Guidelines for the Treatment of Restless Legs Syndrome during Pregnancy and Lactation

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RLS
RESTLESS LEGS SYNDROME FOUNDATION

Conflict of Interest Disclosure

- This was not an industry supported project. M. Manconi was an investigator in a research study in which Vifor Pharma provided iron carboxymaltose but had no other role in the study. C. Trenkwalder is a consultant to Desitin, UCB Pharma, and Mundipharma; is on an advisory board of Novartis; and has received speaker honoraria from Desitin and GlaxoSmithKline. A. Walters is a consultant to and on an advisory board of UCB Pharma and Mundipharma; has received grants from UCB Pharma and Mundipharma; and has received speaker honoraria from Mundipharma.
- The other authors report no personal financial interests associated with the development, testing, manufacture or marketing of any drug or product described in this manuscript.
- These guidelines represent the first comprehensive approach to the diagnosis and treatment of RLS/WED during pregnancy and lactation. Based on the current medical literature and expert clinical opinion, they are intended to aid clinicians in addressing the concerns of women affected by this common condition during pregnancy.

International RLS Study Group (IRLSSG) Consensus Statement Group

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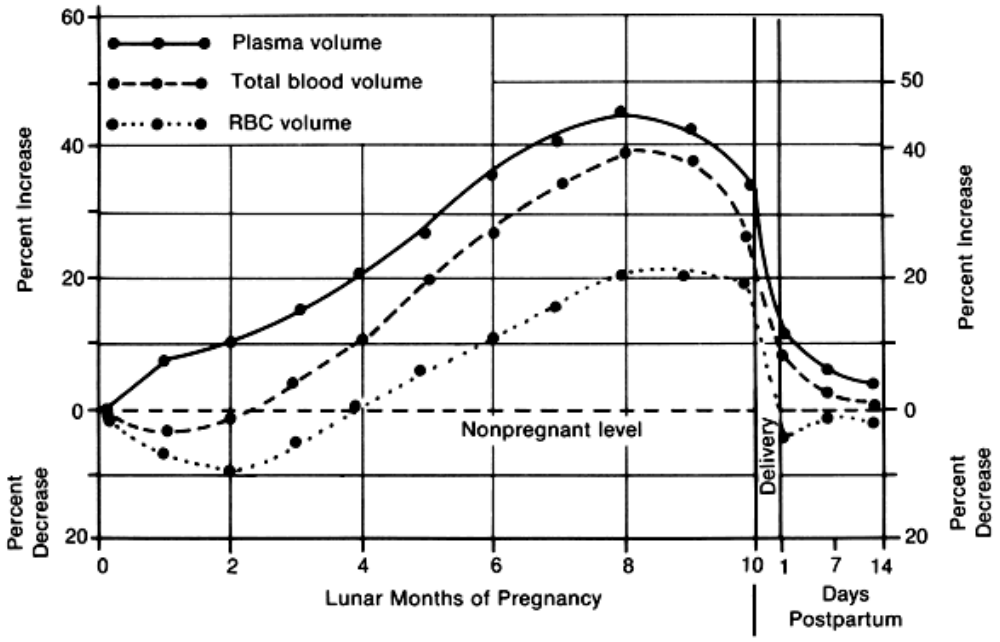
Background: pregnancy trimesters

Human Pregnancy **•288 days from last menstrual period (LMP)** **•40 lunar weeks** **•9-1/2 calendar months**		
1st trimester: LMP to 12-6/7 weeks	2nd trimester: 13 to 27-6/7 weeks	3rd trimester: 28 weeks to delivery
Nausea gravidarum (antiemetics may be dopamine antagonizing)	-Organogenesis complete -Expanding maternal blood volume (iron needs increase)	Iron needs of fetus (RLS symptoms likely to appear)
Postpartum: 4th trimester Delivery to 42 days (RLS symptoms likely to disappear)		

RLS is the 3rd most common reason for pregnancy-related insomnia

Background: pregnancy-related changes

- Expansion of blood volume
  - Physiologic anemia vs. iron deficiency anemia
- Heart rate, metabolic, and renal blood flow changes
- Lower serum albumin
- Placental hormones
  - estrogen, progesterone, relaxin, human placental lactogen, prostaglandins (vasodilatory and vasoconstrictive)



Objectives

1. Present the clinical guidelines developed for the IRLSSG Executive Committee on the diagnosis and management of RLS during pregnancy and lactation.
2. Disseminate 'free to access' article through PubMed:

    -An international consensus statement: Treatment of restless legs syndrome/Willis-Ekbom disease during pregnancy and lactation.

    -Picchietti, D., Hensley, J., Walters, A., Trenkwalder, C., Bainbridge, J., Manconi, M., Lee, K., McGregor, J., & Silver, R.

    -2015. Sleep Medicine Reviews.

RLS Pregnancy Dashboard

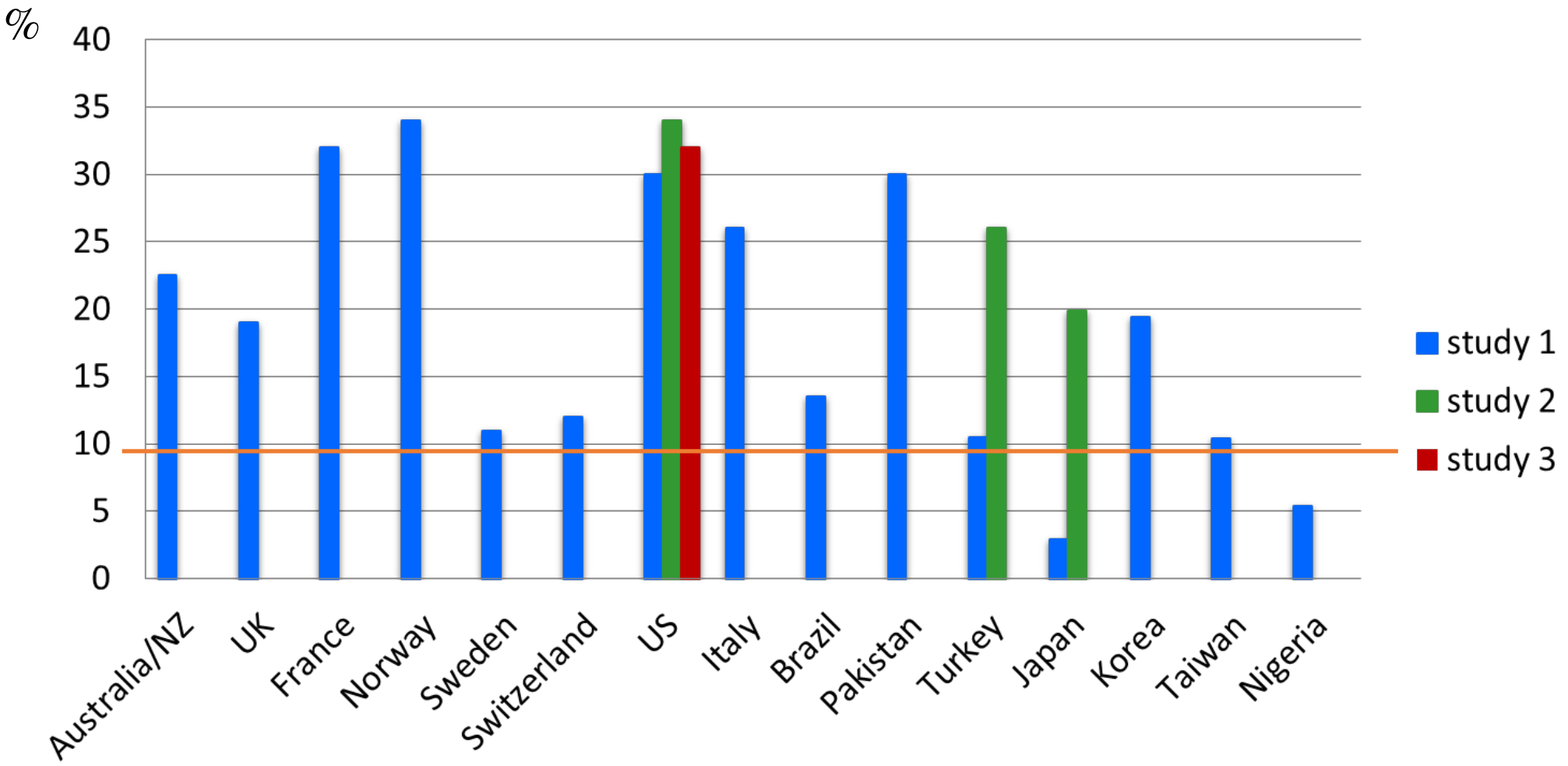
- Pregnant women affected 2-3x more frequently than the general population:
  - Prevalence during pregnancy increases across ethnicities
  - Affects primiparous/multiparous women more than nulliparous
- Associated risk factors:
  - Positive personal history (pre-existing RLS)
  - Positive family history (1st degree relative)
  - History of RLS during a previous pregnancy
  - Hemoglobin < 11g/dL
- Course:
  - Increase in prevalence from 1st to 3rd trimester
  - Increase in PLMs
  - Highest rate of symptoms in 3rd trimester
  - Dramatic resolution of symptoms postpartum
  - 4X increased risk of developing RLS later in life
  - Increased risk of developing RLS during subsequent pregnancy

Differences in Prevalence Rates

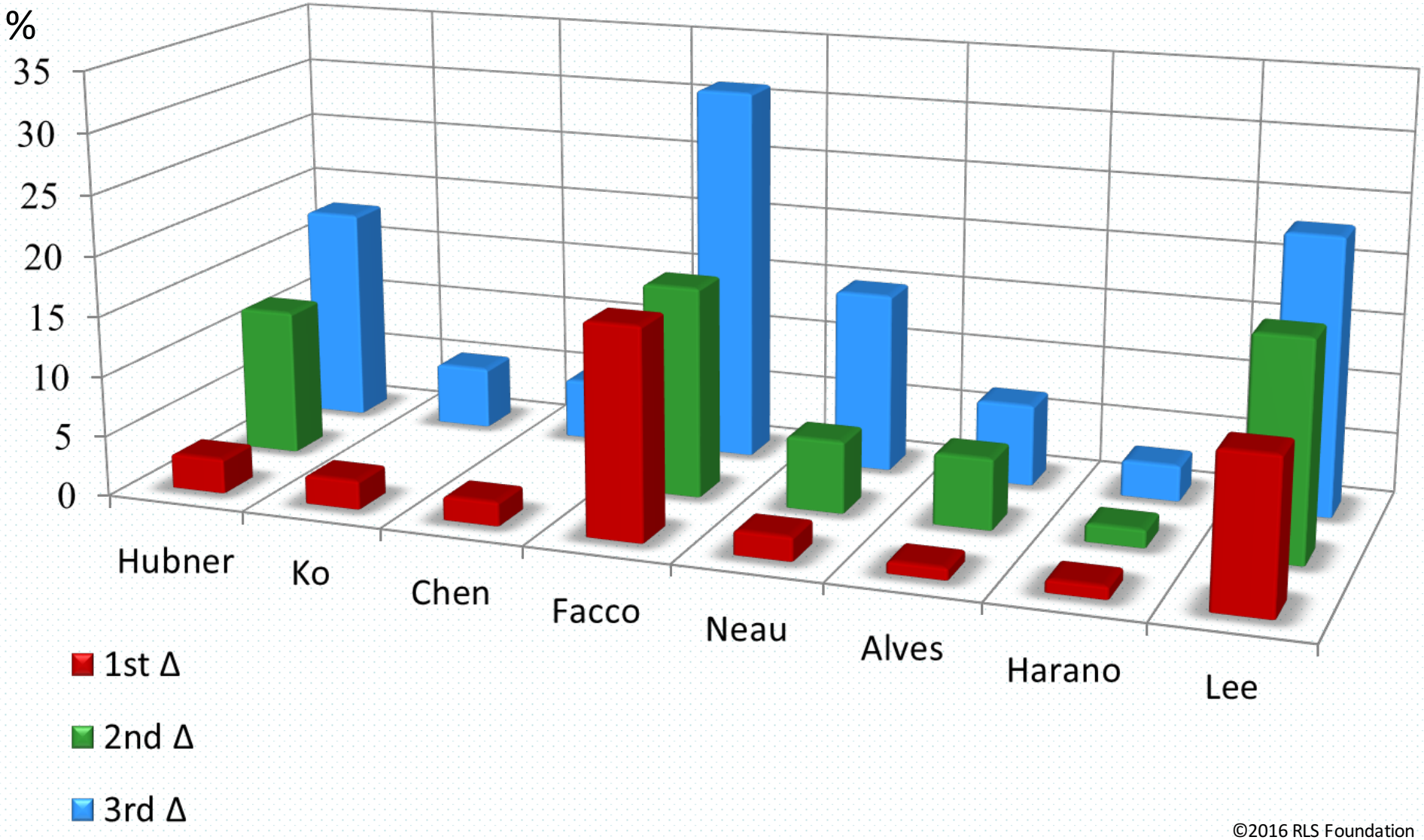
Differences in reported prevalence rates due to:

1. Ethnicity
   - Cultural taboos surrounding disclosure
2. Study methodologies
   - Under-diagnosis due to low awareness of RLS
   - Over-diagnosis due to inclusion of RLS mimics
   - Varying criteria used to diagnose RLS
   - Frequency of symptoms/week
   - Retrospective recall of symptoms

Prevalence of RLS during Pregnancy: 1945-2016

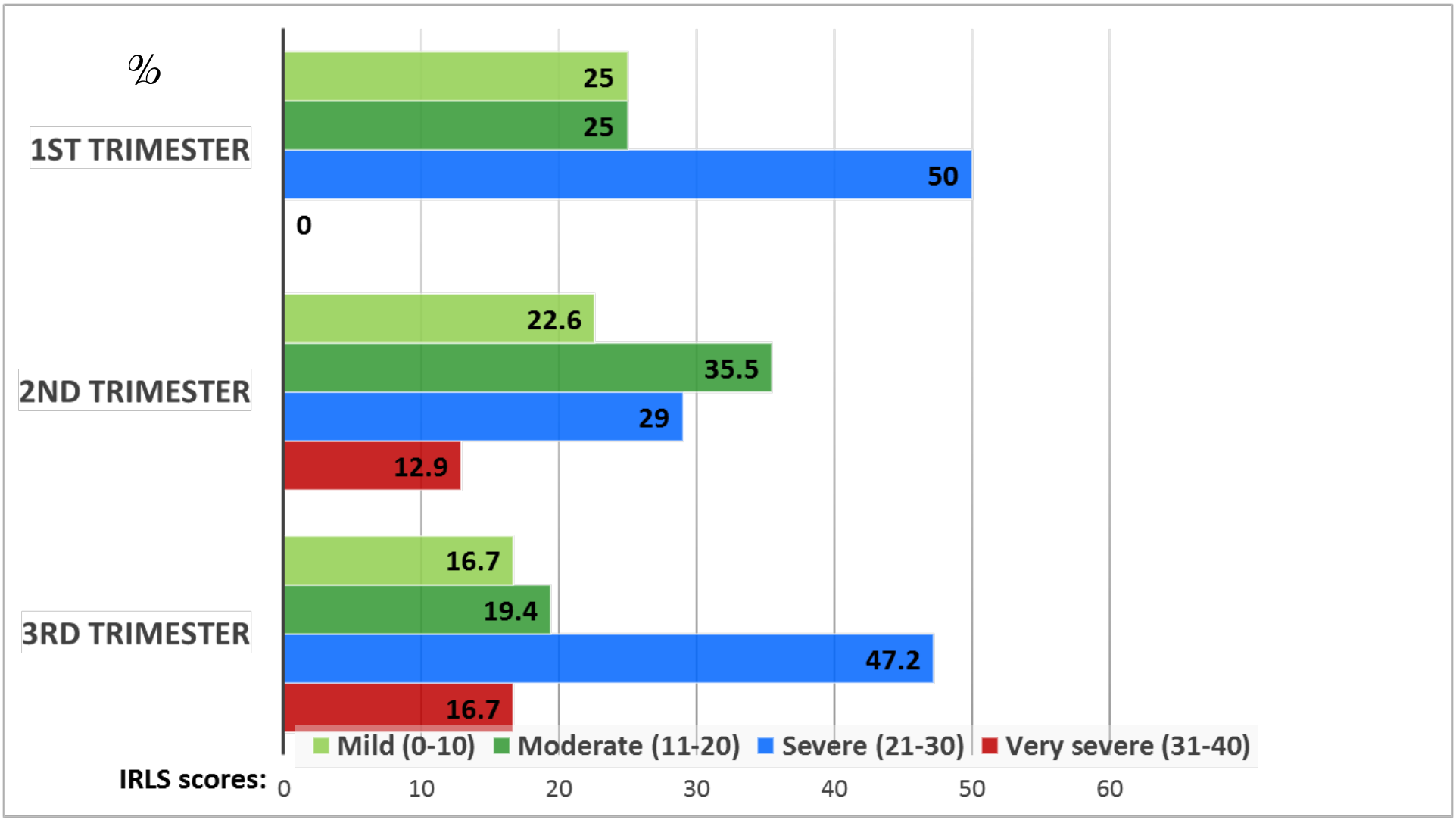


Prevalence of RLS during Pregnancy: increases into the 3rd trimester

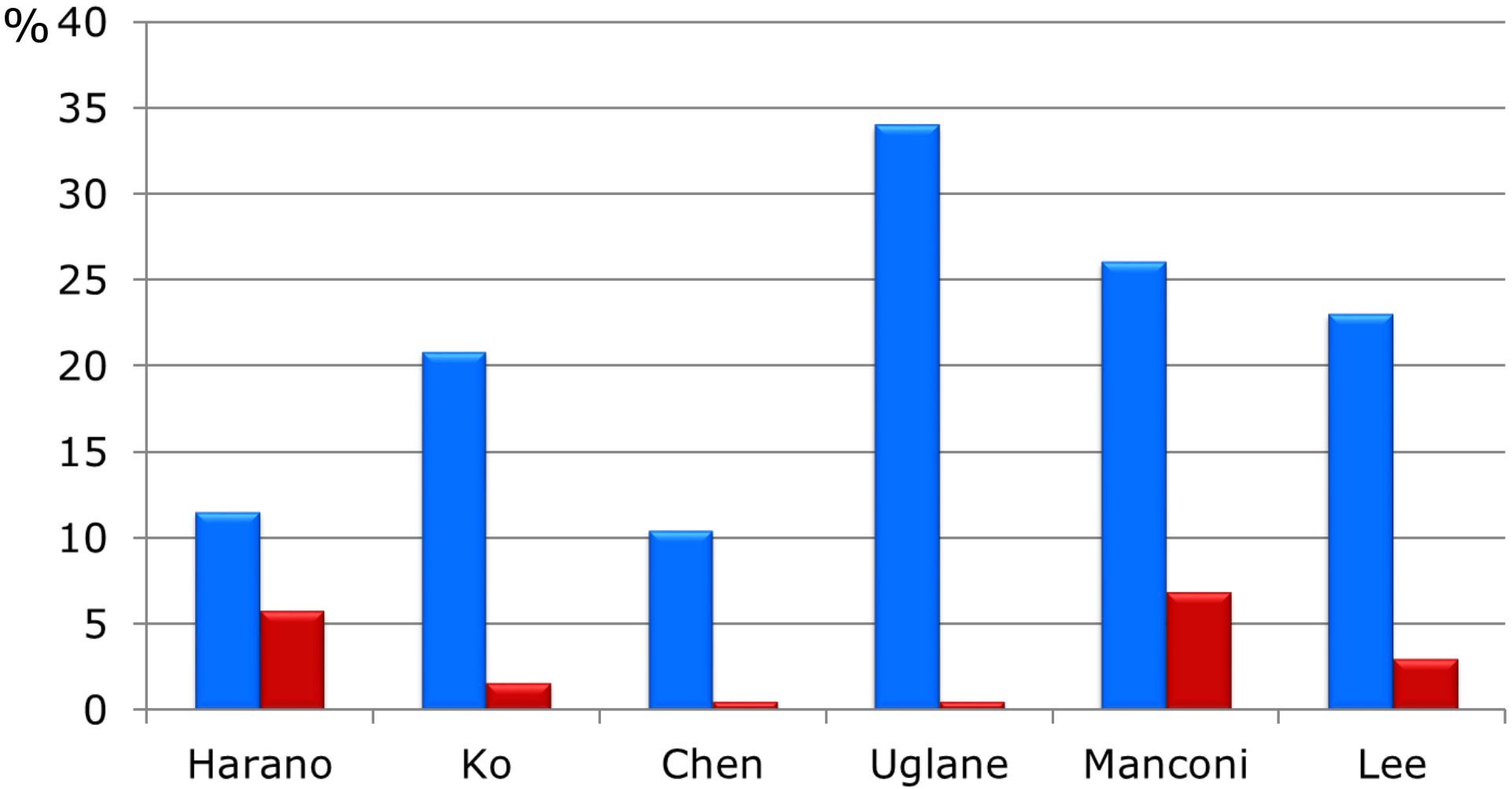


Severity of RLS: increases during pregnancy

Alves et al. *Sleep Med* 2010

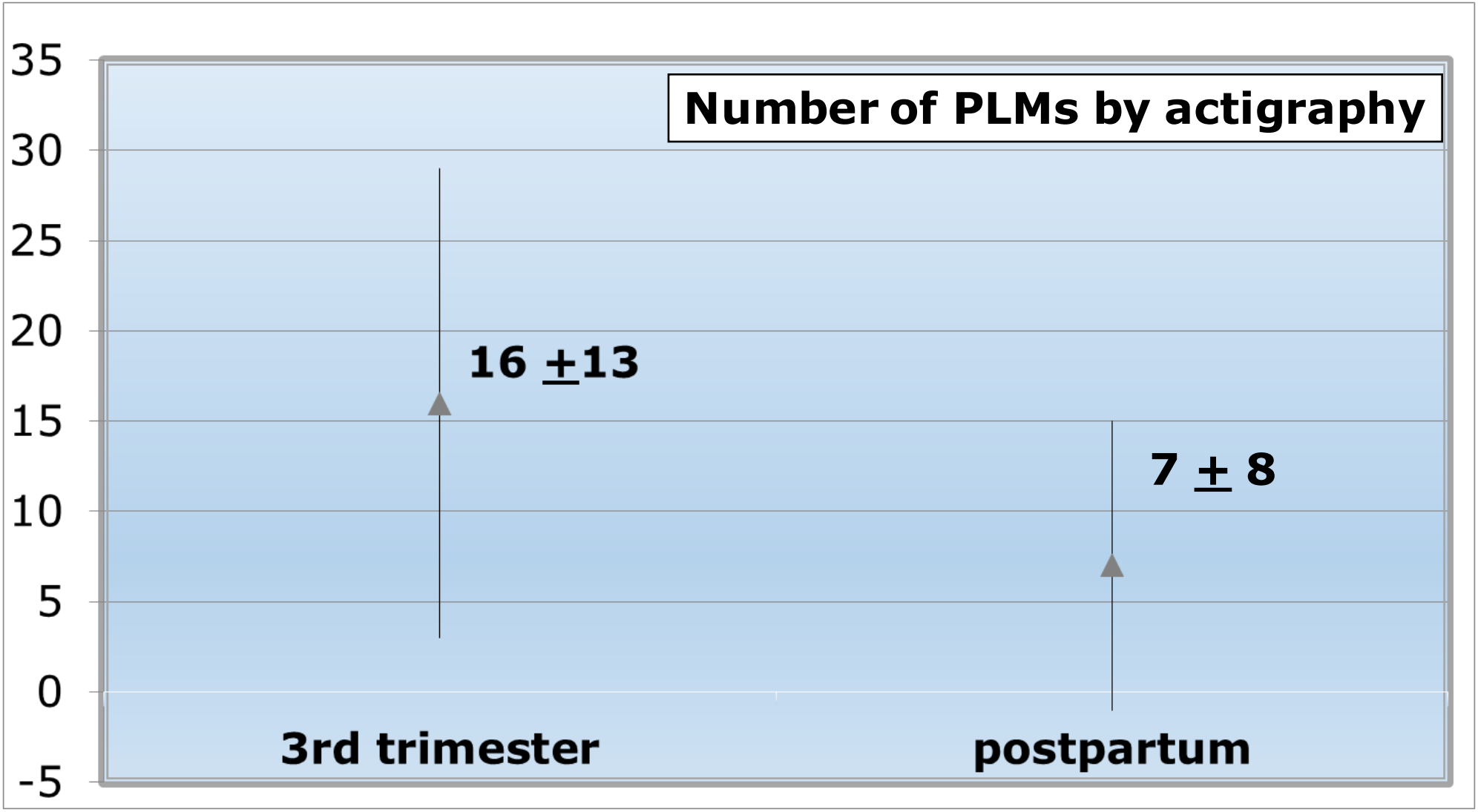


RLS Postpartum: symptoms resolve rapidly



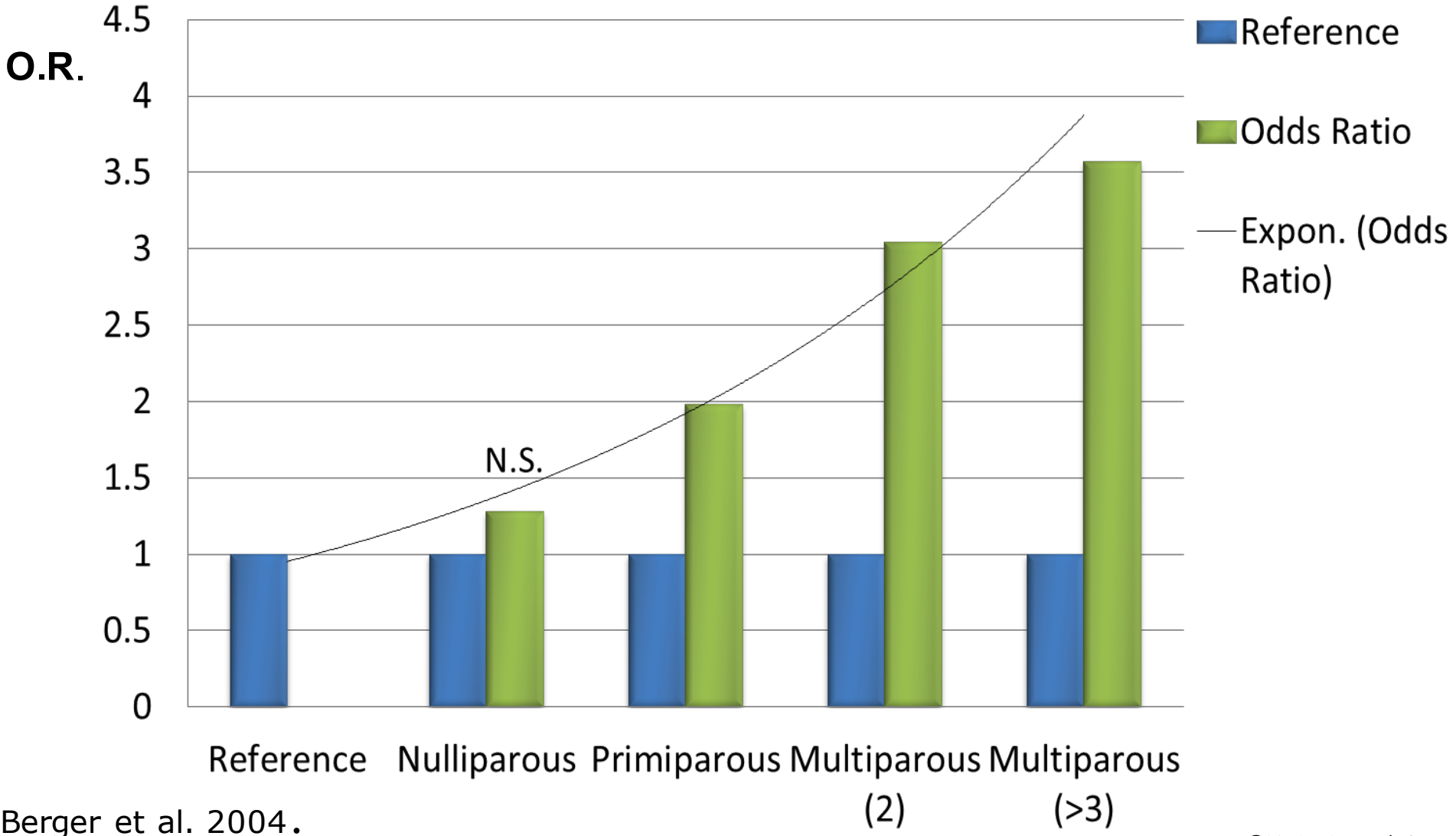
Symptoms resolve a few days prior to birth, or within 6 months PP

PLMs during Pregnancy: more frequent



Hubner et al. *Neurology.* 2013.

RLS and Subsequent Pregnancies: increased risk



Berger et al. 2004.

Literature Search: RLS during Pregnancy and Lactation

- PubMed literature search: "restless legs AND pregnancy":
  - 133 papers
    - 42 original research
    - 5 with treatment data
- In-depth safety/risk reviews of potential treatments included:
  - *Drugs in Pregnancy and Lactation*, Briggs et al.
  - *Medications and Mothers' Milk*, Hale et al.
  - MotherRisk
  - Organization of Teratology Information Specialists (OTIS)
  - LactMed
  - FDA
  - Australia Drug Evaluation Committee (ADEC)
  - AAP
  - Micromedex

5 Criteria for Consensus Recommendation

- Effectiveness for non-pregnancy RLS
- Safety for non-pregnancy RLS
- Effectiveness for RLS during pregnancy and lactation
- Safety/risk profile during pregnancy and lactation
  - Teratogenicity (major/minor congenital malformations)
  - Effects on pregnancy (premature labor, birth weight, etc.)
  - Neonatal opioid withdrawal symptoms (NOWS)
  - Neurodevelopmental considerations
- Expert clinical experience

5 Consensus Recommendation Levels

1) Recommended:
   high level evidence safety/effectiveness

2) May be considered:
   evidence for safety/effectiveness

3) Insufficient evidence

4) Probably should not be considered:
   evidence for risk/ineffectiveness

5) Not recommended:
   high level evidence risk/ineffectiveness

General Comments and Guidelines

1) Accurate diagnosis of RLS is essential.
2) RLS prevalence and severity typically peak in 3rd trimester, after embryogenesis.
3) Soon after delivery there is a marked decrease in the prevalence and severity of RLS.
4) With every pregnancy there is a 3-5% chance of a congenital anomaly.
5) Treatment decisions should be based on symptom severity and impact, risks vs. benefits, and individual patient considerations.
6) Consider non-medication treatments as primary.
7) For medications: use the lowest effective dose and shortest duration possible; reassess periodically; reassess after iron stores are repleted; reassess at delivery.
8) Information on adverse drug reactions should be provided with any new prescription.
9) Understanding that placebo effect is common in RLS and other CNS disorders is important.

9 Treatment Classifications for RLS during Pregnancy and Lactation

- 48 treatments in 9 categories
  - Pharmacologic
    - Anticonvulsants/AEDs (4)
    - Alpha-adrenergic (1)
    - Antidepressants (2)
    - Benzodiazepines and BZRAs (4)
    - Dopaminergics (7)
    - Opioids (6)
  - Non-pharmacologic (15)
    - Nutraceuticals (2)
    - Vitamins and minerals (5)
    - Pneumatic stockings, massage, acupuncture, etc. (15)

Treatment of RLS during Pregnancy and Lactation

Accurate diagnosis:
- 4 criteria
- Mimics
- Severity

Nonpharmacologic options:
- Educate about course
- Assess iron status
- Exercise
- Avoid exacerbating factors
- Consider other options

Iron supplement:
- PO
- IV

√ Consider co-morbid depression

Refractory RLS during pregnancy
- Low-dose clonazepam
- Levodopa/carbidopa

Refractory RLS during lactation
- Reassess iron
- Gabapentin
- Low-dose clonazepam
- Trazodone
- Consider low-dose tramadol for sleep

Accurate Diagnosis

- 4 of 4 core features of RLS present
    - Urge to move the legs
    - Rest exacerbates the urge
    - Relief with movement
    - Worse at night/evening
- Rule out mimics, especially leg cramps and leg edema
- Assess severity: frequency and impact

Rule Out RLS Mimics

Particularly common during pregnancy

- Leg cramps*
- Positional discomfort
- Venous stasis
- Leg edema*
- Compression and stretch neuropathies
- Sore leg muscles
- Ligament sprain/tendon strain
- Positional ischemia
- Dermatitis
- Bruises

Less common mimics

- Arthritis
- Other orthopedic disorders
- Peripheral neuropathy
- Radiculopathy
- Myelopathy
- Myopathy
- Fibromyalgia
- Complex regional pain syndrome
- Drug-induced akathisia
- Sickle cell disease

Eliminate Exacerbating Factors: known and suspected

Known exacerbating factors:

- Iron deficiency
- Prolonged immobility
- Serotonergic antidepressants
  - Consider bupropion (Wellbutrin)

Eliminate Exacerbating Factors

Suspected exacerbating factors:

- Sedating antihistamines
- Dopamine antagonists (antiemetics, antipsychotics)
- Sleep deprivation
- Sleep apnea
- Hypoxia
- Caffeine
- Tobacco
- Alcohol
- Pain
- Peripheral neuropathy
- Radiculopathy
- Venous insufficiency
- Inflammatory/immunological conditions

Iron Assessment and Therapy

- Check serum ferritin level
- Oral iron if ferritin <75 mcg/L
    - 65 mg elemental iron one to two times/day
- Consider IV iron if oral iron repletion fails if:
    - Ferritin is < 30 mcg/L
    - RLS symptoms are problematic

Exercise

	Pregnancy	Lactation	Safety Concern	Efficacy Concern	Comments
Exercise – moderate	2	2	Enough calories		Avoid pain, dehydration, abdominal trauma, late evening; get OB provider approval
Exercise – vigorous	4	3-4	Enough calories	X	If exercise is painful, may aggravate RLS

2) May be considered:
3) Insufficient evidence
4) Probably should not be considered

Moderate Exercise for RLS during Pregnancy & Lactation

- Non-pregnancy evidence:
  - Lack of exercise was a risk factor for RLS in 4 studies
  - RCT showed benefit (Aukerman, et al 2006)
- ACOG: "Women with uncomplicated pregnancies should be encouraged to engage in physical activities before, during, and after pregnancy." (Committee Opinion 650; 2015)
- Committee recommendations:
  - Moderate/low impact exercise, 20-30 minutes/day: e.g., walking, water aerobics, ballroom dancing, general gardening
  - Get approval from OB
  - Avoid painful exercise, dehydration, abdominal trauma, late evening exercise

Vitamins and Minerals: Consensus Committee Ratings

	Pregnancy	Lactation	Safety Concern	Efficacy Concern	Comments
Folate	3	3		X	Efficacy, not safety issues
Iron - oral	2	2			If ferritin <75 may benefit; if <30 likely to benefit
Iron - intravenous	2	3			If ferritin <30 and failure of oral iron; avoid 1st trimester
Magnesium	4	4		X	Efficacy, not safety issues
Vitamin C	3	3	X	X	Preterm labor/fetal loss may be increased
Vitamin D	3	3	X	X	High doses teratogenic in animals
Vitamin E	3	3	X	X	Doses above minimum daily allowance not recommended

2) May be considered: 3) Insufficient evidence; 4) Probably should not be considered

Nutraceuticals: Consensus Committee Ratings

	Pregnancy	Lactation	Safety Concern	Efficacy Concern	Comments
Chinese herbal	3	3			
Valerian	4	4	x	x	Not proven safe during pregnancy; diazepam-like effects

3) Insufficient evidence
4) Probably should not be considered

Other Options: Consensus Committee Ratings

Treatment	Pregnancy	Lactation	Safety concern	Efficacy concern	Comments
Acupuncture	3	3		X	
Cognitive-behavioral	3	3		X	
Hypnosis	3	3		X	
Massage	2	2			Avoid vigorous/ deep w/ hx DVT/known clotting disorder
Meditation/ music/prayer	3	3		x	

2) May be considered: 3) Insufficient evidence

Complementary Modalities: Consensus Committee Ratings

Treatment	Pregnancy	Lactation	Safety Concern	Efficacy Concern	Comments
Mental activity	3	3		X	
Near-infrared therapy	3	3	X	X	Nitric oxide generated and produces vasodilation
Pneumatic devices	2	2			Appears safe, effective
Sexual activity	3	3		X	
Treat OSA	2	2			
Vibration	3	3		X	
Yoga	2	2			Same as moderate exercise?

2) May be considered: 3) Insufficient evidence

Complementary Modalities: Consensus Committee Ratings

The following treatments were reviewed but not rated due to insufficient evidence for efficacy in non-pregnancy RLS:

- forehead wrapping
- injection of Morton neuroma
- L-tyrosine
- sour cherry extract
- rifaxmin for small intestinal bacterial overgrowth
- amantadine
- diazepam
- levorphanol
- botulinum toxin
- deep brain stimulation

Treatment of RLS during Pregnancy & Lactation: **Pharmacologic** Considerations

Comorbid Depression?
- Consider bupropion

Accurate diagnosis
- 4 of 4 core RLS features
- R/O RLS mimics
- Assess severity: frequency & impact

Nonpharmacologic therapy
- Educate about natural course of RLS during pregnancy
- Assess iron status
- Exercise
- Avoid exacerbating factors
- Consider other options

Iron assessment & therapy
- Check ferritin
- PO iron if <75 mcg/L

Consider IV iron:
- Ferritin <30 mcg/L despite PO repletion
- RLS symptoms problematic

Refractory RLS during pregnancy
- Levodopa/carbidopa 125/25 to 250/50 mg in evening or at night
- Low-dose clonazepam 0.25-1 mg in evening
- Very severe, very refractory: low dose oxycodone
- Reassess frequently

Refractory RLS during lactation
- Reassess iron status
- Gabapentin 300-900 mg evening or night
- Low-dose clonazepam 0.25-1 mg evening
- Trazodone 50-100 mg HS if sleep disruption
- If very severe, very refractory consider low-dose tramadol

Pharmacologic Treatment Considerations

- RLS prevalence and symptom severity peak in 3rd trimester
- Medication safer in 3rd trimester
    - Post-organogenesis of the fetus
    - Decreased chance teratogenicity
        - (3-5% risk of congenital anomaly in general population)
- Treatment decisions should be based on:
    - Symptom severity and impact
    - Risks vs. benefits
    - Individual considerations
    - Necessity of medication

Pharmacologic Treatments and Lactation Considerations

- Effects on milk production
  - Dopaminergics block prolactin which blocks milk production
- Amount of drug excreted into breast milk
  - Relative infant dose (RID)
    - <10% considered safe
  - Therapeutic half-life of the drug
  - Long-term effects
- Age of newborn/infant
  - < 2 months = greater adverse effects
  - > 6 months = fewer adverse effects

Opioids

- Oxycodone:
  - Consider: very severe, very refractory RLS after 1st trimester
  - Concern: neonatal opioid withdrawal syndrome (NOWS)
- Codeine:
  - Ultra-rapid metabolizer
    - CYP2D6 enzyme mutation
    - Ultra-rapid metabolism of codeine to parent compound
    - Ethnicities
      - 16-28% North African, Ethiopian, Saudi Arabian
      - 3% African American
      - 1–10% white
      - 0.5-1% Chinese, Japanese, Hispanic
    - No commercially available test for mother
  - CDC: Prescribe 4-day supply of codeine

Refractory RLS during Pregnancy

- Low-dose clonazepam 0.25-1 mg in the evening
- Levodopa/carbidopa 125/25 - 250/50 mg in the evening or at night

Refractory RLS during Lactation

- Reassess iron status
- Gabapentin 300-900 mg in the evening or at night
- Low-dose clonazepam 0.25- 1 mg in the evening
- Trazodone 50- 100 mg at bedtime if sleep disruption is prominent
- If very severe and not responsive to the above, consider low-dose tramadol

Gabapentin for Refractory RLS during Lactation

- Non-pregnancy evidence for gabapentin:
  - AASM practice parameters 2012: Option
- Safety: Approximately 1.3-3.8% of maternal dose to infant
  - RID < 10%
  - No adverse effects noted in infants
  - Hale L2
- Committee recommendation:
  - *For refractory RLS during lactation*
  - 300-900 mg in the evening or at night

Trazodone for Refractory RLS during Lactation

- Non-pregnancy evidence for trazodone:
  - Anecdotal
  - Case series: does not exacerbate PLMs
  - Commonly used for insomnia
- Safety: Approximately 0.6% of maternal dose to breast fed newborn
  - RID < 10%
  - No adverse effects noted in infants
  - Hale L2
- Committee recommendation:
  - *For refractory RLS during lactation*
  - 50-100 mg at bedtime if sleep disruption is prominent

Research Agenda - In the future we need:

1) Genomewide association studies in large populations of pregnant women, which might confirm gene associations already known in non-pregnancy RLS or identify new associations.

2) Prospective investigation aimed to define the potential impact of RLS during pregnancy on fetal/newborn health and on maternal depression.

3) Development of validated severity criteria to identify pregnant women with RLS for whom treatment with medication should be considered.

4) Longitudinal polysomnographic studies during pregnancy and puerperium to delineate the frequency of periodic limb movements and their relationship to other RLS symptoms, including sleep disruption.

5) Randomized, placebo-controlled studies during pregnancy to explore the efficacy and safety of treatments used in non-pregnancy RLS, especially iron and dopamine agonists.

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Q & A

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Our next webinar is May 13 with Dr. John Winkelman presenting
'Depression & RLS'