Pregnancy and Lactation Labeling Rule: Implications for practice

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Objectives

• Upon completion of the presentation the NP will analyze the information and:
  1. Understand and explain the new PLLR.
  2. Adequately counsel pregnant or lactating female patients about risk vs benefit of a medication, enabling them to make an informed decision about taking that medication.
  3. Adequately counsel female and male patients of reproductive potential about medications that have one, associated kidney effects, enabling them to make an informed decision about taking that medication.
  4. Understand and explain the effects of the PLLR on their practice.

Disclosure

• I attest that the CE content for which I am responsible is evidenced-based, fair and balanced, unbiased and free from commercial interest control.
• I attest that I have no financial relationship or interest.
• Many Slides in the presentation are "Reprinted with permission from the Food and Drug Administration (FDA)"
Importance

- 60 million females of reproductive age
- 6.5 million pregnancies yearly in the United States
- Many pregnant and lactating females have health issues that require medication
- 64% of women use at least 1 drug during pregnancy

History

- Thalidomide
  - Introduced early 60s
  - Used to treat nausea and vomiting
  - Caused phocomelia

History of Labeling

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<tbody>
<tr>
<td>Action</td>
<td>Kefauver-Harris amendments</td>
<td>Pregnancy categories established by regulation</td>
<td>Pregnancy labeling initiated</td>
<td>Proposed rule written with new labeling format</td>
<td>Final FDA issued; revised after public comment</td>
<td>PLLR published December 4</td>
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### Slide 7
**Problems with Letters**

- Over simplistic
- Misinterpreted as a grading system
- A drug with adverse information in animals could be labeled as the same category as a drug with no animal information
- Two drugs in the same pregnancy risk category do not necessarily have the same risk

### Slide 8
**Intent of PLLR**

- Provide the prescriber with relevant information for critical decision-making when treating pregnant or lactating women
- More complete statement of the known risks based on the available data
- Considerations of medical/disease factors
- Animal data put in context of human exposure
- Human data added when available
- Explicitly states when no data are available

### Slide 9
**PLLR**

- Effective date June 30, 2015
- Prescription drugs approved on or after June 30, 2001 have additional content and formatting requirements
- ALL prescription drugs to remove pregnancy letter categories by June 2020
8.1 Pregnancy

- Four Headings
  - Pregnancy Exposure Registry
  - Risk Summary
  - Clinical Considerations
  - Data
8.1 Pregnancy Exposure Registry

• If there is a pregnancy exposure registry for the drug, the following statement must appear:
  • There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to TRADENAME during pregnancy.
  • The statement must be followed by contact information needed to enroll in or to obtain information about the registry
  • www.fda.gov/ScienceResearch/SpecialTopics/WomensHealthResearch/ucm251314.htm
  • https://www.fda.gov/science-research/womens-health-research/list-pregnancy-exposure-registries

8.1 Pregnancy Risk Summary

• No drug systemic absorption
  • "TRADENAME is not absorbed systemically following (route of administration) and maternal use is not expected to result in fetal exposure to the drug."

8.1 Pregnancy Risk Summary

• Drugs with systemic absorption
  • When use of a drug is contraindicated during pregnancy, that information must be listed first in the Risk Summary
  • Risk statement based on animal data (required)
  • Risk statement based on pharmacology
  • Background risk information in general population (required)
  • Background risk information in disease population
8.1 Pregnancy Clinical Considerations

- Clinical Considerations (five optional subheadings)
  - Disease-Associated Maternal and/or Embryo/Fetal Risk
  - Dose Adjustments During Pregnancy and the Postpartum Period
  - Maternal Adverse Reactions
  - Fetal/Neonatal Adverse Reactions
  - Labor or Delivery

Pregnancy Data

- Human Data must include the following elements:
  - Data source (e.g., controlled clinical trials, ongoing or completed pregnancy exposure registries, other epidemiological or surveillance studies, case series)
  - Number of subjects
  - Study duration
  - Exposure information (timing, duration, and dose of exposure)
  - Limitations of the data, including potential confounders and biases, if known
  - If available, data from the comparator or control group, and data confidence intervals and power calculations should also be included

Pregnancy data

- Animal Data must include:
  - Species studied
  - Describe doses in terms of human dose equivalents
  - Must provide basis for calculation
8.2 Lactation

- 3 Headings
  - Risk summary
  - Clinical considerations
  - Data

Risk summary

- 8.2 Lactation
- No Drug Systemic Absorption

"[TRADENAME] is not absorbed systemically by the mother following [route of administration] and breastfeeding is not expected to result in exposure of the infant to [drug name]."
Risk summary

- 8.2 Lactation
- Systemic drug absorption
  - Presence of drug in milk*
  - Concentration in milk
    - Actual or estimated infant daily dose
- Effects of drug on the breastfed infant*
- Risk/Benefit Statement
  - *if unknown, must state so

Clinical consideration/Data

- 8.2 Lactation
- Clinical Consideration/Data
  - Clinical Considerations
    - Minimizing exposure to the breastfed infant
    - Minimizing the breastfed infant for adverse reactions

Example 1/Pregnancy and Lactation

- Oral contraceptives: Letter Risk Category X
- Pregnancy
  - Use of contraceptives is pregnancy advised. Combination (oral contraceptives are not
    used in combination with oral contraceptives, when administer and taken without
    interruption, have been associated with serious health consequences, including
    thrombophlebitis and pulmonary embolism. In general, the use of combination
    hormonal contraceptives, when inadvertently used in early pregnancy, have
    not been associated with adverse fetal or maternal effects. Combination
    hormonal contraceptives should not be started until 8-12 weeks after delivery in
    women who choose not to breastfeed. Combination hormonal contraceptives
    should not be started until > 4 weeks after delivery in women who choose not to
    breastfeed. Due to the increased risk of venous thromboembolism (VTE). The risk
    decreases to baseline by postpartum day 42. Individual risk factors for VTE also
    need to be taken into consideration.

- Lactation
  - Estrogenic steroids may be present in breast milk. Adverse health outcomes, as
    persistent effects on infant growth or other neurobehavioural outcomes has not been
    identified. Because of the potential for neurobehavioural effects, infants of
    breastfed women who used combination oral contraceptives should be monitored
    closely. Use of other forms of contraception until the child is weaned.
**Example 2/ Pregnancy and lactation**

- **Insulin Letter Risk Category B**
- Pregnancy
  - Both endogenous and exogenous insulin are present in breast milk (study not conducted with the preparation (AOC 2015; Alexander 2017).
  - Adverse events have not been reported in breastfeeding infants following maternal use of regular insulin for diabetes. Adverse events have not been reported in breastfeeding infants. Adjustments of the mother’s insulin dose may be needed.
  - Breastfeeding is encouraged for all females, including those with type 1, type 2, or gestational diabetes mellitus (AOC 2018; ADA 2019; Berstein 2019). A trial snack before breastfeeding may help decrease the risk of hypoglycemia in infants with gestational diabetes who are breastfed. The decision to breastfeed during therapy should consider the risk of infant exposure, the benefits of breastfeeding to the infant, and benefits of treatment to the mother.

**Example 2 continued**

- **Insulin**
- **Lactation**
- Both endogenous and exogenous insulin are present in breast milk (study not conducted with the preparation (AOC 2015; Alexander 2017).
- Adverse events have not been reported in breastfeeding infants following maternal use of regular insulin for diabetes. Adjustments of the mother’s insulin dose may be needed.
- Breastfeeding is encouraged for all females, including those with type 1, type 2, or gestational diabetes mellitus (AOC 2018; ADA 2019; Berstein 2019). A trial snack before breastfeeding may help decrease the risk of hypoglycemia in infants with gestational diabetes who are breastfed. The decision to breastfeed during therapy should consider the risk of infant exposure, the benefits of breastfeeding to the infant, and benefits of treatment to the mother.

**Example 3/ Pregnancy and lactation**

- **Levothyroxine Letter Risk Category A**
- Hypothyroidism: When thyroid hormone replacement is needed, serum cholesterol and triglycerides levels should be monitored with appropriate adjustments. Thyroid hormone replacement therapy is an essential element of pregnancy management and should be initiated in the preconception period.
- Teratogenicity: Levothyroxine should not be used in pregnant females (ACOG 2015; Alexander 2017). Levothyroxine is the preferred treatment of maternal hypothyroidism; other agents should not be used in pregnant females (ACOG 2015; Alexander 2017).
- Levothyroxine is not known to increase the risk of congenital anomalies (AOC 2015; Alexander 2017).
- Exogenous and endogenous thyroid hormones are present in breast milk (study not conducted with the preparation (AOC 2015; Alexander 2017).
- Adverse events have not been reported in breastfeeding infants following maternal use of levothyroxine for hypothyroidism. Exogenous thyroid hormone in breast milk is not known to cause adverse effects in breastfeeding infants. Adjustments of the mother's levothyroxine dose may be needed.
- Breastfeeding is encouraged for all females, including those with hypothyroidism. Exogenous thyroid hormone in breast milk is not known to cause adverse effects in breastfeeding infants. Adjustments of the mother’s levothyroxine dose may be needed.
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**Example 3 continued**

- **Levothyroxine: Lactation**
  - Levothyroxine is present in breast milk.
  - Levothyroxine was not found to cause adverse events to the infant or mother during breastfeeding. Adequate thyroid hormone concentrations are required to maintain normal lactation.
  - According to the manufacturer, the decision to breastfeed during therapy should consider the risk of infant exposure, the benefits of breastfeeding to the infant, and benefits of treatment to the mother. The World Health Organization (WHO) considers levothyroxine to be compatible with breastfeeding.

**Example 4/Pregnancy and lactation**

- **Propylthiouracil (PTU): Letter Risk Category D**
  - Propylthiouracil crosses the placenta.
  - Nonteratogenic adverse effects, including fetal and neonatal hypothyroidism, have been reported following maternal propylthiouracil use.
  - Uncontrolled maternal hyperthyroidism may result in adverse neonatal outcomes (e.g., prematurity, low birth weight) and adverse maternal outcomes (e.g., preeclampsia, congestive heart failure, stillbirth, and abortion).
  - The pharmacokinetic properties of propylthiouracil are not significantly changed by pregnancy; however, the severity of hyperthyroidism may fluctuate throughout pregnancy (De Groot 2013; Sitar 1979; Sitar 1982).
  - Doses of propylthiouracil may be decreased as pregnancy progresses and discontinued weeks to months prior to delivery.
  - Antithyroid drugs are the treatment of choice for the control of hyperthyroidism during pregnancy (ACOG 2015; Alexander 2017; De Groot 2012).

  **Boxed Warning:** Propylthiouracil may be the treatment of choice when an antithyroid drug is indicated during or just prior to the first trimester of pregnancy. Due to adverse maternal events, other antithyroid medications should be considered after the first trimester. To prevent adverse outcomes, maternal TT4/FT4 should be at or just above the pregnancy specific upper limit of normal (Alexander 2017). Propylthiouracil may be used for the treatment of thyroid storm in pregnant females.

  - Females taking propylthiouracil should notify their health care provider immediately once pregnancy is suspected (Alexander 2017).

**Example 4 continued**

- **Propylthiouracil: Lactation**
  - PTU is present in breast milk. The infant dose (RID) of propylthiouracil is < 2% when calculated using the highest mean breast milk concentration located and compared to a weight-adjusted maternal dose of 400 mg/day.
  - In general, breastfeeding is considered acceptable when the RID of a medication is < 10% (Anderson 2016).
  - The RID of propylthiouracil was calculated using a mean milk concentration of 0.7 mcg/mL, providing an estimated dose of 0.025% of the maternal dose. The total daily propylthiouracil dose to women breastfeeding was 8 mg/kg/day, yielding an estimated daily infant dose of 0.11 mg/kg/day. This milk concentration was obtained following maternal administration of a single dose of propylthiouracil 400 mg/day to nine breastfeeding women, 1-8 month postpartum. The amount of propylthiouracil collected in breast milk over 4 hours was equivalent to 0.025% of the ingested dose (Kampmann 1980).
  - Maternal use of propylthiouracil is considered acceptable while breastfeeding (Anderson 2016). Infants exposed to antithyroid medications via breast milk should be monitored for adequate growth and development. Routine tests of thyroid function are not recommended (Alexander 2017).
Example 5 pregnancy/Lactation

- Lisinopril: Pregnancy Risk Category D
  - Avoid use in pregnancy: Can cause fetal harm (Regitz et al. 2011). In addition, breastfeeding is not recommended for women with PPCM due to the high metabolic demands of lactation and breastfeeding (Regitz et al. 2011). Lisinopril is not the preferred ACE inhibitor (Regitz et al. 2011). The use of ACE inhibitors during pregnancy is generally contraindicated, and breastfeeding is not recommended for women with PPCM (Regitz et al. 2011). Lisinopril is not the preferred ACE inhibitor (Regitz et al. 2011). The use of ACE inhibitors during pregnancy is generally contraindicated, and breastfeeding is not recommended for women with PPCM (Regitz et al. 2011).

Example 5 Continued

- Lisinopril/Lactation
  - It is not known if lisinopril is present in breast milk. Due to the potential for serious adverse reactions in the breastfed infant, breastfeeding is not recommended by the manufacturer.
  - Lisinopril crosses the placenta and is present in breast milk. Due to the potential for serious adverse reactions in the breastfed infant, breastfeeding is not recommended by the manufacturer (Regitz et al. 2011).

Example 6 pregnancy/Lactation

- Sertraline: Pregnancy Risk Category C
  - Breed Mating: Drugs that act on the renin-angiotensin system are associated with abnormalities. Sertraline crosses the human placenta. Available studies evaluating teratogenic effects following maternal use of sertraline during pregnancy have not shown an overall increased risk of major birth defects. Studies evaluating specific birth defect categories have provided inconsistent results. Sertraline crosses the human placenta. Available studies evaluating teratogenic effects following maternal use of sertraline during pregnancy have not shown an overall increased risk of major birth defects. Studies evaluating specific birth defect categories have provided inconsistent results.
  - It is not known if sertraline is present in breast milk. Due to the potential for serious adverse reactions in the breastfed infant, breastfeeding is not recommended by the manufacturer.
Example 6 continued

Sertraline: Lactation

Sertraline and the active metabolite desmethylsertraline are present in breast milk. Using pooled data, the relative infant dose (RID) of sertraline was calculated to be 0.5% to 3.0% of the weight-adjusted maternal dose (Berle 2011); a RID of 3.7% was noted in one review (Orsolini 2015). In general, breastfeeding is considered acceptable when the RID is <10% (Anderson 2016; Ito 2000), however, some sources note breastfeeding should only be considered if the RID is < 5% for psychotropic agents (Larsen 2015). When an RID is >35%, breastfeeding should generally be avoided (Anderson 2016; Ito 2000). When evaluated, desmethylsertraline milk concentrations were higher than sertraline (Stowe 1997; Stowe 2003). Peak milk concentrations occurred 7-8 hours after (sertraline) and 5 to 11 hours (desmethylsertraline) after the maternal dose (Stowe 1997). However, avoiding breastfeeding during the expected peak concentrations will not generally decrease infant exposure significantly for antidepressants with long half-lives (Berle 2011). Most available studies evaluated serum concentrations of sertraline in the breastfeeding infant as opposed to those in breast milk. Using data from 53 mother-infant pairs, the manufacturer notes sertraline concentrations in exclusively breastfed infants is 2% (range: 0 to 15%) of the mother’s serum concentration.

Adverse events have been reported in breastfeeding infants following maternal use of sertraline in some studies (Hale 2010; Muller 2013; Uguz 2016). Infants of mothers using psychotropic medications should be monitored daily for changes in sleep, feeding patterns, and behavior (Bauer 2013) as well as infant growth and neurodevelopment (Sachs 2013; Sriraman 2015). Maternal use of an SSRI during pregnancy may cause delayed lactogenesis.

When first initiating an antidepressant in a breastfeeding woman, sertraline is one of the preferred agents. Women successfully treated with sertraline during pregnancy may continue to use while breastfeeding if there are no other contraindications (Berle 2011). According to the manufacturer, the decision to breastfeed during therapy should take into account the risk of infant exposure, the benefits of breastfeeding to the infant, and benefits of the treatment to the mother.

Females and males of reproductive potential

• Include when there are requirements or recommendations for pregnancy testing and/or contraception and/or when human and/or animal data suggest drug effects on fertility

• Three headings
  • Pregnancy Testing
  • Contraception
  • Infertility

8.3 Females and males of Reproductive Potential

8.3 Females and males of Reproductive Potential

- Example of pregnancy testing specialty populations
- When there is embryofetotoxicity:
  - Pregnancy testing verify the pregnancy status of females of reproductive potential prior to initiating drug treatment.

Example 1 pregnancy testing

- Isotretinoin
- Isotretinoin and its metabolites can be detected in fetal tissue following maternal use during pregnancy. Boxed Warning: Use of isotretinoin is contraindicated in patients who are or may become pregnant. Birth defects (facial, eye, ear, skull, central nervous system, cardiovascular, thymus, and parathyroid gland abnormalities) have been noted following isotretinoin exposure during pregnancy and the risk for severe birth defects is high, with any dose or even with short treatment duration. Low IQ scores have also been reported. The risk for spontaneous abortion and premature births is increased. Because of the high likelihood of teratogenic effects, all patients (male and female), prescribers, wholesalers, and dispensing pharmacists must register and be active in the iPLEDGE™ risk evaluation and mitigation strategy (REMS) program; do not prescribe isotretinoin for patients who are or who are likely to become pregnant while using the drug. If pregnancy occurs during therapy, isotretinoin should be discontinued immediately and the patient referred to an Obstetrician specializing in reproductive toxicity.

This medication is contraindicated in patients of childbearing potential unless they are able to comply with the guidelines of the iPLEDGE™ pregnancy prevention program. Patients of childbearing potential have been aware of potential problems by participating in the iPLEDGE™ program. Upon discontinuation of treatment, patients of childbearing potential should have a pregnancy test after their last dose and again one month after their last dose. Two forms of contraception should be continued during this time. Any pregnancies should be reported to the iPLEDGE™ program (www.ipledgeprogram.com or 866-495-0654) and the FDA through MedWatch (800-FDA-1088).
Example 2

- Carbamazepine
  - Carbamazepine may decrease plasma concentrations of hormonal contraceptives; alternate or back-up methods of contraception should be considered.

8.3 Females and males of Reproductive Potential

- Example Specialty Population
  - Infertility
    - Infertility Females: Based on findings from animal studies, female fertility may be compromised with a particular drug
    - Drug can lead to inhibition of spermatogenesis and may impair fertility in males of reproductive potential.

Example 3

- Testosterone
  - Large doses of testosterone may suppress spermatogenesis; the impact of fertility may be irreversible. Treatment of hypogonadotropic hypogonadism is not recommended for men desiring fertility (Endocrine Society [Bhasin 2018]).
Implications for Practice

- All medications carry some risk so patients should not take any medication if possible.
- Medications should be individualized for each patient.
- Prescribing for pregnant and lactating females, and males and females of reproductive potential should be a multidisciplinary approach.
- The narrative format of new labeling does not facilitate a consistent decision-making process for prescribers.
- The process will be very time consuming.
- Practitioners should use caution and sound clinical judgment when assessing the safety data provided to support the use of medications when weighing potential benefits to the risks they propose.
- Continued education of clinicians of the new PLLR changes is essential.

Future Challenges

- Most human data related to drug use during pregnancy and lactation do not come from adequate and well-controlled trials.
- Ongoing discussions about what to do when:
  - Data are limited
  - Lack of specific or consistent safety findings
  - Whether to include case reports

Questions
References