithium and tetracycline were not concordant with animal studies
  - Some drugs have teratogenic effects in animals when they are administered in high doses that are not teratogenic in humans when given in clinically relevant doses
- Although studies in animals may identify teratogenic effects, it can be difficult to extrapolate these effects back to humans

Pharmacosurveillance in pregnancy: the way forward



Saskatchewan Health Linked Database (1977-2001)

Study I. C,D,X drug exposure in pregnant population



1.1. Primary objective

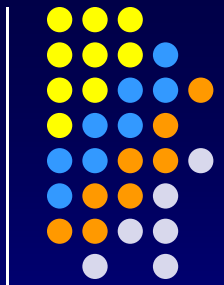
To estimate the **prevalence** of pregnancy exposure to FDA category C, D, X drugs

1.2. Secondary objective

To estimate the prevalence of pregnancy exposure to **specific category** of FDA C, D, X drugs

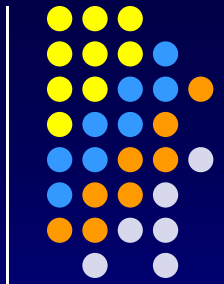
To analyze the **determinants** of pregnancy exposure to FDA category C, D, X drugs

Study I. C,D,X drug exposure in pregnant population



- Total prevalence of prescribing FDA Class C, D, and X drugs
  - All women: 19.4%
  - Women with chronic diseases: 58.6%
  - women without chronic diseases: 14.5%
- proportions of prescribing FDA Class C, D and X drugs during pregnancy period
  - Category C : 15.8 %
  - Category D: 5.2%
  - Category X: 3.9 %

Study I. C,D,X drug exposure in pregnant population



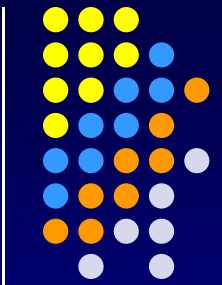
- Prevalence of prescribing at least one FDA Class C,D,X drugs during three-stage pregnancy

  First trimester: 11.2%

  Second trimester: 7.3 %

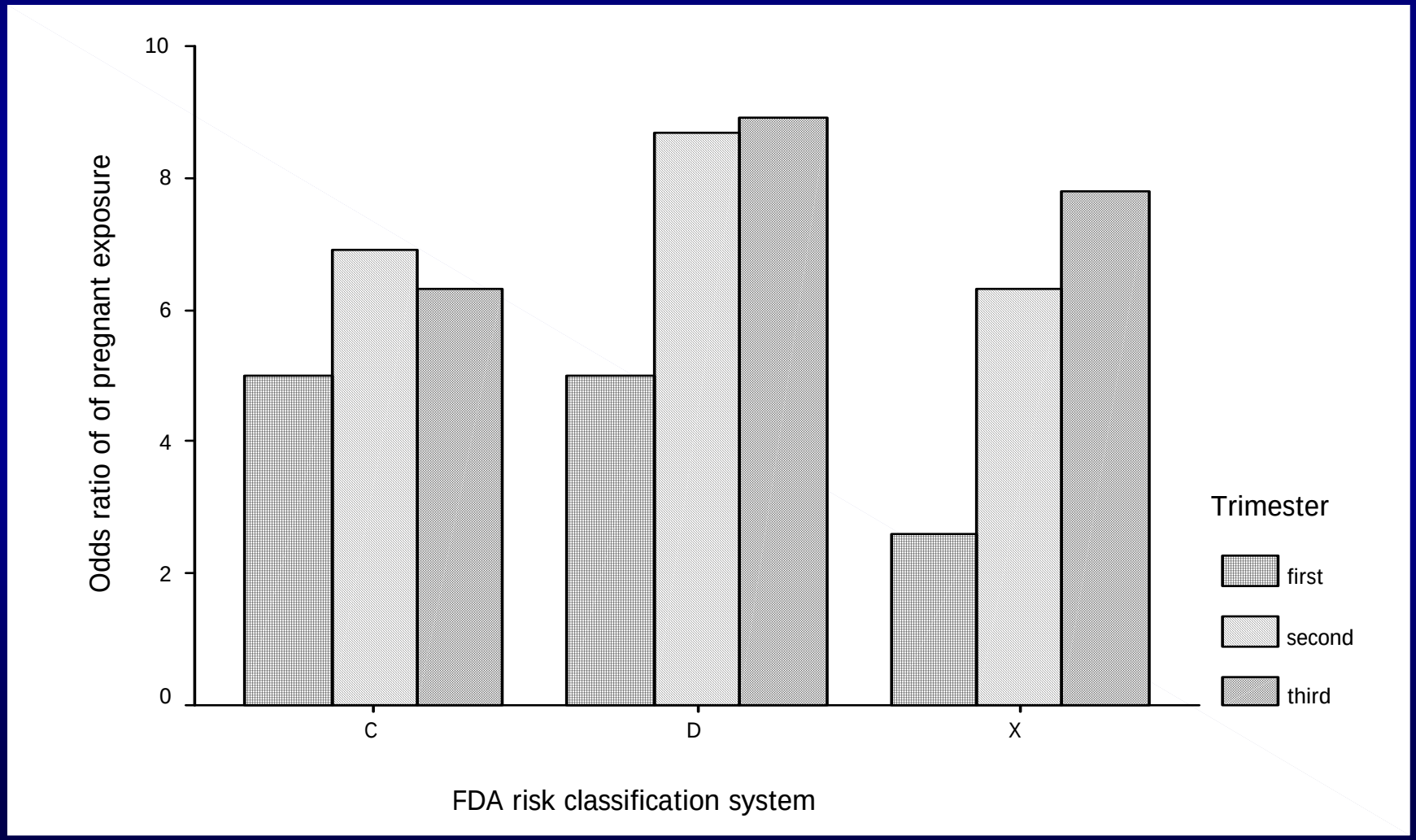
  Third trimester: 8.2 %

Study I. Determinants of C,D,X drug exposure

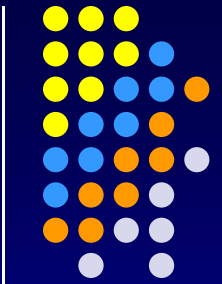


- Chronic health problem was the most important determinant of pregnancy exposure to CDX drugs (OR>4)
- In women without chronic health problem, 8.5%, 4.5%, and 5.1% received one of a FDA C, D, and X drugs, respectively, in the first, second, and third trimester
- There was a tendency of increased risk of pregnancy exposure in women with chronic health problem as compared with those without in later than in earlier gestation, especially for drugs of higher fetal risk
- Younger women with high parity (≥3) or on social assistant plan were at increased risk of pregnancy exposure to C, D and X drugs

Odds ratio of C,D,X drug exposure for women with chronic disease

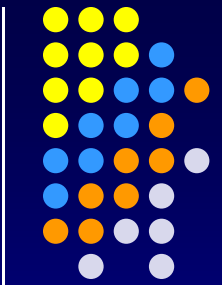


Study II. SSRIs uses in pregnancy



- The safety of SSRIs in pregnancy is uncertain
- The fetal risk of SSRIs cannot be excluded (all SSRIs fall in category “C” of FDA labeling system for drug use in pregnancy)
- On the other hand, untreated depression during pregnancy is also associated with various adverse maternal and infant outcomes

Study II. SSRIs uses in pregnancy



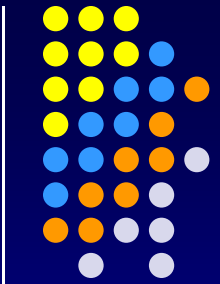
- Previous studies have linked SSRIs in pregnancy to neonatal withdrawal syndrome and other fetal neurotoxicity
- The association between SSRIs and birth defects has found a weak association
- Methodological limitations exist in studies assessing the safety of SSRIs during pregnancy, including small sample size, selection bias, and recall bias

Study II. SSRIs uses in pregnancy

Objective

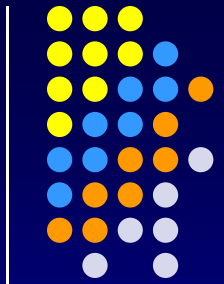
- To make a comprehensive assessment of the safety of prescription SSRIs in pregnancy, using a large population data

Study II. SSRIs uses in pregnancy Methods



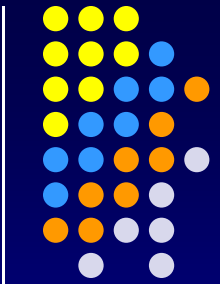
- Retrospective cohort study, using the linked maternal/infant/prescription records from Saskatchewan
- Any women with one SSRIs prescription dispensed in the one year period prior to delivery were exposed
- For each exposed, 4 non-exposed subjects were selected from the remainder of the data, matched by year of birth (within two years), type of institute at birth (same), and mother's postal code (first 3 digits)

Study II. SSRIs uses in pregnancy Methods



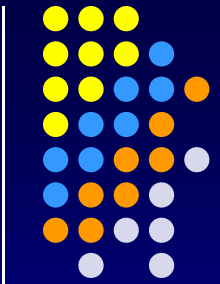
- Outcomes of study included pre-eclampsia, gestational diabetes, placenta previa, placental abruption, low birth weight, preterm birth, birth defects, fetal death, sepsis, seizures, mechanical ventilation, and infant death
- Fetal death is defined as a stillbirth with a birth weight >= 500 g or gestational age >= 20 weeks
- Birth defects, sepsis and seizures were coded by ICD-9 codes and mechanical ventilation was coded by the CCP
- Infant death is defined as deaths which occurred at or less that one year of age

Study II. SSRIs uses in pregnancy Methods



- The observation periods were from one year prior to delivery to one year after delivery, which covered a 3-month preconception period
- For fetal death, low birth weight, and preterm birth, the observation period was to birth
- For neonatal morbidity, the observation period was to 28 days after birth
- For birth defects and infant death, the observation period was to one year after delivery

Study II. SSRIs uses in pregnancy Methods



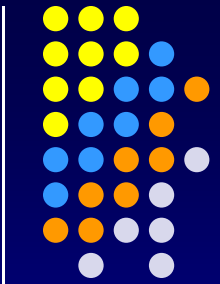
- Distributions of baseline characteristics of the study subjects were compared
- Frequency of SSRIs dispensation during different pregnancy periods were described
- Occurrence of adverse pregnancy outcomes between the two study groups was compared
- Multiple regression analyses were performed to examine the independent effects of SSRIs
- Potential confounding variables included maternal age, social assistance, parity, multi-gestation, and drug dependence

Table 1.Comparison of baseline characteristics between exposed and non-exposed groups, Saskatchewan,1989-2000

Characteristics	Exposed (n=972)	Non-exposed (n=3787)
Maternal age**		
<19	66 (6.8)	303 (7.8)
20-29	494 (50.8)	2187 (56.4)
30+	412 (42.4)	1388 (35.8)
Social assistance (%)**	225 (23.2)	482 (12.4)
Drug dependence (%)**	17 (1.8)	16 (0.4)
Parity >= 1 (%)**	655 (67.4)	2409 (62.1)
Multi-gestations (%)*	37 (3.8)	92 (2.4)

* P<0.05, **p<0.01

Table 2. Pregnancy period dispensation of SSRIs



Pregnancy Period of Prescription	# SSRIs in any GA	# SSRIs only in specified GA
Pre-pregnancy	736	391
First trimester	456	113
Second trimester	201	26
Third trimester	210	45

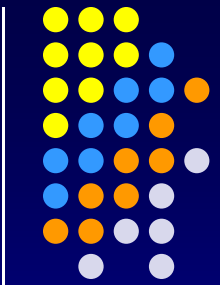
Table 3. Comparison of maternal outcomes between and non-exposed groups

Outcomes	Exposed	Non-exposed	AOR (95% CI)
Preeclampsia (%)	66 (6.8)	223 (5.8)	1.20 (0.90,1.61)
Urinary tract infection (%)	12 (1.2)	31 (0.8)	1.53 (0.76,3.09)
Gestational diabetes (%)	32 (3.3)	83 (2.1)	1.31 (0.86,2.01)
Placentae previa (%)	9 (0.9)	27 (0.7)	1.20 (0.55,2.60)
Placental abruption (%)	30 (3.1)	69 (1.8)	1.56 (0.99,2.46)

Table 4. Comparison of infant outcomes between exposed non-exposed groups

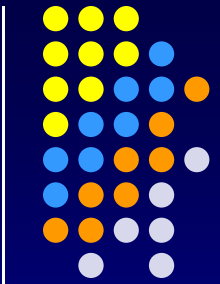
Outcome	Exposed	Non-exposed	AOR (95% CI)
Birth weight <2500 grams (%)	87 (9.0)	205 (5.3)	**1.58 (1.19,2.11)**
Gestational age <37weeks (%)	188 (19.3)	465 (12.0)	**1.57 (1.28,1.92)**
Major structural anomalies (%)	20 (2.1)	76 (2.0)	0.98 (0.59,1.64)
Minor structural Anomalies (%)	35 (3.6)	133 (3.4)	1.02 (0.69,1.51)

Table 5. Comparison of infant outcomes between exposed non-exposed groups



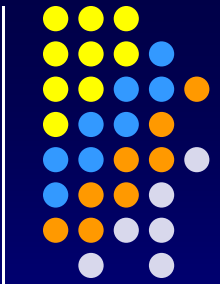
Outcomes	Exposed	Non-exposed	AOR (95% CI）
Fetal death（%）	11 (1.1)	17 (0.4)	**2.23 (1.01, 6.40)**
Infant death (%)	15 (1.5)	22 (0.6)	1.96 (0.97, 3.94)
Sepsis (%)	10 (1.0)	23 (0.6)	1.41 (0.65,3.06)
Seizures (%）	4 (0.4)	5 (0.1)	**3.87 (1.00,14.99)**
Ventilation (%)	34 (3.5)	87 (2.2)	1.14 (0.74, 1.75)

Study II. SSRIs uses in pregnancy Mechanisms



- Serotonin had a strong vasoconstriction effect on human umbilical arteries
- Increased serotonin level after maternal use of SSRIs may increase the risk of adverse outcomes that are sensitive to the placental blood flow (IUGR, PTB)
- The pathophysiological changes in human umbilical arteries observed in labs may help to explain why infants born to mothers with prenatal SSRIs exposure had higher risks of IUGR and PTB

Study II. SSRIs uses in pregnancy Implications



- A balanced approach to simultaneously weigh the need to control maternal depression against the potential risk of fetal exposure should be taken in dealing with the individual patient

- Larger scale studies are needed to make conclusive assessment of the safety of SSRIs use in pregnancy

Study III. Folic acid antagonists in pregnancy

Background

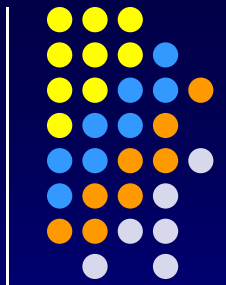
- About 10 percent of women of reproductive age used folic acid antagonists in any particular calendar year
- Maternal exposure to folic acid antagonists was associated with increased risks of neural tube defects, cardiovascular defects, oral clefts, and urinary tract defects

Study III. Folic acid antagonists in pregnancy

Objective

- To assess the effect of folic acid antagonists use in pregnancy on placenta-mediated adverse pregnancy outcomes

Study III. Folic acid antagonists in pregnancy



Methods

- Retrospective cohort study: 1980 to 2000 Canadian province of Saskatchewan
- Placenta-mediated outcomes : preeclampsia, placental abruption, fetal growth restriction, and fetal death
- Conditional logistic regression analysis
- Supplementary analyses:

  Tight matching with propensity score

  Restricting study subjects to first and second trimester exposure

  Restricting to specific categories of folic acid antagonists

Table 1. Comparison of baseline characteristics between exposed and non exposed groups, Saskatchewan,1980-2000

Characteristics	Exposed (N=14982) n(%)	Unexposed(N=14982) n(%)
Maternal age		
<20	1637 (10.99)	4902 (8.19)
20-29	9820 (65.55)	39503 (66.03)
30+	3525 (23.53)	15420 (25.78)
Social assistance (%)	2083 (13.94)	5400 (9.05)
Hospital at birth		
Provincial	7428 (49.97)	29702 (50.03)
Community	4232 (28.47)	16879 (28.43)
Regional	3204 (21.56)	12789 (21.54)
Year of baby born		
1980-1986	7810 (52.13)	33002 (55.16)
1987-1991	1896 (12.16)	7076 (11.83)
1992-2001	5276 (35.22)	19747 (33.01)
Male sex(%)	7703 (51.42)	30628 (51.20)
Parity		
Primigravida	6174 (41.21)	22987 (38.42)
Multipara	8808 (58.79)	36838 (61.58)

Table 2. Comparison of adverse pregnancy outcomes between exposed and matched non-exposed groups, Saskatchewan, 1980-2000

Outcomes	Exposed N=14982	Non-exposed N=59825	Adjusted OR (95%CI)*
Preeclampsia	789 (5.27)	2065 (3.45)	1.52 (1.39, 1.66)
Severe preeclampsia	94 (0.63)	201 (0.34)	1.77 (1.38, 2.28)
Placental abruption	189 (1.26)	549 (0.92)	1.32 (1.12, 1.57)
Fetal growth restriction (<3rd percentile)	622 (4.16)	2022 (3.39)	1.22 (1.11, 1.34)
Fetal growth restriction (<10th percentile)	1746 (11.68)	6498 (10.88)	1.07 (1.01, 1.13)
Fetal death	101 (0.67)	301 (0.50)	1.35 (1.07, 1.70)

Table 3. The risk of adverse pregnancy outcomes associated with number of tablets/capsuls of folic antagonist exposure, Saskatchewan, 1980-2000

Outcomes	Number of cases	Adjusted OR (95%CI)*
Severe preeclampsia		
Non-exposure	139	Reference
1-20	21	1.55 (0.93-2.58)
21-40	24	1.93 (1.18-3.16)
40+	20	1.97 (1.13-3.43)
Trend test		**P < 0.01**
Placental abruption		
Non-exposure	502	Reference
1-20	61	1.38 (1.03-1.86)
21-40	48	1.13 (0.82-1.57)
40+	58	1.30 (1.12-1.55)
Trend test		**P < 0.01**

Table 3. The risk of adverse pregnancy outcomes associated with number of tablets/capsuls of folic antagonist exposure, Saskatchewan, 1980-2000

Outcomes	number of women	Adjusted OR (95%CI)*
Fetal growth restriction (<3rd percentile)		
Non-exposure	2022	Reference
1-20	172	1.07 (0.90-1.27)
21-40	238	1.24 (1.07-1.44)
40+	212	1.32 (1.12-1.55)
Trend test		**P < 0.01**
Fetal death		
Non-exposure	266	Reference
1-20	18	0.89 (0.53-1.49)
21-40	28	1.08 (0.71-1.64)
40+	30	1.40 (0.92-2.14)
Trend test		**P < 0.05**

Table 4. Results of sensitivity analysis of the association between maternal exposure to folic acid antagonists and adverse pregnancy outcomes, Saskatchewan, 1980-2000*

Outcomes	Exposed	Non-exposed	Adjusted OR (95%CI)*
Matching by propensity score (within one decimal)**	N=14982	N=14982	
Severe preeclampsia	64	33	1.95 (1.28-2.97)
Placental abruption	166	119	1.40 (1.11-1.78)
Fetal growth restriction (<3rd percentile)	613	498	1.24 (1.10-1.40)
Fetal death	76	71	1.07 (0.77-1.48)

Table 4. Results of sensitivity analysis of the association between maternal exposure to folic acid antagonists and adverse pregnancy outcomes, Saskatchewan, 1980-2000*

Outcome	Exposed	Non-exposed	Adjusted OR (95%CI)*
Restricting to first and second trimester exposure			
Severe preeclampsia	27	49	2.08 (1.30-3.35)
Placental abruption	64	229	1.08 (0.82-1.43)
Fetal growth restriction (<3rd percentile)	316	885	1.40 (1.23-1.60)
Fetal death	29	116	0.98 (0.65-1.47)

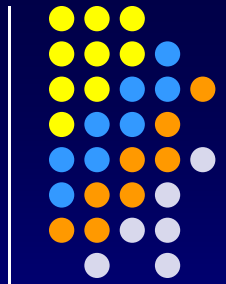
Table 4. Results of sensitivity analysis of the association between maternal exposure to folic acid antagonists and adverse pregnancy outcomes, Saskatchewan, 1980-2000*

Restricting to exposure to sulfamethoxazole/trimethoprim Outcome	Exposed	Unexposed	Adjusted OR (95%CI)*
Severe preeclampsia	41	111	1.37 (0.95-1.98)
Placental abruption	127	387	1.26 (1.03-1.55)
	451	1493	1.20 (1.07-1.33)
Fetal growth restriction (<3rd percentile)			
Fetal death	51	200	1.03 (0.75-1.40)

Table 4. Results of sensitivity analysis of the association between maternal exposure to folic acid antagonists and adverse pregnancy outcomes, Saskatchewan, 1980-2000*

Restricting to exposure to antiepileptics*** Outcome	Exposed N=1335	Unexposed N=5332	Adjusted OR (95%CI)*
Severe preeclampsia	5	12	1.63 (0.57-4.68)
Placental abruption	20	61	1.20 (0.72-2.01)
Fetal growth restriction (<3rd percentile)	67	189	1.37 (1.03-1.83)
Fetal death	9	25	1.42 (0.65-3.07)

Study III. Folic acid antagonists in pregnancy



Conclusion

- Maternal exposure to folic acid antagonists increases the risk of placenta-mediated adverse pregnancy outcomes.

Study IV. Comparison of effects of trimethoprim/sulfamethoxazole and other antibiotics on pregnancy outcomes

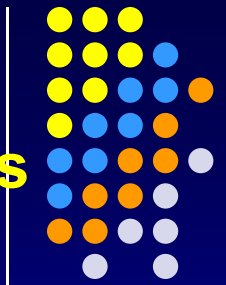


Table 1. Odds ratios of birth outcomes of different exposed groups

Exposure	Premature birth (≤37W)		Low weight birth (≤2500g)	
	Unadjusted Odds ratios (95%CI)	Adjusted Odds ratios (95%CI)	Unadjusted Odds ratios (95%CI)	Adjusted Odds ratios (95%CI)
Trimethoprim/sulfamethoxazole	1.70 (1.25, 2.30)	1.52 (1.12, 2.07)	1.85 (1.34, 2.56)	1.66 (1.19, 2.32)
Other antibiotics	0.98 (0.54, 1.76)	0.87 (0.48, 1.57)	0.83 (0.41, 1.68)	0.74 (0.36, 1.51)
Other CDX drugs	1.47 (1.28, 1.70)	1.27 (1.09, 1.48)	1.52 (1.30, 1.78)	1.29 (1.08, 1.53)
No exposure	1	1	1	1

Study IV. Comparison of effects of trimethoprim/sulfamethoxazole and other antibiotics on pregnancy outcomes

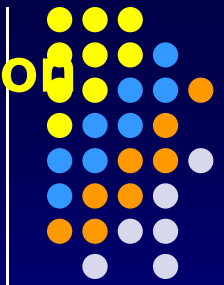


Table 2. Prevalence of trimethoprim/sulfamethoxazole and other antibiotics in FDA drug category C, D and X use by pregnant women during pregnancy

Drug	Number	%
Trimethoprim/sulfamethoxazole	464	2.5
Fluconazole	111	0.6
Doxycycline	63	0.34
Tetracycline	26	0.14
Clarithromycin	6	0.03

These drugs all can use to treat urinary tract infections

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