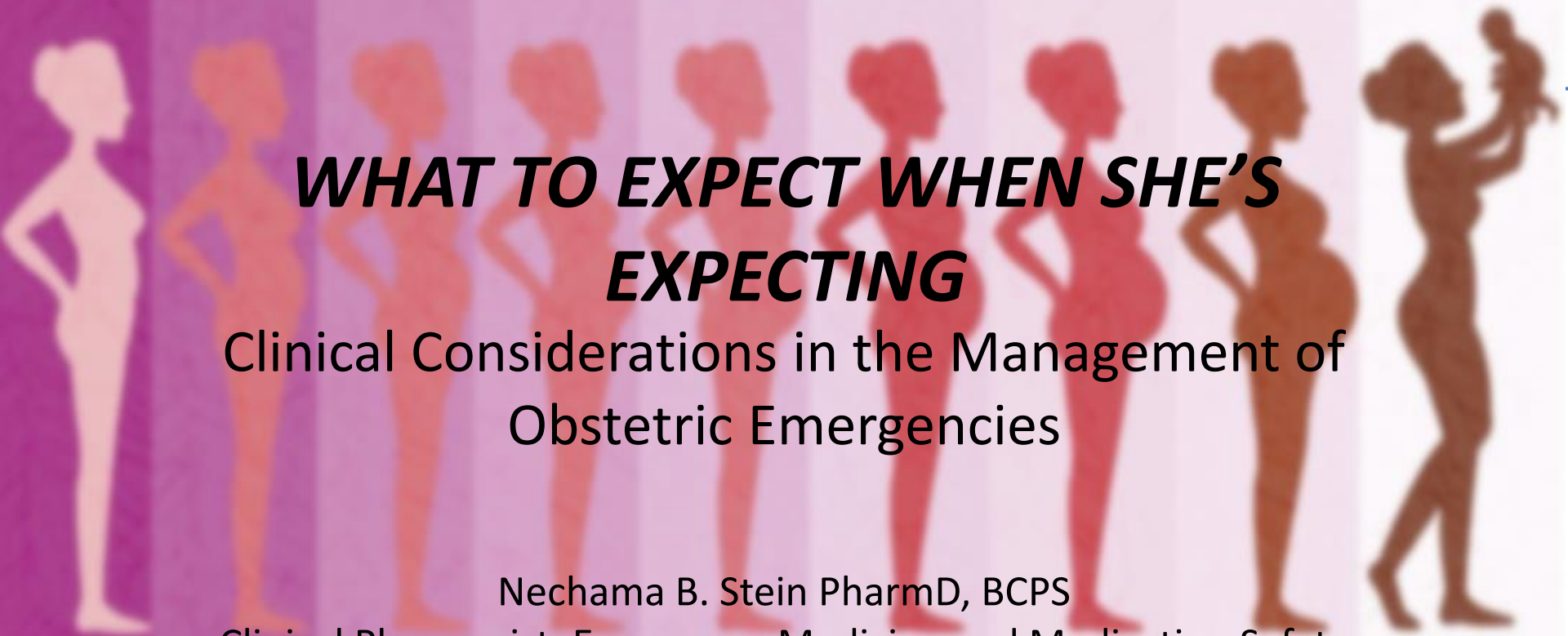


WHAT TO EXPECT WHEN SHE'S EXPECTING

Clinical Considerations in the Management of Obstetric Emergencies

Nechama B. Stein PharmD, BCPS
Clinical Pharmacist, Emergency Medicine and Medication Safety
Maimonides Medical Center

NYSCHP CE Event
September 2020

DISCLOSURES

I have no financial interest/arrangement or affiliation with one or more organizations that could be perceived as a real or apparent conflict of interest in the content of the subject of this presentation

Brand names of all products in this presentation are included for identification purposes only

PHARMACIST OBJECTIVES

- Describe pharmacokinetic and pharmacodynamic alterations in pregnant patients
- Review updated FDA labeling requirements for medication use in pregnancy
- Discuss clinical considerations in managing select obstetric emergencies:
  - Hypertensive crises
  - Obstetric hemorrhage
- Apply clinical knowledge to specific patient case

OBJECTIVES: PHARMACY TECHNICIANS

- Describe physiologic changes in the pregnant patient
- Review updated FDA pregnancy categories
- Identify key concepts in management of select obstetric emergencies:
  - Hypertensive crises
  - Obstetric hemorrhage
- Apply clinical knowledge to specific patient case

MAIMONIDES MEDICAL CENTER

- Community, academic hospital
- Emergency room visits: 100,000 per (non-COVID) year
- Births: 8000 per year

- Emergency Medicine Pharmacists

PREGNANCY PK/PD CONSIDERATIONS

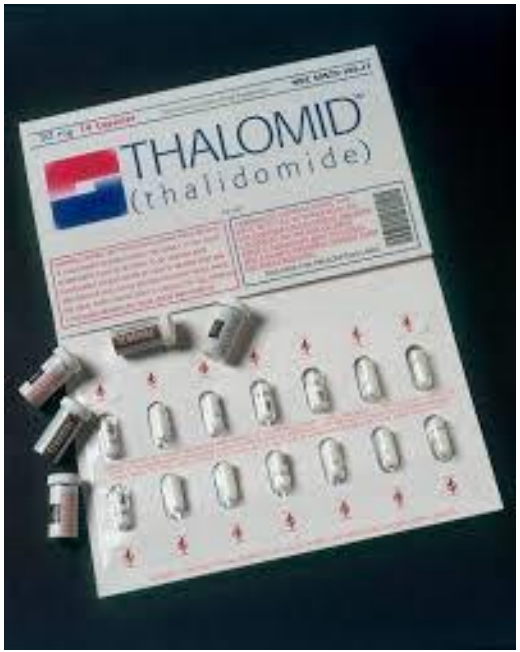
- Marked changes in human physiology → altered drug pharmacokinetics
  - Increased cardiac output → increased blood flow → **altered renal/hepatic drug clearance**
  - Increased total body water → hemidilution → **altered drug binding**
  - Increased body weight → **altered volume of distribution**
  - Alterations in cytochrome P450 enzymes → **altered drug metabolism**

- Consider ability of drug to cross placenta

Clin Pharmacol Ther. 2016;100(1):53-62.

THE LESSON OF THALIDOMIDE

THE LESSON OF THALIDOMIDE



PREGNANCY DRUG LABELING

- Kefauver-Harris amendments (1962): tight FDA regulation of drug approval
- 1979 Labeling for Drugs Used in Man: introduced pregnancy letter risk categories

Pregnancy Category	FDA Statement	Example
Category **A**	Adequate, well controlled (AWC) studies in pregnant women failed to show 1st trimester risk	Levothyroxine
Category **B**	Animal reproductive studies failed to show fetal risk, with no studies in pregnant women available OR adverse effect in animal study but no risk seen in AWC studies in 1st trimester pregnancy	Acetaminophen
Category **C**	Animal reproductive study show adverse effect on fetus, but no AWC studies in humans with benefit outweighing risk OR no animal or AWC human studies	Vancomycin
Category **D**	Positive evidence of human fetal risk, but potential benefits in pregnant women may be acceptable despite risk	Phenytoin
Category **X**	Studies in animals or humans demonstrate fetal abnormalities OR positive evidence of fetal risk outweighs any possible benefit	Isotretinoin Oral contraceptives

Pharmacotherapy. 2014;34(4):389-95.

UPDATED PREGNANCY DRUG LABELING REQUIREMENTS

Dilantin®

(Phenytoin Sodium) 100 mg Extended Oral Capsule

Usage In Pregnancy:

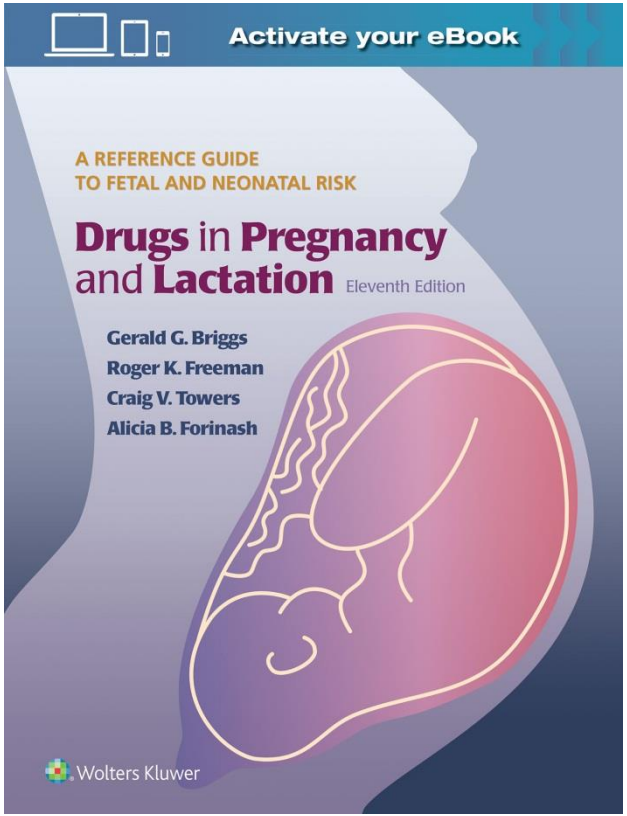
Clinical:

A. *Risks to Mother.* An increase in seizure frequency may occur during pregnancy because of altered phenytoin pharmacokinetics. Periodic measurement of plasma phenytoin concentrations may be valuable in the management of pregnant women as a guide to appropriate adjustment of dosage (see PRECAUTIONS, Laboratory Tests). However, postpartum restoration of the original dosage will probably be indicated.

B. *Risks to the Fetus.* If this drug is used during pregnancy, or if the patient becomes pregnant while taking the drug, the patient should be apprised of the potential harm to the fetus.

Prenatal exposure to phenytoin may increase the risks for congenital malformations and other adverse developmental outcomes. Increased frequencies of major malformations (such as orofacial clefts and cardiac defects), minor anomalies (dysmorphic facial features, nail and digit hypoplasia), growth abnormalities (including microcephaly), and mental deficiency have been reported among children born to epileptic women who took phenytoin alone or in combination with other antiepileptic drugs during pregnancy. There have also been several reported cases of malignancies, including neuroblastoma, in children whose mothers received phenytoin during pregnancy. The overall incidence of malformations for children of epileptic women treated with antiepileptic drugs (phenytoin and/or others) during pregnancy is about 10%, or two- to three-fold that in the general population. However, the relative contributions of antiepileptic drugs and other factors associated with epilepsy to this increased risk are uncertain and in most cases it has not been possible to attribute specific developmental abnormalities to particular antiepileptic drugs.

Patients should consult with their physicians to weigh the risks and benefits of phenytoin during



Select Obstetric Emergencies

Hypertensive Crises

Obstetric Hemorrhage

HYPERTENSIVE CRISES: PRE-ASSESSMENT QUESTION

PR is a 34 year old woman (100 kg) in her 26th week of pregnancy sent in by her OB for hypertension. Upon arrival to the ED she is found with a blood pressure of 205/110. Which agent should be utilized to reduce PR's blood pressure at this time?

a. PR does not require any anti-hypertensive agent as there is allowance of permissive hypertension in the second trimester of pregnancy

b. Enalaprilat 1.25 mg IV push x 1

c. Labetalol 10 mg IV push x 1

d. Magnesium sulfate 6 grams IVPB over 20 minutes x 1

HYPERTENSIVE CRISES: PRE-ASSESSMENT QUESTION

PR is a 34 year old woman (100 kg) in her 26th week of pregnancy sent in by her OB for hypertension. Upon arrival to the ED she is found with a blood pressure of 205/110. As she is being placed on a monitor, she shrieks, loses consciousness and begins to exhibit signs of a self-limiting tonic-clonic seizure. Which agent is indicated to prevent recurrent seizures in PR?

a. Levetiracetam 4500 mg IVPB over 15 minutes STAT

b. Fosphenytoin 1500 mg IVPB over 10 minutes STAT

c. Lorazepam 4 mg IV push over 2 minutes STAT

d. Magnesium 6000 mg IVPB over 20 minutes STAT

HYPERTENSIVE DISORDERS IN PREGNANCY

- **Chronic pre-gestational hypertension:** 2+ isolated pressure readings of 140/90 mmHg before the 20th week of pregnancy
- **Pre-eclampsia:** systolic blood pressure ≥ 140 mmHg OR diastolic blood pressure ≥ 90 mmHg with proteinuria or end organ damage
- **Gestational hypertension:** systolic blood pressure ≥ 140 mmHg OR diastolic blood pressure ≥ 90 mmHg without evidence of proteinuria after 20th week of pregnancy, disappears within 3 months of childbirth
- **Overlapping pre-eclampsia:** chronic hypertension + preeclampsia

Obstet Gynecol. 2019;133(1):e1-e25.

GESTATIONAL HYPERTENSIVE CRISES

- **Pre-eclampsia: systolic blood pressure ≥ 140 mmHg OR diastolic blood pressure ≥ 90 mmHg with new onset of:**
  - Proteinuria > 300 mg in 24 hour urine specimen
  - Platelet count < 100,000
  - Serum creatinine > 1.1 or doubling in level from baseline
  - Liver transaminases ≥ 2 x upper limit normal
  - Pulmonary edema
  - Cerebral or visual symptoms
- **Eclampsia:** grand mal seizures due only to preeclampsia
- **HELLP syndrome:** severe preeclampsia subtype
  - **H**emolysis, **e**levated **l**iver enzymes, **l**ow **p**latelets

Obstet Gynecol. 2019;133(1):e1-e25.

PREECLAMPSIA: RISK FACTORS

- **Risk factors:**
  - Pre-gestational diabetes
  - Chronic hypertension
  - Systemic lupus erythematosus
  - Antiphospholipid syndrome
  - Pre-pregnancy body mass index > 25
  - Chronic kidney disease
  - Multifetal pregnancy/first pregnancy
  - Previous placental insufficiency
  - Advanced maternal age
  - Use of assisted reproductive technology

Obstet Gynecol. 2019;133(1):e1-e25.

PREECLAMPSIA: PROPHYLAXIS

- Hypothesis: pathogenesis due to imbalance of prostacycline and thromboxane A_2

Table 1. Clinical Risk Factors and Aspirin Use*

Level of Risk	Risk Factors	Recommendation
High†	• History of preeclampsia, especially when accompanied by an adverse outcome • Multifetal gestation • Chronic hypertension • Type 1 or 2 diabetes • Renal disease • Autoimmune disease (ie, systemic lupus erythematosus, the antiphospholipid syndrome)	Recommend low-dose aspirin if the patient has one or more of these high-risk factors
Moderate‡	• Nulliparity • Obesity (body mass index greater than 30) • Family history of preeclampsia (mother or sister) • Sociodemographic characteristics (African American race, low socioeconomic status) • Age 35 years or older • Personal history factors (eg, low birth weight or small for gestational age, previous adverse pregnancy outcome, more than 10-year pregnancy interval)	Consider low-dose aspirin if the patient has more than one of these moderate-risk factors§
Low	• Previous uncomplicated full-term delivery	Do not recommend low-dose aspirin

Obstet Gynecol. 2019;133(1):e1-e25.

PREECLAMPSIA: MANAGEMENT

- Pre-eclampsia with features of severe disease
  - Delivery management: ≥ 34 weeks gestation
  - Expectant management:
    - Preterm pregnancies with features of severe disease
    - Gestation ≥ 24 weeks and < 34 weeks
- Pre-eclampsia without features of severe disease
  - Delivery management: term pregnancy
  - Expectant management:
    - Monitor/treat hypertension
    - Patient education
    - Laboratory follow up
    - Timing of delivery

Obstet Gynecol. 2019;133(1):e1-e25.

BLOOD PRESSURE MANAGEMENT

- Indications for antihypertensive therapy:
  - Blood pressure ≥ 150/100 mmHg for ≥ 15 minutes
  - Signs of cardiac decompensation or cerebral symptoms
  - Younger women with baseline “low” blood pressure
- Considerations for specific agents:
  - Acute treatment versus longer term BP control
  - Safety, efficacy and use in pregnancy
  - Clinician experience, familiarity

Obstet Gynecol. 2019;133(1):e1-e25.

BLOOD PRESSURE MANAGEMENT:

Recommended Agents

- Labetalol IV
- Hydralazine IV
- Nifedipine IR oral

Agents to Avoid

- ACE-I/ARBS
- Spironolactone
- Nitroprusside
- Nimodipine
- Diazoxide

Obstet Gynecol. 2019;133(1):e1-e25.

BLOOD PRESSURE MANAGEMENT

Labetalol

- Dosing: 10-20 mg IV x 1 over 2 minutes
- Not at goal in 10 minutes: repeat 40 mg slow IV injection
- Remains not at goal after 10 minutes: repeat 80 mg slow IV injection
- BP threshold remains exceeded: switch to hydralazine, consult specialist

Hydralazine

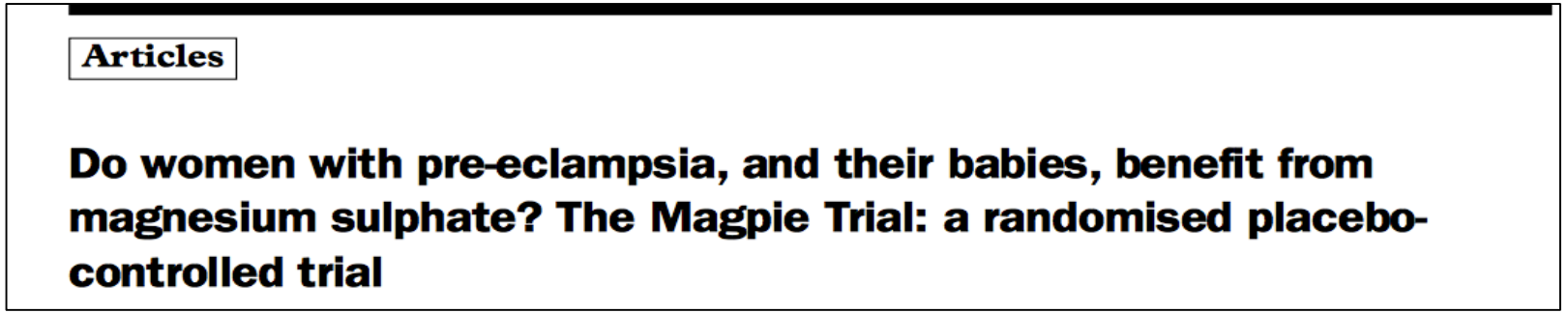
- Dosing: 5 mg IV or IM, then 5-10 mg IV every 20-40 minutes
- Maximum cumulative dose: 20 mg
- Continuous infusion (not preferred): 0.5-10 mg/hr initiated within 30-60 minutes

Nifedipine

- Dosing: 10-20 mg PO, repeated in 20 minutes if needed. Follow with 10-20 mg PO every 2-6 hours within 30-60 minutes.
- Maximum dose: 180 mg/day

Obstet Gynecol. 2019;133(1):e1-e25.

PREECLAMPSIA: SEIZURE PROPHYLAXIS



Articles

Do women with pre-eclampsia, and their babies, benefit from magnesium sulphate? The Magpie Trial: a randomised placebo-controlled trial

- Magnesium: drug of choice for eclampsia prevention
  - More effective than placebo (RR: 0.41, 95% CI 0.29-0.58; 6 trials, n: 11,444
  - More effective than phenytoin (RR: 0.08, 95% CI 0.01-0.60; 3 trials, n: 2291
  - More effective than nimodipine alone (RR: 0.33, 95% CI 0.14-0.77) 1 trial, n: 1650
- Dosing: non-standardized, high doses recommended
  - 6 grams IV over 15-20 minutes bolus, then 2 grams/hr IV
  - 5 grams IM into each buttock (10 grams total), then 5 grams IM every 4 hours

Lancet. 2002;359(9321):1877-90. • Cochrane Database Syst Rev. 2010;(11):CD000025.

MAGNESIUM SULFATE

- Mechanism: unknown
- Monitoring
  - Maintenance dose considerations:
    - Ensure patellar reflex present (level: 7-10)
    - Respiratory rate > 12/min (level: 10-13)
    - Urine output > 100 mL over 4 hours
  - Avoid rapid infusion

- Antidote: calcium gluconate 10%: 15-30 mL IV over 2-5 minutes if cardiac toxicity + furosemide to accelerate urinary magnesium clearance
- Safety: utilizing highly concentrated magnesium at high doses

Clin Pharmacokinet. 2000;38(4):305-14. • Obstet Gynecol. 2019;133(1):e1-e25.

ECLAMPSIA

- Preeclampsia with new onset, generalized, tonic-clonic seizures/coma
- Management
  - Supplemental oxygen, trauma protection
  - Treatment of hypertension
  - Prevention of recurrent seizures
- Magnesium sulfate: anticonvulsive of choice for recurrent seizure prevention
- Usually indicates need for emergent delivery
  - Symptoms resolve post-partum

Obstet Gynecol. 2019;133(1):e1-e25.

Select Obstetric Emergencies

Hypertensive Crises

Obstetric Hemorrhage

OBSTETRIC HEMORRHAGE PRE-ASSESSMENT QUESTION

You are called to the emergency bay to respond to BW, a 29 year old woman who delivered her baby while en route to the hospital. The OB fellow requests oxytocin STAT as BW is experiencing continued hemorrhage post partum. Which of the following statement(s) is/are correct regarding oxytocin?

A. Oxytocin is a prostaglandin that results in uterine muscle contraction to decrease post-partum hemorrhage (PPH)

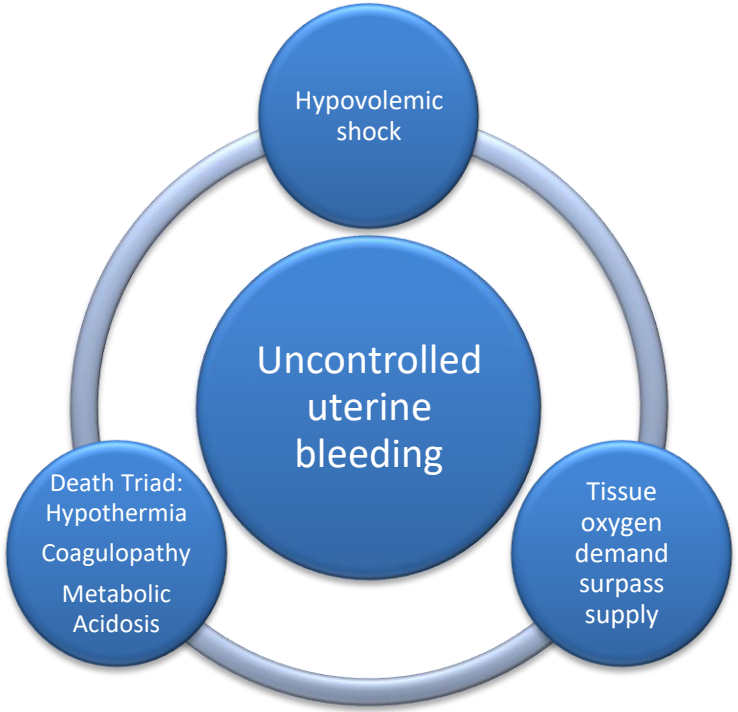
B. Oxytocin is first-line uterotonic as it has a comparatively favorable safety profile and is generally effective

C. Oxytocin has an equal dose-dependent effect on all patients

D. Optimal dosing of oxytocin is not defined, but institutions should follow ISMP safety recommendation of standardized concentrations, dosing and administration via infusion pump as it is a high-risk medication

OBSTETRIC HEMORRHAGE

- Post-partum hemorrhage: complication of ~5% deliveries
  - 60% of cases: no identifiable risk factors
- Most common cause: uterine atony
- Management:
  - Drug of choice: oxytocin
    - Prophylaxis during third stage of labor
- Rapid infusion of crystalloids
- Packed red blood cells
- If bleeding persists
  - Uterotonic therapy
    - Carboprost tromethamine
    - Methylergonovine
  - If unavailable/contraindicated: misoprostol



Clin Obstet Gynecol. 2002;45(2):330-44.

OBSTETRIC HEMORRHAGE: MEDICATION CONSIDERATIONS

- **Oxytocin** (Pitocin®): Stimulates uterine contraction
  - Used for prevention and treatment of post-partum hemorrhage
- Dosing:
  - IM: 10 units IM after delivery of placenta
  - IV: Optimal regimen not established
    - 40 units/1 L LR running fluid; rate adjusted to sustain uterine contraction

- **Methylergonovine** (Methergine®): Ergot alkaloid, increases tone, rate and amplitude of uterine smooth muscle
- Dosing: 0.2 mg IM, repeat PO for at least 24-48 hours after IM dose
  - IV administration: severe hypertension, myocardial ischemia

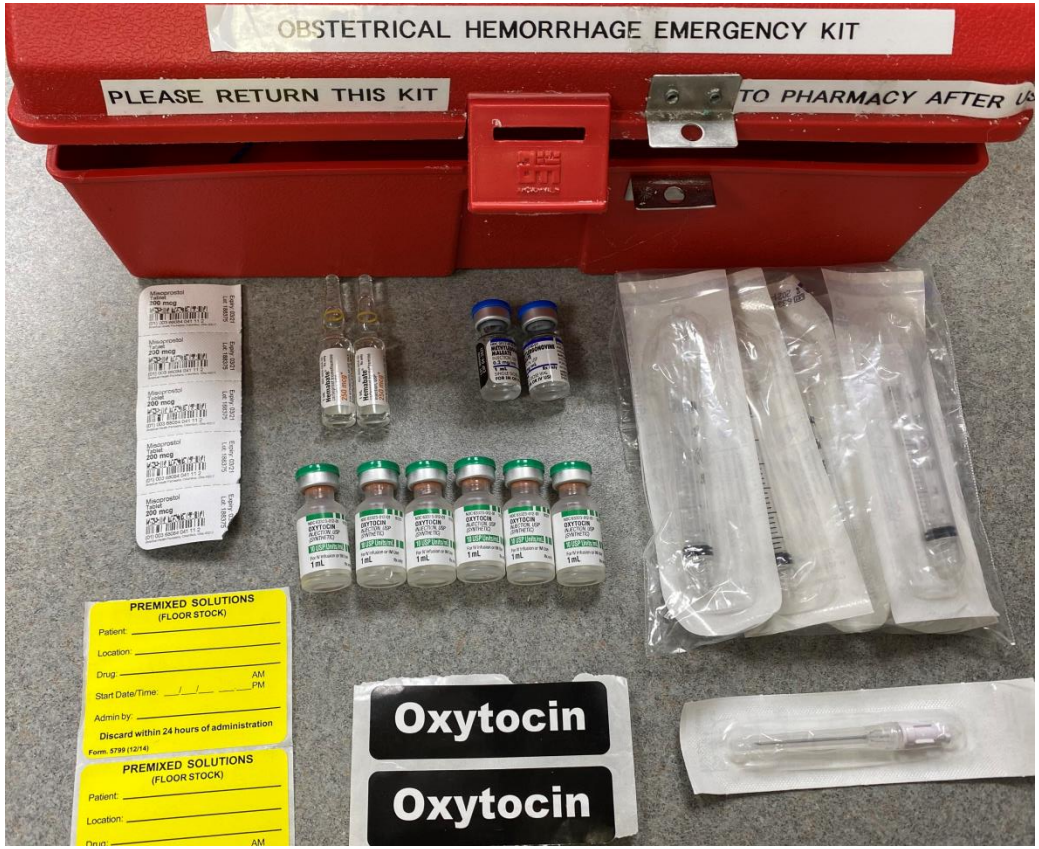
Clin Obstet Gynecol. 2002;45(2):330-44.

OBSTETRIC HEMORRHAGE: MEDICATION CONSIDERATIONS

- Prostaglandins: alternative second-line agents in hypertensive women
- **Carboprost tromethamine** (15-methyl prostaglandin F2α) [Hemabate®]
  - Significant smooth muscle contraction (60% rate diarrhea)
  - Dose: 250 mcg IM
  - Contraindication: asthma (bronchoconstriction)
- **Dinoprostone** (Prostaglandin E2) [Prostin E2®]
  - Naturally occurring oxytocic
  - Increases temperature due to effect on hypothalamic regulation
  - Vaginal suppository: 20 mg PV or PR stored in freezer
- **Misoprostol** (synthetic prostaglandin E_1 analogue) [Cytotec®]
  - Rectal, oral, sublingual administration; lack of studies in PPH
  - Dose: 800 -- 1000 mcg, vaginal route not recommended in PPH

Clin Obstet Gynecol. 2002;45(2):330-44.

OB HEMORRHAGE KIT



ASSESSMENT QUESTION

Which of the following are potential benefits of the updated FDA regulation for Pregnancy and Lactation Labeling? Select all that apply:

a) Improved guidance for accidental exposures and nature, severity, timing, incidence rate or treatability of potential fetal injury

b) Improved description of maternal to fetus benefit versus risk assessment

c) Increased confusion regarding drug use and fetal health risk

d) Standardized language to assess risk for drugs in which only animal studies are available

ASSESSMENT QUESTION

Which of the following are potential benefits of the updated FDA regulation for Pregnancy and Lactation Labeling? Select all that apply:

a) Improved guidance for accidental exposures and nature, severity, timing, incidence rate or treatability of potential fetal injury

b) Improved description of maternal to fetus benefit versus risk assessment

c) Increased confusion regarding drug use and fetal health risk

d) Standardized language to assess risk for drugs in which only animal studies are available

HYPERTENSIVE CRISES: ASSESSMENT QUESTION

PR is a 34 year old woman (100 kg) in her 26th week of pregnancy sent in by her OB for hypertension. Upon arrival to the ED she is found with a blood pressure of 205/110. Which agent should be utilized to reduce PR's blood pressure at this time?

a. PR does not require any anti-hypertensive agent as there is allowance of permissive hypertension in the second trimester of pregnancy

b. Enalaprilat 1.25 mg IV push x 1

c. Labetalol 10 mg IV push x 1

d. Magnesium sulfate 6 grams IVPB over 20 minutes x 1

HYPERTENSIVE CRISES: ASSESSMENT QUESTION

PR is a 34 year old woman (100 kg) in her 26th week of pregnancy sent in by her OB for hypertension. Upon arrival to the ED she is found with a blood pressure of 205/110. Which agent should be utilized to reduce PR's blood pressure at this time?

a. PR does not require any anti-hypertensive agent as there is allowance of permissive hypertension in the second trimester of pregnancy

b. Enalaprilat 1.25 mg IV push x 1

c. Labetalol 10 mg IV push x 1

d. Magnesium sulfate 6 grams IVPB over 20 minutes x 1

HYPERTENSIVE CRISES: ASSESSMENT QUESTION

PR is a 34 year old woman (100 kg) in her 26th week of pregnancy sent in by her OB for hypertension. Upon arrival to the ED she is found with a blood pressure of 205/110. As she is being placed on a monitor, she shrieks, loses consciousness and begins to exhibit signs of a self-limiting tonic-clonic seizure. Which agent is indicated to prevent recurrent seizures in PR?

a. Levetiracetam 4500 mg IVPB over 15 minutes STAT

b. Fosphenytoin 1500 mg IVPB over 10 minutes STAT

c. Lorazepam 4 mg IV push over 2 minutes STAT

d. Magnesium 6000 mg IVPB over 20 minutes STAT

HYPERTENSIVE CRISES: ASSESSMENT QUESTION

PR is a 34 year old woman (100 kg) in her 26th week of pregnancy sent in by her OB for hypertension. Upon arrival to the ED she is found with a blood pressure of 205/110. As she is being placed on a monitor, she shrieks, loses consciousness and begins to exhibit signs of a self-limiting tonic-clonic seizure. Which agent is indicated to prevent recurrent seizures in PR?

a. Levetiracetam 4500 mg IVPB over 15 minutes STAT

b. Fosphenytoin 1500 mg IVPB over 10 minutes STAT

c. Lorazepam 4 mg IV push over 2 minutes STAT

d. **Magnesium 6000 mg IVPB over 20 minutes STAT**

OBSTETRIC HEMORRHAGE ASSESSMENT QUESTION

You are called to the emergency bay to respond to BW, a 29 year old woman who delivered her baby while en route to the hospital. The OB fellow requests oxytocin STAT as BW is experiencing continued hemorrhage post partum. Which of the following statement(s) is/are correct regarding oxytocin?

A. Oxytocin is a prostaglandin that results in uterine muscle contraction to decrease post-partum hemorrhage (PPH)

B. Oxytocin is first-line uterotonic as it has a comparatively favorable safety profile and is generally effective

C. Oxytocin has an equal dose-dependent effect on all patients

D. Optimal dosing of oxytocin is not defined, but institutions should follow ISMP safety recommendation of standardized concentrations, dosing and administration via infusion pump as it is a high-risk medication

OBSTETRIC HEMORRHAGE ASSESSMENT QUESTION

You are called to the emergency bay to respond to BW, a 29 year old woman who delivered her baby while en route to the hospital. The OB fellow requests oxytocin STAT as BW is experiencing continued hemorrhage post partum. Which of the following statement(s) is/are correct regarding oxytocin?

A. Oxytocin is a prostaglandin that results in uterine muscle contraction to decrease post-partum hemorrhage (PPH)

B. Oxytocin is first-line uterotonic as it has a comparatively favorable safety profile and is generally effective

C. Oxytocin has an equal dose-dependent effect on all patients

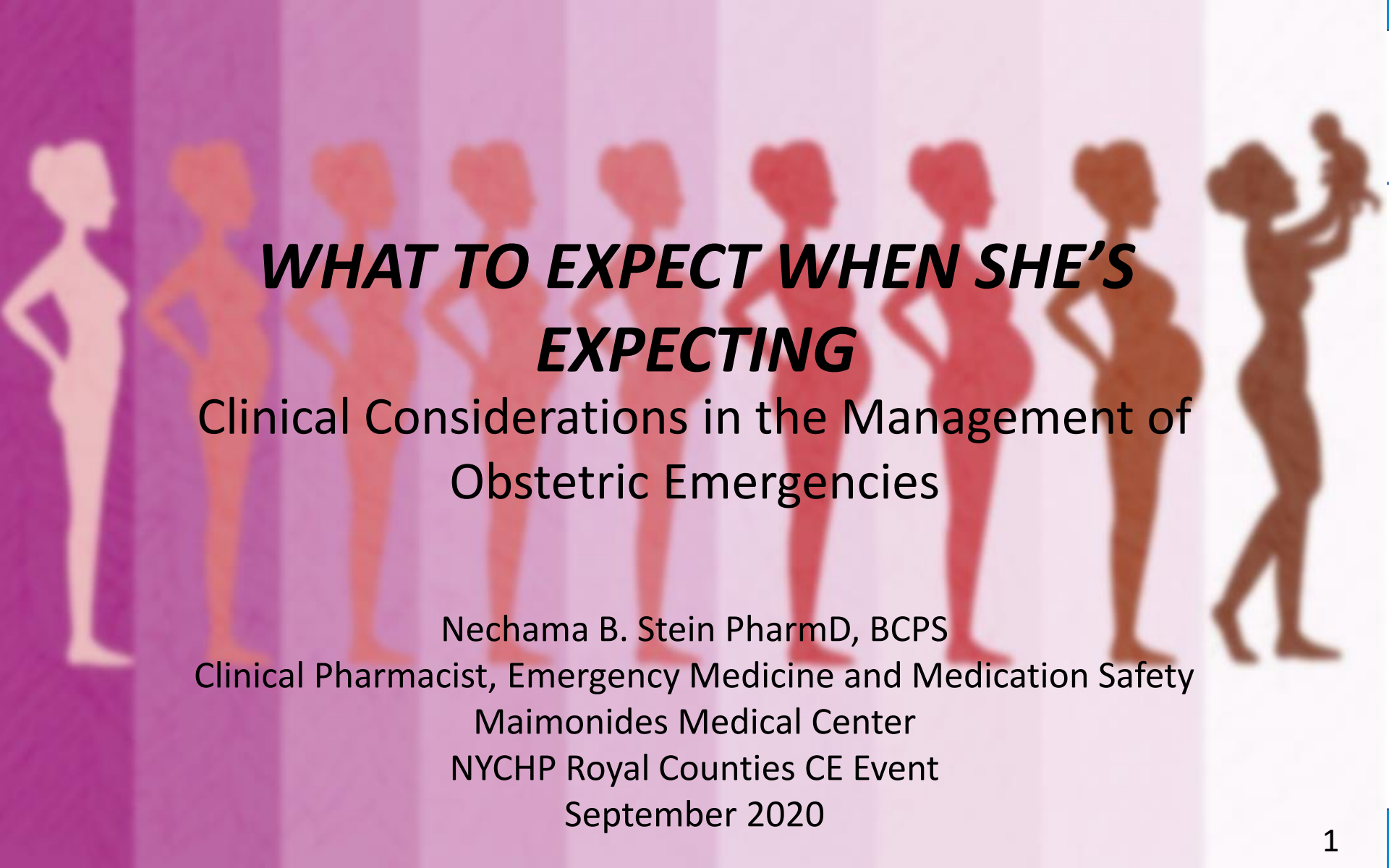
D. Optimal dosing of oxytocin is not defined, but institutions should follow ISMP safety recommendation of standardized concentrations, dosing and administration via infusion pump as it is a high-risk medication

SUMMARY

- Obstetric emergencies represent a small fraction of our ED visits
  - Early recognition and appropriate management is KEY
- Pharmacists play an important role in medication management in obstetric emergencies
  - Alterations of drug dosing
  - Safety in pregnancy/effect(s) on fetus
- Updates to FDA pregnancy Labeling requirements aid in providing comprehensive clinical considerations of medications used in pregnancy

REFERENCES

1. Tasnif Y, Morado J, Hebert MF. Pregnancy-related pharmacokinetic changes. Clin Pharmacol Ther. 2016;100(1):53-62.
2. Ramoz LL, Patel-shori NM. Recent changes in pregnancy and lactation Labeling: retirement of risk categories. Pharmacotherapy. 2014;34(4):389-95.
3. ACOG Practice Bulletin No. 202: Gestational Hypertension and Preeclampsia. Obstet Gynecol. 2019;133(1):e1-e25.
4. Altman D, Carroli G, Duley L, et al. Do women with pre-eclampsia, and their babies, benefit from magnesium sulphate? The Magpie Trial: a ran
5. Duley L, Gülmezoglu AM, Henderson-smart DJ, Chou D. Magnesium sulphate and other anticonvulsants for women with pre-eclampsia. Cochrane Database Syst Rev. 2010;(11):CD000025.domised placebo-controlled trial. Lancet. 2002;359(9321):1877-90.
6. Lu JF, Nightingale CH. Magnesium sulfate in eclampsia and pre-eclampsia: pharmacokinetic principles. Clin Pharmacokinet. 2000;38(4):305-14.
7. Dildy GA. Postpartum hemorrhage: new management options. Clin Obstet Gynecol. 2002;45(2):330-44.



WHAT TO EXPECT WHEN SHE'S EXPECTING

Clinical Considerations in the Management of Obstetric Emergencies

Nechama B. Stein PharmD, BCPS
Clinical Pharmacist, Emergency Medicine and Medication Safety
Maimonides Medical Center
NYCHP Royal Counties CE Event
September 2020