

# **Clinical considerations**

**Anthony R. Scialli, M.D.**

Scialli Consulting LLC

[ascialli@scialliconsulting.com](mailto:ascialli@scialliconsulting.com)



# What are clinical considerations?

- Pregnancy
  - Disease-associated maternal or fetal risks
  - Dose adjustments during pregnancy and postpartum
  - Maternal adverse reactions
  - Fetal/neonatal adverse reactions
  - Labor or delivery
- Lactation
  - Minimizing exposure
  - Monitoring for adverse reactions

Clinical Considerations (omit if none of the headings are applicable)

Provides information to further inform prescribing and risk-benefit counseling.  
Relevant information is presented under the following 5 subheadings:

*Disease-associated maternal and/or embryo/fetal risk* (omit if not applicable)

*Dose adjustments during pregnancy and the postpartum period* (omit if not applicable)

*Maternal adverse reactions* (omit if not applicable)

*Fetal/Neonatal adverse reactions* (omit if not applicable)

*Labor or delivery* (omit if not applicable)

# 1. Disease-Associated Maternal or Fetal Risks

- Examples for which there are good data
- Examples for which there are mixed data
- Examples of which data are inadequate

# Good data

## ■ Diabetes mellitus

- Malformation risk related to peri-conceptual control
- Fetal growth
- Maternal complications

## ■ Asthma

## ■ Hypothyroidism

**TABLE 4. NEUROPSYCHOLOGICAL TEST SCORES AMONG THE CHILDREN OF WOMEN WITH HYPOTHYROIDISM DURING PREGNANCY AS COMPARED WITH THE CHILDREN OF MATCHED CONTROL WOMEN, STRATIFIED ACCORDING TO WHETHER THE HYPOTHYROIDISM WAS BEING TREATED.\***

TEST	CHILDREN OF TREATED WOMEN WITH HYPOTHYROIDISM (N=14)		CHILDREN OF UNTREATED WOMEN WITH HYPOTHYROIDISM† (N=48)		CONTROL CHILDREN (N=124)
	VALUE‡	P VALUE§	VALUE§	P VALUE§	
Intelligence					
WISC-III full-scale IQ score	111	0.20	100	0.005	107
WISC-III full-scale IQ score ≤85 (%)	0	0.90	19	0.007	5
Attention					
WISC-III freedom-from-distractibility score	103	0.80	97	0.03	102
Continuous Performance Test score >8 (%¶)	50	0.01	33	0.04	19
Language					
Test of Language Development score					
Word articulation	10.5	0.60	10.0	0.6	10.2
Word discrimination	11.4	0.90	10.3	0.02	11.4
WISC-III verbal IQ score	111	0.30	101	0.006	107
School performance					
PLAT-R reading-recognition score	101	0.80	95	0.05	100
PLAT-R reading-comprehension score	105	0.40	96	0.09	101
School difficulties and learning problems (%¶)	29	0.08	21	0.09	11
Repeated a grade (%¶)	7	0.50	8	0.3	4
Visual-motor performance					
Score on Developmental Test of Visual-Motor Integration	102	0.30	94	0.1	97
WISC-III performance IQ score	109	0.30	99	0.01	105
Pegboard-test score					
Dominant hand¶	79	0.40	88	0.06	83
Nondominant hand¶	87	0.70	96	0.04	89

**Table 2.** Haemoglobin A<sub>1c</sub> in early pregnancy in women with Type 1 diabetes and the risk for major fetal malformations compared with non-diabetic control subjects

HbA <sub>1c</sub> < 14 weeks		No. offspring malformed/all	Relative risk (95 % CI)
%	SD		
Not known	Not known	4/49	6.0 (2.0–17.1)
≥ 9.4	≥ 14	4/61	4.8 (1.6–13.9)
8.1–9.3	10.0–13.9	6/133	3.3 (1.3–8.6)
6.9–8.0	6.0–9.9	8/252	2.3 (1.0–5.7)
5.6–6.8	2.0–5.9	7/170	3.0 (1.2–7.5)
< 5.6	< 2.0	1/47	1.6 (0.3–9.5)
All offspring of diabetic women		30/709	3.1 (1.6–6.2)
Control offspring		10/735	1.0

Suhonen et al., Diabetologia 2000;43:79

Haddow et al. NEJM 1999;341:549

## Mixed data

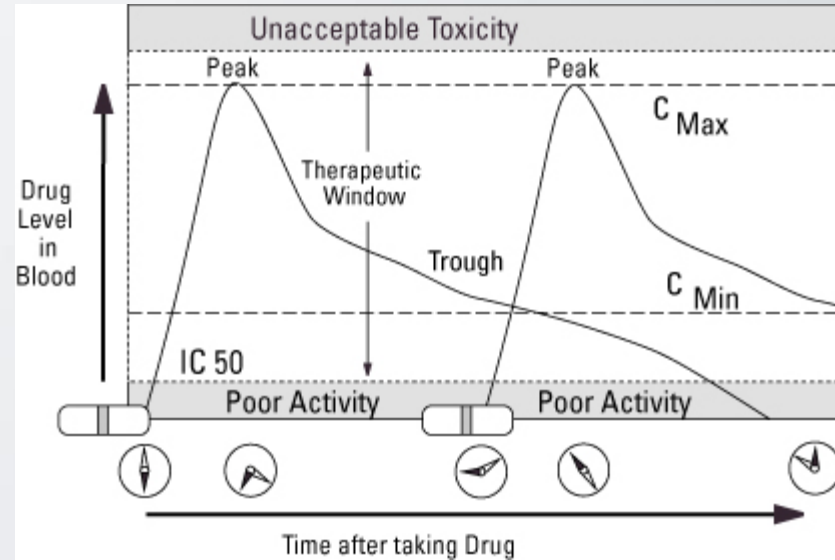
- Depression
  - Decreased gestation length?
  - Impaired fetal growth?
  - Malformations?
- Seizure disorder
  - Increased malformations separate from medications?
  - Effects of untreated seizures?

## Inadequate data

- Hypertension
  - Maternal risks at high levels of blood pressure
  - Fetal risks not altered by treatment
- Hyperthyroidism
  - Mild hyperthyroidism without reported effects
- Hyperlipidemia

## 2. Dose adjustment

- Anticonvulsants
- Psychotropics
- Thyroxine



### 3. Maternal adverse reactions

- Procoagulants
  - Thromboembolic disorders
- Inhalation anesthetics
  - Increased minute ventilation





## 4. Fetal/neonatal adverse reactions

- Serotonin reuptake inhibitor discontinuation syndrome
- Opioids and respiratory depression

## 5. Labor/delivery

- Oxytocics
- Prostaglandins
- Beta-sympathomimetics
- Calcium-active agents



# Lactation

## 8.2 Lactation

Replaces the Nursing Mothers subsection

### Risk Summary (required subheading)

Summarizes information on the presence of a drug and/or its active metabolite(s) in human milk, the effects of a drug and/or its active metabolite(s) on the breastfed child, and the effects of a drug and/or its active metabolite(s) on milk production

### Clinical Considerations (omit if not applicable)

Provides information to further inform prescribing and risk-benefit counseling.

Minimizing exposure  
Monitoring for adverse reactions

### Data (omit if not applicable)

Describes the data that provide the scientific basis for the information presented in the Risk Summary and Clinical Considerations

# Infant benefits of breast feeding (NICHD)

- Nutritionally balanced
- Protects against childhood illness and infection
- Better survival including protections from SIDS
- Decrease in some allergic disease
- Decrease in type 1 diabetes mellitus
- Physical and emotional benefits

<https://www.nichd.nih.gov/health/topics/breastfeeding/conditioninfo/Pages/benefits.aspx>

## Maternal benefits of breast feeding (NICHD)

- Reduced postpartum bleeding
- Better weight loss
- Less postpartum depression
- Decrease in rheumatoid arthritis, cardiovascular disease, and breast cancer
- Physical and emotional benefits

<https://www.nichd.nih.gov/health/topics/breastfeeding/conditioninfo/Pages/benefits.aspx>

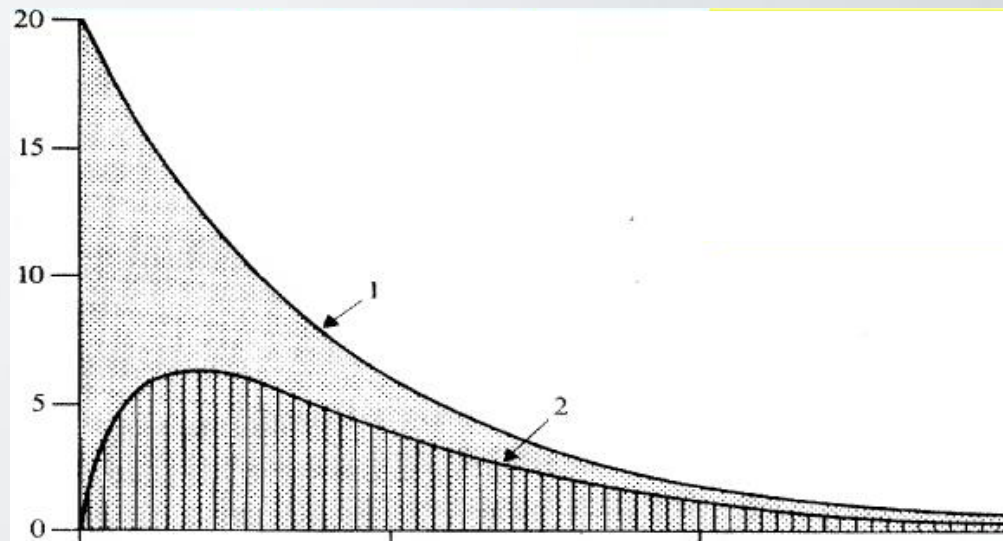
## Economic benefits of breast feeding (NICHD)

- Hundreds of dollars per year per child (formula)
- Fewer insurance claims for preventable diseases
- Fewer parental sick days caring for sick kids
- Fewer funeral costs for preventable deaths

<https://www.nichd.nih.gov/health/topics/breastfeeding/conditioninfo/Pages/benefits.aspx>

# Minimizing exposure

- Not nursing
- Not taking medication
- Timing of medication and nursing



# Monitoring

- When to evaluate?
- What to evaluate?
  - Sedation
  - Irritability
  - Jitteriness
  - Urine output
  - Stool quality/quantity
  - Laboratory tests
    - Clinical chemistry
    - Hematology
    - Drug/metabolite concentrations



# Standardization – Professional societies?

- American College of Radiology
- American College of Rheumatology
- The American Congress of Obstetricians and Gynecologist
- Society for Maternal-Fetal Medicine
- The Teratology Society
- The American Academy of Pediatrics



# Standardization – consultants?



# Standardization – the Agency?



# Who makes risk-benefit decisions?

- The patient with the assistance of her provider
  - Even if she makes the wrong decision
- Patients are trusted to make the best decisions for their children
- Labeling supports the patient and provider
  - So what about contraindications?
- Language is important.

# Risk is a four-letter word

## ▶ Risk

- A statistical concept
- For patients: You hurt your baby
- For providers: Call your insurer

## ▶ Modifiers

- No risk or Low risk = Safe
- Moderate risk or high risk = You hurt your baby

## ▶ Quantified risk

- $1/1000$  to  $1/10000$  =  $1/100$  to  $1/1000$  =  $1/1$  = ME
- 30,000 in 1 million vs. 30,001 in 1 million.

## Different decisions for different indications

- Seizure control vs. bipolar disorder vs. migraine
- Cancer vs. inflammation



## Preferred alternatives in the labeling: Wild and crazy idea

- Hypertension
  - Usually treated with labetalol or nifedipine
  - Sometimes methyldopa
- Diabetes
  - Usually treated with insulin
  - Sometimes glyburide or metformin
- Systemic lupus erythematosus
  - Hydroxychloroquine and/or sulfasalazine for everyone

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