Depression

Jamie Stern MD, MPH

Case: A 30 year old married woman presents with a 1 month history of depressed mood, tearfulness, fatigue. She is 10 weeks pregnant. Two years ago, she was diagnosed with MDD (moderate to severe) and treated with sertraline for 6 months at a dose of 100 mg/day. She self discontinued it after that time. She does not want to take any medications with this pregnancy, but feels so poorly that she will consider it if you recommend it.

1. The most appropriate pharmocologic treatment of our case patient would include:
   A. Buproprion
   B. Desipramine
   C. Paroxitine
   D. Sertraline

2. Which of the following are true regarding antidepressant therapy and depression in our patient?
   A. There is strong RCT evidence assessing the safety and efficacy of antidepressants during pregnancy
   B. Women with moderate to severe depression are best managed with psychotropic medication during pregnancy
   C. It is recommended to start with a high dose of antidepressant therapy because she has a history of depression in the past.

3. The majority of women with a history of MDD who discontinue their SSRI before or early in pregnancy experience a clinically significant relapse?
   A. True
   B. False

Pregophobia: Guiding Your Patients Through Pregnancy from Asthma to Zoloft
2012 SGIM Annual Meeting, Orlando, FL

Asthma

Rachel Bonnema MD, MEd

Case 1:

Krysta is a 23-year-old patient who is referred to you by her midwife for evaluation of shortness of breath. She is 14 weeks pregnant. She has a history of asthma, but has not been on medication for some time as she has had no insurance. She is now on Medicaid and can afford treatment. She is SOB with exertion, has occasional nonproductive cough and wakes at night with SOB about once every week or so. She does not smoke, but works as a waitress at the casino. Exam is significant for expiratory wheezes throughout. What do you do for her today?

A. Her job is obviously contributing to her symptoms, advise her to find other employment.

B. Provide her an albuterol inhaler for her exertional symptoms.

C. Start an inhaled corticosteroid for daily treatment along with albuterol rescue inhaler.

D. Start her on a long-acting beta agonist for daily treatment.

E. Start oral steroid treatment as it has the best safety data in pregnancy.

Case 2:

A patient of yours with moderate asthma has recently become pregnant. Her asthma is well controlled on salmeterol/fluticasone (250/50), 1 puff bid. She has no other medical conditions. She wonders whether she should continue with this medication during pregnancy. What do you do?

A. Continue her on the same medication

B. Decrease her dose of the medication

C. Refer her to MFM for management

D. Stop her medication

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Hypertension

Jennifer Corbelli MD

1. A 35 year old woman presents to your office. She happily reports that she is 6 weeks pregnant. She has no past medical history except for hypertension which has been well-controlled on HCTZ 25 mg. Her ranges from 120-130/60-70 and today is 122/62. Before treatment, her BP averaged 150/85. She asks if she should continue her HCTZ. How would you counsel her regarding her HCTZ?

   A. She should continue her HCTZ

   B. She should stop her HCTZ and start a different antihypertensive

   C. She should stop her HCTZ and you would not recommend starting a different antihypertensive agent at this time.

2. A 28 year old female who is 10 weeks pregnant presents to your office. Her blood pressure is borderline elevated and you are considering treatment. What changes, if any, would you expect in her BP as she enters her second trimester?

   A. Her BP will likely increase because of expansion of plasma volume during pregnancy

   B. Her BP will likely decrease because of decreased systemic vascular resistance

   C. No change: whatever a woman's BP is during her 1st trimester is likely where it will remain for the duration of her pregnancy

3. A 38 year old female presents in her 14th week of pregnancy. She brings in readings from home that are persistently elevated (~170/100). You decide that she needs treatment. She has no comorbidities and no other issues at this time. Which of the following blood pressure will you target with your treatment?

   A. <150/95

   B. <140/90

   C. <130/85

   D. <120/80

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Diabetes

Anu Munshi MD, MS

Case 1: 33 year old female who is 8 weeks pregnant and wants to establish care with you. She is required to have a physical and blood work done by her new health insurance.
Physical Exam – all normal except BMI is 35 (has only gained 5 lbs so far in pregnancy)
Labs – all normal except:
Fasting blood sugar – 210
Repeat fasting BS – 220

What is your next step?

A. Order a HgbA1C to get an idea about past few months
B. Tell patient she has gestational diabetes
C. Tell patient she has diabetes mellitus II
D. Refer her to her OB because you are unsure

Case 2: Well known patient to your practice. She is a 27 year old at 20 weeks who was recently diagnosed with gestational diabetes by her OB. She comes to you for a second opinion regarding starting medication for her GDM. Her fasting sugars are roughly between 95 and 100 and her 1-hour postprandial sugars are 130-140. Do you initiate medical therapy for her?

A. Yes, I would start her on meds right away
B. No, I would try diet control first
C. No, I would check a few more fasting sugars
D. No, I would recommend exercise first

Case 3: 25 year old with PCOS and newly diagnosed GDM at 25 weeks who needs to be started on medication. Her OB is out of town. She has been a diet controlled GDM during her last pregnancy but currently her fasting sugars are high enough to need medication.

A. Insulin
B. Glyburide
C. Metformin
D. Glipizide
E. Actos

Case 4: 25 year old Type II diabetic who comes to you for preconception counseling as she is thinking about starting a family. She is on maximum doses of Metformin and Glyburide.
PE – normal, BMI 33
A1C – 10.0
U/A – proteinuria

What option(s) does she have for improving her sugar control and still staying safe if she does get pregnant?

A. NPH
B. Aspart
C. Glargine
D. Lispro
E. Regular insulin

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Thyroid Disorders

Sarah Tilstra MD

1. Who Should be Screened for Thyroid Disease? Choose all that apply.

   A. 27 yo with no PMH or complaints. Mother has hypothyroidism. She is trying to conceive

   B. 27 yo with no PMH or complaints. Had a miscarriage at 8 weeks last year, wants to try to conceive again

   C. All pregnant women

   D. All women trying to conceive and all pregnant women

2. You are seeing a 27 yo with a history of hypothyroidism who presents for pre-conception counseling. She has no complaints. Her TSH last month was 3.6 mIU/L. She has been on levothyroxine 100mcg for one year. You adjusted her levothyroxine to 112.5mcg as you know her pre-pregnancy goal TSH is <2.5. Her TSH 6 weeks later is 2.3uU/ml. Three months later, your patient returns. She took a pregnancy test this week and it's positive. Urine dip in the office confirms her pregnancy. Her LMP was ~ 6 weeks ago. TSH is 2.1 mIU/L and free T4 is normal.

   Should you adjust her levothyroxine dose at this visit?

   A. Yes, increase by 30%

   B. Yes, increase to 150mcg

   C. Yes, decrease by 30%

   D. No adjustment is needed

3. Who should be started on levothyroxine? Choose all that apply.

   A. 8 weeks pregnant, TSH 3.6 mIU/L, free T4 just below normal limits

   B. 8 weeks pregnant, TSH 10.4 mIU/L, free T4 in the high-normal range

   C. 8 weeks pregnant, TSH 6.3 mlU/L, free T4 in the normal range, negative TPO antibodies

4. You are seeing one of your well-known patients as a carve-out for intermittent palpitations and severe nausea/vomiting. She is 10 weeks pregnant and was not able to contact her OB. You astutely check her thyroid studies which show an undetectable TSH and fT4 above the normal limits. TSH receptor antibodies are negative. You diagnose gestational hyperthyroidism.

   What is the most appropriate management of gestational hyperthyroidism?

   A. Start propylthiouracil (PTU) now, change to methimazole at the start of the second trimester

   B. Start methimazole now, change to PTU at the start of second trimester

   C. Symptom management only, do not start PTU or methimazole

FDA Medication Classification

A: Controlled studies in pregnant women fail to demonstrate a risk to the fetus in the first trimester with no evidence of risk in later trimesters.

Example: Prenatal Vitamins

B: Presumed safety based on animal studies, with no controlled studies in pregnant women, or animal studies have shown an adverse effect not confirmed in controlled studies.

Example: penicillin, methyldopa, hydrochlorothiazide

C: studies in animals have shown adverse fetal effects **or** there are no controlled data from studies in women. Use if potential benefits outweigh risks.

Example: fluoroquinolones, glipizide

D: Studies have shown a risk to the fetus. Only indicated if life-threatening illness.

Example: ACE inhibitors, lorazepam

X: Highly unsafe: risk of use outweighs any potential benefit.

Example: statins, warfarin

Pregophobia:

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Jamie Stern, MD, MPH
Rachel Bonnema, MD, MS
Jennifer Corbelli, MD
Anu Munshi, MD, MS
Sarah Tilstra, MD

Workshop Format

- Introductions and brainstorming (10 minutes)
- Split into small groups
- 5 content areas (15 minutes each)
  - Depression, asthma, HTN, DM, thyroid disorders
  - 5 minutes for questions/answers in small groups
  - 10 minutes content
- Discussion (10 minutes)

Brainstorming:

- Why are you here?
- What is hard about managing pregnant patients in the primary care setting?

Depression

Jamie Stern, MD, MPH
University of Pittsburgh School of Medicine

Case

- A 30 year old married woman presents with a 1 month history of depressed mood, tearfulness, fatigue. She is 10 weeks pregnant. Two years ago, she was diagnosed with MDD (moderate to severe) and treated with sertraline for 6 months at a dose of 100 mg/day. She self discontinued it after that time. She does not want to take any medications with this pregnancy, but feels so poorly that she will consider it if you recommend it.

Question #1

- The most appropriate pharmacologic treatment of our case patient would include:

    A. Bupropion

    B. Desipramine

    C. Paroxetine

    D. Sertraline

Question #2

- Which of the following is true regarding antidepressant therapy and depression in our patient?
  A. There is strong RCT evidence assessing the safety and efficacy of antidepressants during pregnancy
  B. Women with moderate to severe depression are best managed with psychotropic medication during pregnancy
  C. It is recommended to start with a high dose of antidepressant therapy because she has a history of depression in the past.

Question #3

- True or False: The majority of women with a history of MDD who discontinue their SSRI before or early in pregnancy experience a clinically significant relapse?

Prevalence

- 12.7% of women report depression during pregnancy
- Compare to 7% of adults reporting depression in the past 12 months

Bennett, HA. Prevalence of depression during pregnancy: systematic review. Obstet Gyn 2004;130:698-709

Risk Factors for Depression during Pregnancy

- **History of Depression**
- FH of depression/BP
- Childhood maltreatment and sexual abuse
- Single motherhood
- > 3 children
- Cigarette smoking
- Low income
- Age <20 years
- Insufficient social supports
- Domestic violence

Risks of Untreated Depression for Mom and Child

- Difficulty performing ADL's
- No prenatal care
- Inadequate diet
- Use of tobacco, alcohol and other substances
- Risk of self harm or suicide
- Miscarriage
- Impaired fetal growth/preterm birth
- Infant temperament issues- increased irritability
- Fewer facial expressions
- Behavior issues in childhood

Management

- Multidisciplinary care:
  - PCP
  - Ob/Gyn
  - Mental health professional
- The patient should be informed about the risks/benefits of untreated vs. treated depression

Antidepressant Therapy

- There are no data from RCT's assessing the safety and efficacy of antidepressants during pregnancy
- Current recommendations are derived from cohort, case-control studies, meta-analyses or population-based registries

Stewart, Donna. Depression during pregnancy. NEJM 2011;365;1605-1611.

SSRI Teratogenicity

- 2 large case-control trials in the June 28, 2007 issue of the NEJM
  - Louik – First-Trimester Use of SSRI's and the Risk of Birth Defects
  - Alwan – Use of SSRI's in Pregnancy and the Risk of Birth Defects

Louik, Carol. First-trimester use of SSRI's and the risk of birth defects. NEJM 2007;356:2675-83.
Alwan, sura. Use of SSRI's in pregnancy and the risk of birth defects. NEJM 2007; 356:2684-92.

Louik Study

- Assessed associations between first trimester maternal use of SSRI's and the risk of birth defects among 9849 infants with and 5860 infants without birth defects participating in the Slone Epidemiology Center Birth Defects Study

Louik Results

- Craniosynostosis: OR 0.8, 95% CI 0.2-3.5
  115 subjects, 2 exposed
- Omphalocele: OR 1.4, 95% CI 0.4-4.5
  127 subjects, 3 exposed
- Heart defects overall: OR 1.4, 95% CI 0.9-1.6
  3724 subjects, 100 exposed

Louik Results – Individual SSRI's

- Sertraline:
  - Omphalocele — **OR 5.7, 95% CI 1.6-20.7**, 3 exposed subjects
  - Septal Defects — **OR 2.0, 95% CI 1.2-4.0**, 13 exposed subjects
- Paroxetine:
  - RV outflow tract obst — **OR 3.3, 95% CI 1.3-8.8**, 6 exposed subjects

Louik Study

- No evidence that first trimester SSRI use is associated with craniosynostosis, omphalocele, or heart defects
- However, sertraline and paroxitine may contribute to the risk of certain birth defects
- The absolute risks of these rare defects are small

Alwan Study

- Obtained data on 9622 case infants with major birth defects and 4092 control infants
- Mothers completed a standardized telephone interview
- Exposure to SSRI's was defined as treatment with any SSRI from 1 month before to 3 months after conception

Alwan Results

- Anencephaly: **OR 2.4, 95% CI 1.1-5.1**

  214 infants, 9 exposed

- Craniosynostosis: **OR 2.5, 95% CI 1.5-4**

  432 infants, 24 exposed

- Omphalocele **OR 2.8, 95% CI 1.3-5.7**

  181 infants, 11 exposed

Alwan Study

- No significant associations between the use of SSRI's in early pregnancy and the risks of the majority of birth defects assessed
- Data shows associations between SSRI use and the occurrence of anencephaly, craniosynostosis, and omphalocele

Teratogenicity of SSRI's: Louik and Alwan

- Both studies used similar case-control methods
- Results differ in some respects
- The similar conclusion from both studies is that any increased risk of malformations in association with the use of SSRI's is likely to be small in absolute risk
- Unfortunately, there is no clear line separating "risk" and "no risk"

Risk of Relapse – Cohen Study

- Prospective study of 201 pregnant women enrolled between March 1999 and April 2003
- Enrollment criteria
  - History of major depression prior to pregnancy
  - Less than 16 weeks gestation
  - Euthymic for at least 3 months prior to their LMP
  - Currently or recently receiving antidepressants

Cohen, Lee. Relapse of major depression during pregnancy in women who maintain or discontinue antidepressant treatment. JAMA 2006; 295:499-507.

Cohen Study

- 43% (86/201) experienced a relapse of major depression during pregnancy
  - Maintained medication -> 26% relapsed (21/82)
  - Discontinued medication -> 68% relapsed (44/65)
  - **Hazard ratio 5.0, 95% CI 2.9-9.1, p<.001**

Cohen Study

- Pregnancy is not “protective” with respect to risk of relapse of major depression
- Relapse is common amongst women who discontinue their antidepressant therapy.

Take Home Points!

- Decision to use SSRI's during pregnancy must consider the risks/benefits
  - Mild/moderate depression-> psychotherapy
  - Moderate/severe depression -> SSRI's are reasonable
- Any increased risk of malformations in association with the use of SSRI's is likely to be small in absolute risk
- Many authors recommend sertraline as first line therapy (over fluoxetine and paroxetine)
- Use the lowest dose possible to minimize risk
- The risk of relapse is high in women who discontinue their antidepressants during pregnancy

Asthma

Rachel Bonnema, MD, MS
University of Nebraska Medical Center

Case 1

Krysta is a 23-year-old patient who is referred to you by her midwife for evaluation of shortness of breath. She is 14 weeks pregnant. She has a history of asthma, but has not been on medication for some time as she has had no insurance. She is now on Medicaid and can afford treatment. She is SOB with exertion, has occasional nonproductive cough and wakes at night with SOB about once every week or so. She does not smoke, but works as a waitress at the casino. Exam is significant for expiratory wheezes throughout. What do you do for her today?

Case 1

A. Her job is obviously contributing to her symptoms, advise her to find other employment.
B. Provide her an albuterol inhaler for her exertional symptoms.
C. Start an inhaled corticosteroid for daily treatment along with albuterol rescue inhaler.
D. Start her on a long-acting beta agonist for daily treatment.
E. Start oral steroid treatment as it has the best safety data in pregnancy.

Case 2

A patient of yours with moderate asthma has recently become pregnant. Her asthma is well controlled on salmeterol/fluticasone (250/50), 1 puff bid. She has no other medical conditions. She wonders whether she should continue with this medication during pregnancy. What do you do?

A. Continue her on the same medication
B. Decrease her dose of the medication
C. Refer her to MFM for management
D. Stop her medication

Background

- Asthma is the most common medical condition to affect pregnancy, 8-13%*
- Has been linked to a number of adverse outcomes with conflicting reports
- Patients (and physicians) may have concerns regarding safety of medications in pregnancy/lactation†
  - 2/5 pregnant women discontinue or reduce asthma meds
  - 2/3 pregnant women were undertreated for ≥3 months

*Murphy VE, et al. BJOG, 2011.
†Lim AS, et al. BMC Fam Prac, 2011.

Asthma Complications

Complication	RR (CI)
Low birthweight*	1.46 (1.22-1.75)
Small for Gestational Age (SGA)	1.23 (1.11-1.37)
Preterm delivery*	1.41 (1.23-1.62)
No active management	1.50 (1.28-1.75)
Active management	1.07 (0.91-1.26)
Preeclampsia	1.54 (1.32-1.81)

*Risks vary in subgroups of different severity, such as those with severe or uncontrolled asthma

Murphy VE, et al. BJOG, 2011.

Course of disease in Pregnancy

- Asthma can worsen, improve or remain unchanged

  ~25% worsen, ~25% improve

- Infections affect the course of gestational asthma
  - Sinusitis 6x more common in pregnant women
  - Pneumonia >5x more common in asthmatic women during pregnancy

Namazy and Shatz. J Allergy Clin Immunol, 2011.

Diagnosis and Evaluation

- Most patients will already have a diagnosis
- New diagnosis based on typical symptoms
  - Couth, wheeze, chest tightness, shortness of breath
  - Most common differential is dyspnea of pregnancy
    - Lack of associated cough, wheeze
- Can obtain PFTs
  - Reversible airway obstruction on spirometry

Diagnosis and Evaluation

Asthma Severity* (Control†)	Symptom Frequency	Nighttime Awakening
Intermittent (well controlled)	2 days per week or less	Twice per month or less
Mild persistent (not well controlled)	More than 2 days per week, but not daily	More than twice per month
Moderate persistent (not well controlled)	Daily symptoms	More than once per week
Severe persistent (very poorly controlled)	Throughout the day	Four times per week or more

- In patients with diagnosis, not on treatment
  - Assess severity classification

ACOG Practice Bulletin #90, 2008.

Guideline #1

Continue pregnant women on the same asthma therapy used prior to the pregnancy if asthma is well controlled on that regimen

Management

- Asthma management during pregnancy should follow the stepwise management of asthma in adults
- Identify triggers, counsel appropriately

- Pregnant patients may need monthly visits to monitor control/adherence

Guideline #2

Severity: **Clinical Features Before Treatment**	**Symptoms** **Day**	**Night**	**Medications**
STEP 4: Severe Persistent	Continual	Frequent	High-dose ICS and LABA If needed: Oral steroid (reduce if possible)
STEP 3: Moderate Persistent	Daily	>1 night/wk	Low-dose ICS and LABA OR Medium-dose ICS
STEP 2: Mild Persistent	>2days/wk but <daily	>2 nights/mo	Low-dose ICS
STEP 1: Mild Intermittent	≤2 days/wk	≤2 nights/mo	No daily medication

Guideline #3/4

All pregnant asthma patients should have albuterol inhaler for symptoms

Budesonide is the preferred steroid inhaler in pregnant women (most studied)

…but no data indicating other ICS are unsafe

Asthma Medications in Pregnancy

- Effectiveness assumed to be the same as in nonpregnant

- Cromolyn, leukotriene receptor antagonists, theophylline listed as alternatives…but not preferred
  - Theophylline has very narrow therapeutic window
  - No differences in outcomes, increased side effects and discontinuation

NAEPP Working Group, J Allergy Clin Immunol, 2005.
ACOG Practice Bulletin, #90. 2008.

Guideline #5

Salmeterol is preferred LABA in pregnant women

Asthma Medications in Pregnancy

- Long-acting and short-acting β_2-agonists have similar pharmacology and toxicology
  - Have similar safety profile based on observational data
- Salmeterol "preferred" LABA based on longer availability in US
- Little data on montelukast
  - Alternative but not preferred

NAEPP Working Group, J Allergy Clin Immunol, 2005.
ACOG Practice Bulletin, #90. 2008.
Koren G, et al. Can Fam Phys, 2010.

Guideline #6

Use of prednisone, inhaled corticosteroids, β_2-agonists, not contraindicated for breastfeeding

Nor is use of cromolyn, antihistamines, theophylline

NAEPP Working Group, J Allergy Clin Immunol, 2005.
ACOG Practice Bulletin, #90. 2008.

Hypertension

Jennifer Corbelli, MD
University of Pittsburgh School of Medicine

Question #1

A 35 year old woman presents to your office. She happily reports that she is 6 weeks pregnant. She has no past medical history except for hypertension which has been well-controlled on HCTZ 25 mg. Her ranges from 120-130/60-70 and today is 122/62. Before treatment, her BP averaged 150/85. She asks if she should continue her HCTZ. How would you counsel her regarding her HCTZ?

1. She should continue her HCTZ
2. She should stop her HCTZ and start a different antihypertensive
3. She should stop her HCTZ and you would not recommend starting a different antihypertensive agent at this time.

Question #2

A 28 year old female who is 10 weeks pregnant presents to your office. Her blood pressure is borderline elevated & you are considering treatment. What changes, if any, would you expect in her BP as she enters her 2nd trimester?

1. Her BP will likely increase because of expansion of plasma volume during pregnancy
2. Her BP will likely decrease because of decreased systemic vascular resistance
3. No change: whatever a woman's BP is during her first trimester is likely where it will remain for the duration of her pregnancy

Question #3

A 38 year old female presents in her 14th week of pregnancy. She brings in readings from home that are persistently elevated (~170/100). You decide that she needs treatment. She has no comorbidities and no other issues at this time. Which of the following blood pressure will you target with your treatment?

1. <155/95
2. <140/90
3. <130/85
4. <120/80

Definitions

- Preexisting HTN
  - Mild 140-159/90-99
  - Severe ≥ 160/100 (169/110 in some studies)
  - Manifests in women <20 weeks gestation
- Gestational HTN: BP ≥140/90 in ≥ 20th week
  - No pre-pregnancy HTN
  - Usually occurs ≥ 37 weeks (dec SVR 2nd trimester)
- Preeclampsia (gestational HTN + proteinuria)
- Pre-existing HTN + Preeclampsia (RR if pre-existing HTN: 2.0 to 4.0)

Preexisting HTN

- Falls under domain of PCP
- Address with preconception counseling
  - Medications to choose/avoid same as in pregnancy
  - Goal blood pressure differs
    - Pregnancy: 140-159/90-99
    - Pre-conception: <140/90
- Risks related to impaired placental circulation. Lead to:
  - Small for gestational age (SGA) and preterm birth
  - Placental abruption
  - Preeclampsia (ischemic placenta → release of inflammatory markers → endothelial dysfunction)

Absolute Risks (4 Observational Studies)

	Placental Abruption	Preterm Birth	Small for Gestational Age (SGA)	Pre-Eclampsia
Mild (variable treatment: 13-50%)	0.7-1.4%	12-35%	8-16%	10-25%
Severe (all treated)	5-10%	62-70%	31-40%	~50%

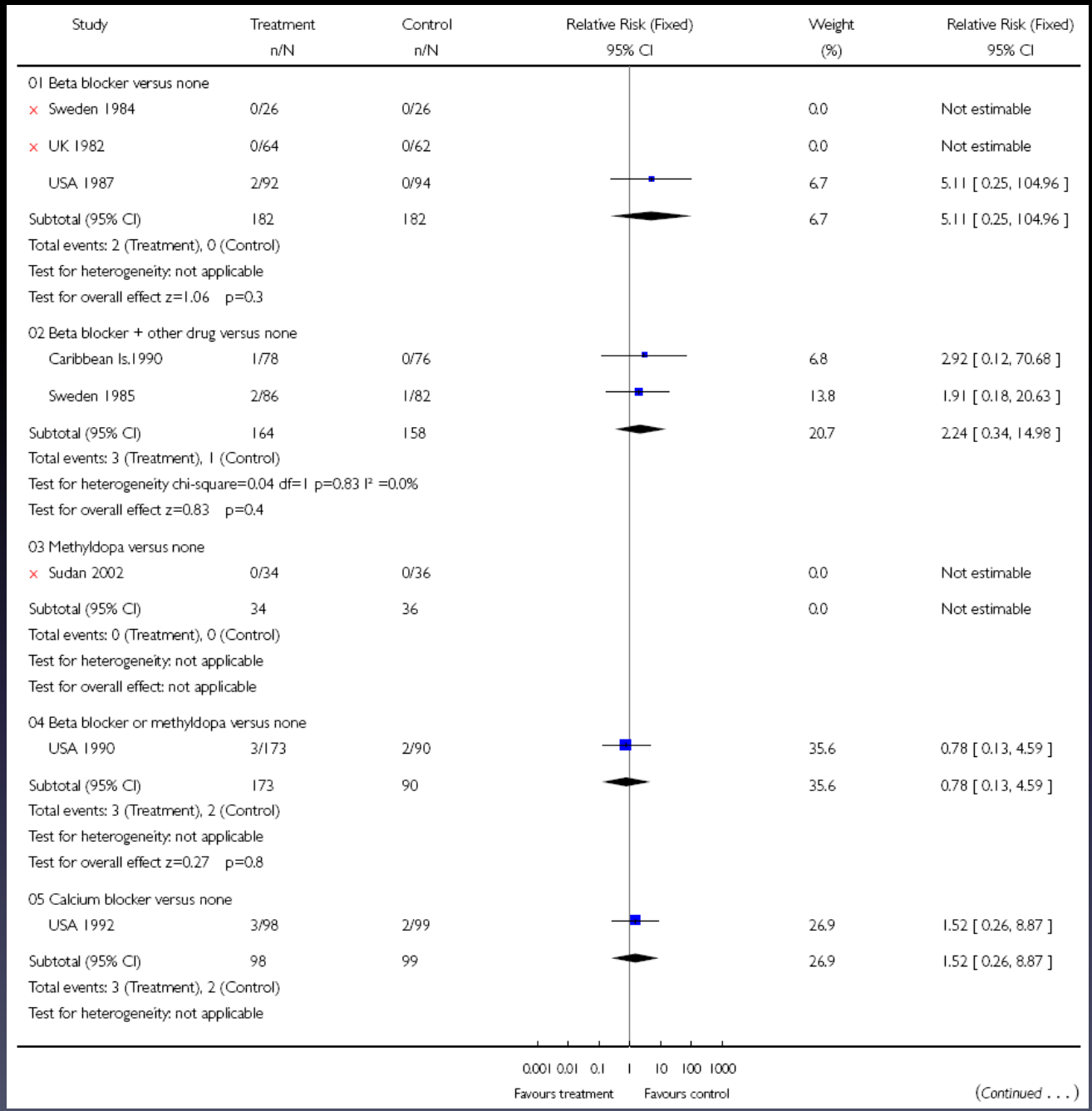
Mild: 140-159/90-99
Severe: >160/100 vs 169/110

Sibai, *Obstet Gynecol* 2002

Mild HTN: Treatment Benefits

- Negative maternal/fetal effects of HTN ≠ tx benefit
- Meta-analysis (assessed overall impact of tx):
  - Only included RCTs (46): defined severe HTN as 170/110
  - No significant difference in treatment vs. placebo for:
    - Preeclampsia
    - Fetal mortality
    - Preterm birth
    - SGA
    - Placental Abruption
  - *Tx decreased progression to severe HTN* (NNT 8-13)
  - Authors' conclusions: Data do not support treatment of mild to moderate HTN

Abalos, *Cochrane Database*, 2007


Study
Treatment n/N
Control n/N
Relative Risk (Fixed) 95% CI
Weight (%)
Relative Risk (Fixed) 95% CI
01 Beta blocker versus none
× Sweden 1984 0/26 0/26 0.0 Not estimable
× UK 1982 0/64 0/62 0.0 Not estimable
USA 1987 2/92 0/94 6.7 5.11 [0.25, 104.96]
Subtotal (95% CI) 182 182 6.7 5.11 [0.25, 104.96]
Total events: 2 (Treatment), 0 (Control)
Test for heterogeneity: not applicable
Test for overall effect z=1.06 p=0.3
02 Beta blocker + other drug versus none
Caribbean Is.1990 1/78 0/76 6.8 2.92 [0.12, 70.68]
Sweden 1985 2/86 1/82 13.8 1.91 [0.18, 20.63]
Subtotal (95% CI) 164 158 20.7 2.24 [0.34, 14.98]
Total events: 3 (Treatment), 1 (Control)
Test for heterogeneity chi-square=0.04 df=1 p=0.83 I² =0.0%
Test for overall effect z=0.83 p=0.4
03 Methyldopa versus none
× Sudan 2002 0/34 0/36 0.0 Not estimable
Subtotal (95% CI) 34 36 0.0 Not estimable
Total events: 0 (Treatment), 0 (Control)
Test for heterogeneity: not applicable
Test for overall effect: not applicable
04 Beta blocker or methyldopa versus none
USA 1990 3/173 2/90 35.6 0.78 [0.13, 4.59]
Subtotal (95% CI) 173 90 35.6 0.78 [0.13, 4.59]
Total events: 3 (Treatment), 2 (Control)
Test for heterogeneity: not applicable
Test for overall effect z=0.27 p=0.8
05 Calcium blocker versus none
USA 1992 3/98 2/99 26.9 1.52 [0.26, 8.87]
Subtotal (95% CI) 98 99 26.9 1.52 [0.26, 8.87]
Total events: 3 (Treatment), 2 (Control)
Test for heterogeneity: not applicable
0.001 0.01 0.1 1 10 100 1000
Favours treatment
Favours control
(Continued . . .)

Mild/Moderate HTN: Treatment Harms

- Meta-analysis: HTN treatment and restricted fetal growth
  - 45 RCTs
  - Definitions (used mean arterial pressure)
    - Mild-Moderate: >140/90
    - Severe >170/110
  - Beta blockers, thiazides, CCB, hydralazine, clonidine (17 drugs total)
- Findings: 10 mm Hg drop in MAP (ie 160/100 to 150/90)
  - Associated with 176 g decrease in birth weight (6 oz)
  - Finding persistent in patients with severe HTN
  - Found with all meds and all durations of treatment

Von Dadelszen, *Lancet*, 2000

Recommendations: Tx of Mild HTN

- *Generally* avoid treatment of pregnant women with uncomplicated, stable mild HTN, especially at lower end of range (<150/90)
  - Even mild HTN increases risk of complications
  - Best data has not shown treatment benefit
- Lower threshold for treating if BP has not declined by second trimester (when SVR naturally decreases)
- Closely monitor for evidence of progression toward severe HTN (NNT 8-13)

Treatment: General Principles

- Treatment always indicated for ≥160/100 (severe)
- Use lowest possible medication dose to achieve goal of ~155/95
- Monitor closely for relative hypotension (few indications for BP <140/90)
- Women who require treatment for gestational HTN will generally require it through delivery (~15% develop chronic hypertension)

Drugs of Choice

- First line:
  - Methyldopa: class B
    - mild anti-HTN effect sedating
    - sedating
  - Labetalol : *class C* (but decades observational data)
    - vs. methyldopa, decreased progression of mild to severe HTN: RR 0.75 (Abalos 2007)
- Second Line:
  - Calcium Channel Blockers: class B
    - nifedipine best-studied
  - HCTZ: class B
    - volume depletion a concern but not born out in epidemiologic studies

Treatment: Third-Line

- Hydralazine (Class C)
  - Commonly used for acute inpatient management
  - Less effective, more adverse effects vs. nifedipine (Fenakel, *Obstet Gynecol* 1991)
  - Concern for increased maternal hypotension, C-sections and placental abruption (Magee *BMJ* 2003)
- Clonidine (Class C)
  - Shown comparable to methyldopa in pregnancy outcomes in mild HTN (Horvath *Obstet Gynecol* 1985)

Treatment: Meds to Avoid

- ACE-inhibitors
- ARBs
- Direct renin inhibitors (aliskiren)

- 1st trimester = FDA Class C
- 2nd and 3rd trimester =FDA Class D
- Risk: renal abnormalities → oligohydramnios, other congenital abnormalities

Treatment Goals

- If no end organ damage, <155/95
  - Also if no concomitant:
    - DM (goal ~ <130/80, no data)
    - History of CVA
    - History of miscarriage

(No recommendations)

- If end organ damage, 140/90 (unclear benefit of targeting lower goal, i.e. 120/80)

Diabetes Mellitus

Anu Munshi, MD, MS
University of Pittsburgh School of Medicine

Serious Complications GDM

Fetus

- Macrosomia
- Hypoglycemia
- Hyperbilirubinemia
- Hypocalcemia
- RDS
- Miscarriage
- Stillbirth

Mother

- C-section
- Pre-eclampsia
- Infection
- DKA
- Retinopathy
- Nephropathy

Patient 1

- 33 year old female, 8 weeks pregnant
- Wants to establish care with you and required to have blood work done by her new job's insurance
- Physical Exam – all normal except BMI is 35
- Fasting blood sugar – 210
- Repeat fasting BS - 220

Patient 1

- What is your next step?

A. Order a HgbA1C

B. Tell patient she has gestational diabetes

C. Tell patient she has diabetes mellitus II

D. Refer her to her OB because you are unsure

Gestational Diabetes

- Fasting plasma glucose ≥92 but <126
- At 24 to 28 weeks : 75g 2-hour GTT with at least one abnormal results
  - Fasting ≥92 but <126
  - one hour ≥180
  - two hour ≥153
- FPG >126 at any gestational age is consistent with overt diabetes

GDM Treatment

- 2 RCTs, both blinded to the diagnosis of mild GDM
- Differed slightly in definitions of abnormal glucose
- Treatment resulted in a significant decrease in the incidence of macrosomia (6 vs 14% and 10 vs 21%)
  - Associated with a decrease in shoulder dystocia in 1 trial and composite of birth trauma in the other

Crowther CA, et al. NEJM 2005;352:2477

Landon MB, et al. NEJM 2009;361:1339

Gestational Diabetes

- Rate of cesarean delivery was reduced in 1 trial but not the other
- Treatment did not reduce the incidence of neonatal metabolic abnormalities
- Both trials reported lower pregnancy weight gain in the treated group than in the control group
- Pre-eclampsia rates lower in both trials

Long-Term Risks

- 1/3-2/3 of women with GDM will have GDM in a subsequent pregnancy
- 7-fold higher risk of developing type 2 diabetes than women without GDM
- Waist circumference and BMI strongest predictors of type 2 diabetes
  - Type 2 diabetes develops in 50-75 % of obese women compared to <25% of women who achieve normal body weight
- Higher risks for cardiovascular disease

Getahun D, et al. AJOG 2010;203:467
Bellamy L, et al. Lancet 2009;373:1773

Patient 2

- Well known patient to your practice
- 27 years old at 20 weeks recently diagnosed with gestational diabetes by her OB. She comes to you for a second opinion regarding starting medication for her GDM.
- Her fasting sugars are roughly between 95 and 100 and her 1 hour postprandial sugars are 130-140

Do you initiate medical therapy for Patient 2?

A. Yes, I would start her on meds right away

B. No, I would try diet control first

C. No, I would check a few more fasting sugars

D. No, I would recommend exercise first

Optimal Blood Glucose Targets

- ACOG
  - Fasting glucose ≤95 mg/dL
  - Preprandial glucose ≤100 mg/dL
  - 1 hr postprandial glucose ≤140 mg/dL
  - 2 hr postprandial glucose ≤120 mg/dL
  - Mean capillary glucose 100 mg/dL and A1C ≤6%
- ADA
  - Preprandial, bedtime, and overnight glucose 60-99 mg/dL
  - Peak postprandial glucose 100-129 mg/dL
  - A1C less than 6%

ACOG Practice Bulletin #60 2005;105:675
ADA Guidelines Diabetes Care 2009;32:Suppl 1:513

Blood Glucose Management

- Which values should drive treatment?
  - Management based on post-prandial blood sugars associated with:
    - Better glycemic control (HgA1c value 6.5 vs 8.1%)
    - Lower incidence of LGA infants (12 vs 42%)
    - Lower rate of c-section for CPD (12 vs 46%)

de Veciana, et al. NEJM 1995;333:1237:

Who needs medical therapy?

- Pre-gestational diabetics will almost always require therapy
- ACOG suggests administration of insulin to reduce the risk of macrosomia when:
  - Fasting glucose concentrations >95 mg/dL
  - 1 hr postprandial glucose >130-140 mg/dL
  - 2 hr postprandial glucose >120 mg/dL

When to initiate therapy

- Decision to initiate therapy
  - ≥50% abnormal values during a single time period
- Don't wait too long to start therapy
  - GDM patients who achieve control with diet alone will commonly do so in the initial 1-2 weeks
- Exercise can help

Gestational diabetes mellitus Diabetes Care 2004;27 Suppl 1:S88.

Patient 3

- 26 year old with GDM at 25 weeks needs to be started on medication
- What are her options?

A. Insulin
B. Glyburide
C. Metformin
D. Glipizide
E. Actos

Patient 4

- 25 year old Type II diabetic who comes to you for preconception counseling as she is thinking about starting a family
- She is maxed out on Metformin and Glyburide
- PE – normal, BMI 33
- A1C – 10.0
- U/A - proteinuria

Patient 4

- What option(s) does she have for improving her sugar control and still staying safe if she does get pregnant?

A. NPH
B. Aspart
C. Glargine
D. Lispro
E. Regular insulin

Insulin Requirements

- Insulin requirements increase by 30-50% during pregnancy
- Requirements may drop after 35 weeks

Treatment Options

- Glyburide
- Metformin
- Insulin
  - Regular insulin
  - Lispro / Aspart
  - NPH insulin
  - Lantus
- Insulin pumps

Oral hypoglycemic agents

- ADA and ACOG recommend insulin
- "Safety of oral anti-hyperglycemic agents has not been assured during early pregnancy"

Diabetes Care 2009;Suppl1:S13
ACOG Practice Bulletin #60 Obstet Gynecol 2005;105:675

Glyburide and Metformin

- Glyburide - No differences in the frequency of macrosomia, neonatal hypoglycemia, or other neonatal morbidities when compared to Insulin
- Metformin - Small studies suggesting that metformin may help “prevent” GDM
- Metformin may reduce the risk of GDM in a subsequent pregnancy in high risk women

Insulin Choices

- Pregnant patients with type 1 DM randomized to aspart or regular insulin
  - No sig difference in hypoglycemic events
  - HgA1c was similar
  - Mean post-prandial glucose was a little lower with aspart
  - Maternal and neonatal outcomes were similar
- Congenital anomalies in pregnancies with lispro use similar to expected rates

Mathiesen ER, et al. Diabetes Care 2007;30:771 Wyatt JW, et al. Diabet Med 2005;22:803

Lantus

- Case series examining outcomes of 115 pregnancies with type 1 DM treated with Lantus
  - Rates of live births, congenital malformations, pre-eclampsia all reasonable
- Retrospective cohort study of 107 women with type 1 DM, 57% stopped lantus in the 1st trimester vs 43% of women who continued
  - Rate of congenital malformations, birthweight, and adverse outcomes were similar between groups

Follow up of GDM

- All women should undergo oral glucose tolerance test 6-12 weeks after delivery
  - If initially normal, repeat every 3 years at a minimum
- Dietary and exercise counseling
- Weight loss
- Metformin may have a role in preventing type 2 diabetes
  - Both metformin and intensive lifestyle intervention reduced rates of type 2 diabetes in women with GDM

Ratner RE, et al. JCEM 2008;93:4774

Thyroid Disorders

Sarah Tilstra, MD
University of Pittsburgh School of Medicine

Who Should be Screened for Thyroid Disease?

A. 27 yo with no PMH or complaints. Mother has hypothyroidism. She is trying to conceive
B. 27 yo with no PMH or complaints. Had a miscarriage at 8 weeks last year, wants to try to conceive again
C. All pregnant women
D. All women trying to conceive and all pregnant women

(Choose all that apply)

Preconception Screening

Who should be screened?

- Hx thyroid disorder (hyper/hypo/PPT/lobectomy)
- Fam hx of thyroid disease
- Goiter on exam
- Known thyroid antibodies (TPO & thyroglobulin)
- Symptoms of thyroid disease
- DM I, autoimmune disease
- Head and neck radiation
- Miscarriage (recurrent?)/pre-term delivery

Endocrine Society's Clinical Guidelines, 2007

Case

You are seeing a 27 yo with a history of hypothyroidism who presents for pre-conception counseling. She has no complaints. Her TSH last month was 3.6 mIU/L. She has been on levothyroxine 100mcg for one year. You adjusted her levothyroxine to 112.5mcg as you know her pre-pregnancy goal TSH is <2.5. Her TSH 6 weeks later is 2.3uU/ml.

Three months later, your patient returns. She took a pregnancy test this week and it's positive. Urine dip in the office confirms her pregnancy. Her LMP was ~ 6 weeks ago. TSH is 2.1 mIU/L and free T_4 is normal.

Question 2

Should you adjust her levothyroxine dose at this visit?

A. Yes, increase by 30%

B. Yes, increase to 150mcg

C. Yes, decrease by 30%

D. No adjustment is needed

Question 2

- Answer: increase dose by 30% OR increase to 150mcg
- Recommendation: treated patients should increase their dose of levothyroxine by 25-30% upon a missed menstrual cycle (increase by 2 tablets per week)
- Even in the setting of appropriate TFTs at 6 weeks, production of T3 and T4needs to increase by 50%
- Dosing varies, may change dose from 10-80%
- Goal TSH first trimester <2.5 mIU/L

Endocrine Society's Clinical Guidelines, 2007
American Thyroid Association, 2011
USPSTF Level B Recommendation

Monitoring TFTs

- On levothyroxine:
  - Monitor TSH/fT4 every 4 weeks for first trimester, once during 26-32 weeks
- Subclinical or TAb+ euthyroid: q4weeks for first trimester, once during 26-32 weeks

Endocrine Society's Clinical Guidelines, 2007
American Thyroid Association, 2011
USPSTF Level I Recommendation

Question 3

Who should be started on levothyroxine?

A. 8 weeks pregnant, TSH 3.6 mIU/L, free T_4 just below normal limits
B. 8 weeks pregnant, TSH 10.4 mIU/L, free T_4 in the high-normal range
C. 8 weeks pregnant, TSH 6.3 mIU/L, free T_4 in the normal range, negative TPO antibodies

Question 3

Who should be started on levothyroxine?

A. 8 weeks pregnant, TSH 3.6 mIU/L, free T_4 just below normal limits (OVERT)
B. 8 weeks pregnant, TSH 10.4 mIU/L, free T_4 in the high-normal range (OVERT)
C. 8 weeks pregnant, TSH 6.3 mIU/L, free T_4 in the normal range, negative TPO antibodies (SUBCLINICAL)

Hypothyroidism

- Overt:
  - TSH >2.5 mIU/L and low fT4
  - TSH >10 mIU/L despite normal fT4
  - Treat: 150mcg levothyroxine (Level A)

Endocrine Society's Clinical Guidelines, 2007
American Thyroid Association, 2011
USPSTF

Hypothyroidism

- Subclinical:
  - Asymptomatic
  - TSH >2.5 mIU/L but < 10 mIU/L, normal fT_4
  - May have +/- antibodies
  - Definitely treat if antibody positive (Level B)
  - May treat if antibody negative (Level I, favored by Endocrine Society)

Endocrine Society's Clinical Guidelines, 2007
American Thyroid Association, 2011
USPSTF

Post-Partum Pearl

- Resume pre-conception thyroxine dosing regimen
- Check TFTs 6 weeks later
- Watch out for post-partum flare of autoimmune dysfunction (may end up on higher dose than required pre-pregnancy)

Endocrine Society's Clinical Guidelines, 2007
American Thyroid Association, 2011
USPSTF Level B Recommendation

Case

- You are seeing one of your well-known patients as a carve out for intermittent palpitations and severe nausea/vomiting. She is 10 weeks pregnant and was not able to contact her OB. You astutely check her thyroid studies which show an undetectable TSH and fT4 above the normal limits. TSH receptor antibodies are negative. You diagnose gestational hyperthyroidism.

Question 4

- What is the most appropriate management of gestational hyperthyroidism?
  A. Start propylthiouracil (PTU) now, change to methimazole at the start of the second trimester
  B. Start methimazole now, change to PTU at the start of second trimester
  C. Symptom management

Gestational Hyperthyroidism

- Answer: symptom management
- Antithyroid drugs not indicated (no change in pregnancy outcome) (Level D)
- Methimazole = congenital anomalies, PTU rec 1st trimester
- Usually serum fT_4 returns to normal 14-18wks
- Supportive therapy (transient use of beta blockade, anti-nausea/emetics)

Endocrine Society's Clinical Guidelines, 2007
American Thyroid Association, 2011
USPSTF

Clinical Pearls:

1. The overall risk of birth defects following SSRI exposure during pregnancy appears to be low.
2. The risk of relapse of major depression is high in women who discontinue their antidepressants during pregnancy.
3. Sertraline seems to be a safe first option when treating depression in pregnancy.
4. Continue previous meds in an asthmatic throughout pregnancy if the patient is well controlled.
5. Start a steroid inhaler or augment dose of medications if asthma is not controlled during pregnancy, as untreated asthma is more dangerous than any inhaled steroid.
6. The threshold for treatment of hypertension in pregnancy is blood pressure $\geq$ 160/100. If anti-hypertensives are initiated (assuming no end-organ damage), the treatment target is <160/100, but no lower than 140/90.
7. There is no overall proven benefit to the fetus with treatment of mild and moderate hypertension during pregnancy. However, these patients require close monitoring, as untreated mild/moderate hypertension ($\leq$159/99) is the greatest risk factor for severe hypertension ($\geq$160/100). The NNT is 8-13 cases of mild HTN to prevent one progression to severe HTN.
8. Insulin is the ideal choice for treating gestational diabetes. Avoid Lantus if possible
9. ADA and ACOG HgbA1C goal for diabetes during pregnancy is < 6%
10. There is no indication to screen all pregnant women for hypothyroidism.
11. Increase thyroxine dose by 30% when a patient with hypothyroidism becomes pregnant regardless of current thyroid studies; follow thyroid studies every 4 weeks for mediation titration.