Perinatal Substance Use: From Research to Practice to Public Health

Compassionate Care: The Scientific and Clinical Rationale for Methadone Split Dosing during Pregnancy

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Disclosure Information (Required)

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- NO DISCLOSURES

Learning Objectives

- Describe Methadone and rationale behind split dosing
- Describe split dose benefits for fetus, birthing parent and provider
- Describe Washington state pilot to standardize Methadone split dosing

“Whenever you face a tough question in biology just say enzymes. It is the correct answer to most questions in biology.”

- Quote by Feng Zhang, CRISPER researcher, from his high school AP biology teacher
- From The Codebreaker, by Walter Isaacson on Jennifer Doudna and Emmanuelle Charpentier, Nobel laureates in Chemistry 2020 for developing a CRISPR gene editing tool

Pregnancy Questions

- **Why is dosing methadone in pregnancy more complicated and demanding than 'routine' methadone patients?**

ANS: enzymes

Why is divided dosing of methadone necessary for maternal/fetal stability?

ANS: enzymes

- **Why is the postpartum period especially important for monitoring serum methadone levels?**

ANS: enzymes

Pregnancy:
A Predictable Metabolic Gene Inducer

- **Increases of progesterone during the luteal phase of the menstrual cycle induce transcription of the 2D6 enzyme. So, if conception occurs, the metabolic system is primed to accelerate metabolism. As pregnancy hormones increase, so does metabolism.**

- **The system is designed to protect the fetus from toxins. What we are dealing with, in trying to use medications in pregnancy, is an evolutionary system designed to frustrate us.**

- A pregnant patient has unique pharmacokinetics; increased:
  - metabolism (maternal and placental, and fetal)
  - renal clearance of methadone
  - P-glycoprotein (multidrug resistance protein)

  - Altered pharmacokinetics decrease methadone concentration in serum and at the mu receptor

Problems Achieving Optimal Methadone Dosing

- Genetic variability of methadone metabolism is a clinical challenge at the extremes of the metabolic spectrum: ultra-rapid and ultra slow. Most non-pregnant patients (maybe only 70%) do well with once daily dosing based on just clinical assessment because they have a ½ life of about 24 hrs.

- However, ½ lives between 6 and 50 hours have been reported. When dosing is pharmacokinetically blind (the doctor doesn't know an individual's metabolism) some patients will be underdosed, reducing efficacy, and some will be overdosed, increasing risks.

- Optimizing MAT requires individualized science-based dosing, not regulation-based dosing.

- Assessing metabolic genes is not clinically useful. But, with therapeutic drug monitoring we can measure the net metabolic effect of all the genes involved.

Reimagining patient-centered care in opioid treatment programs: Lessons during COVID-19.

- 42 CFR Part 8.12 (3) of the Federal opioid treatment standards does not preclude split-dosing. It calls for special attention to their needs and indicates:
- *Special services for pregnant patients. OTPs must maintain current policies and procedures that reflect the special needs of patients who are pregnant. Prenatal care and other gender specific services or pregnant patients must be provided either by the OTP or by referral to appropriate healthcare providers*
- https://www.govregs.com/regulations/expand/title42_chapterI_part8_subpartC_section8.12#regulation)

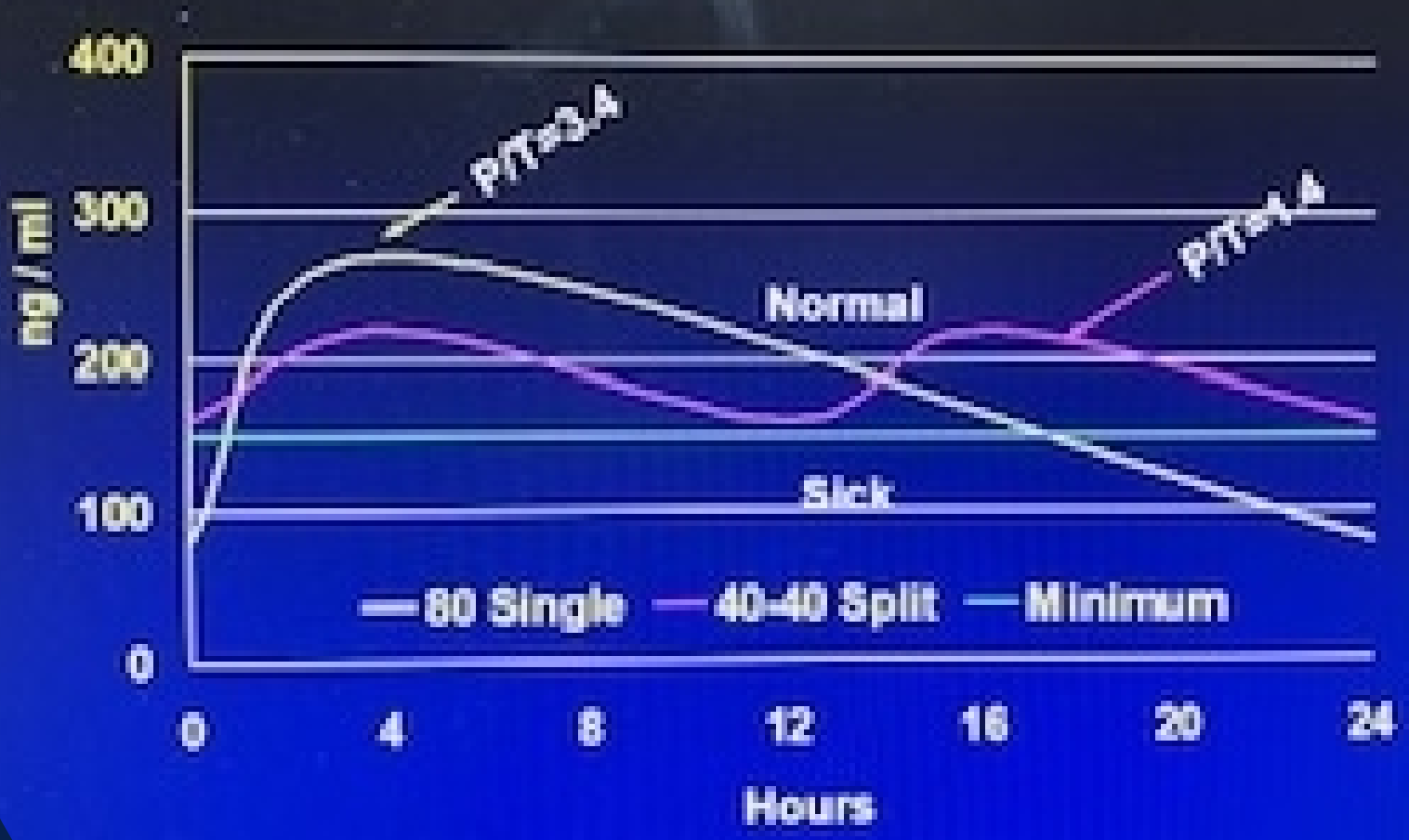
- Concentrate instead on patient-centered measures—engagement in care, and patient goals
- SAMHSA, AATOD, WAG, ASAM, ACOG

https://pixabay.com/photos/mother-baby-parent-parenthood-951190/

Torres-Lockhart et al. Reimagining patient-centered care in opioid treatment programs: Lessons from the Bronx during COVID-19. *J Subst Abuse Treat*. 2021(Mar);122:108219. doi:10.1016/j.jsat.2020.108219

Pregnancy Case Study @ 6 mo.

"I wake up sick & my baby moves a lot!"



Split Dosing in Pregnancy: Maternal Benefits and Risks

Benefits

- **Safety**
  - Prevents over-sedation
  - Prevents potential QT prolongation
- **Efficacy**
  - Avoids insufficient trough levels = prevents withdrawal
- **Engagement**
  - Patient involvement in effective dosing = facilitates trust
- **Trauma-responsive**
  - A take-home dose reduces nighttime withdrawal fear

Risks

- **Diversion**
  - Someone could take the dose from her
- **Less Structure**
  - Taking the take home dose early might reduce stability

Therapeutic Drug Monitoring: Three Methadone Serum Laboratory Tests

Trough serum levels have established therapeutic ranges (V. Dole:150-600ng, other studies show 400ng for best efficacy). They reassure the mother (and the doctor) about fetal exposure. Methadone dose is not an accurate proxy for fetal exposure. Only the serum level measures fetal exposure.

Peak/trough ratio (PTR): Peak is 3-4 hrs after the AM dose and trough is just before the next AM dose. A ratio of serum methadone at peak divided by methadone at the trough of 2 or greater means ultra-rapid metabolism, e.g. 800ng peak/400ng trough =2. The drop of 400ng is too much to assure stability of mu receptor occupancy. A drop from 800 to 200 (PTR = 4) would cause major withdrawal.

Methadone/metabolite serum ratio (MMR) . The ratio of parent drug to its metabolite is a tool of pharmacogenetic research on genes coding for P450 enzymes that metabolize most medicines. That research has categorized drug metabolism as: Ultra rapid (URM), Extensive, normal (EM), Intermediate (IM), and Ultra slow (USM). All P450 substrate medications have a spectrum of metabolism because people have different metabolic genetics

Changes in the Methadone/Metabolite Ratio (MMR) during Pregnancy and Post-partum

- Average serum MMR in two studies of non-pregnant methadone maintenance patients is roughly 11-13
- First trimester mean 7.2
- Second trimester 5.9
- Third trimester 5.1
- Postpartum 7.2 -> return to 12 after a few weeks
- Monitor post-partum carefully for oversedation, adjust dose as indicated

Split Dosing in Pregnancy: Fetal Benefits and Risks

Benefits

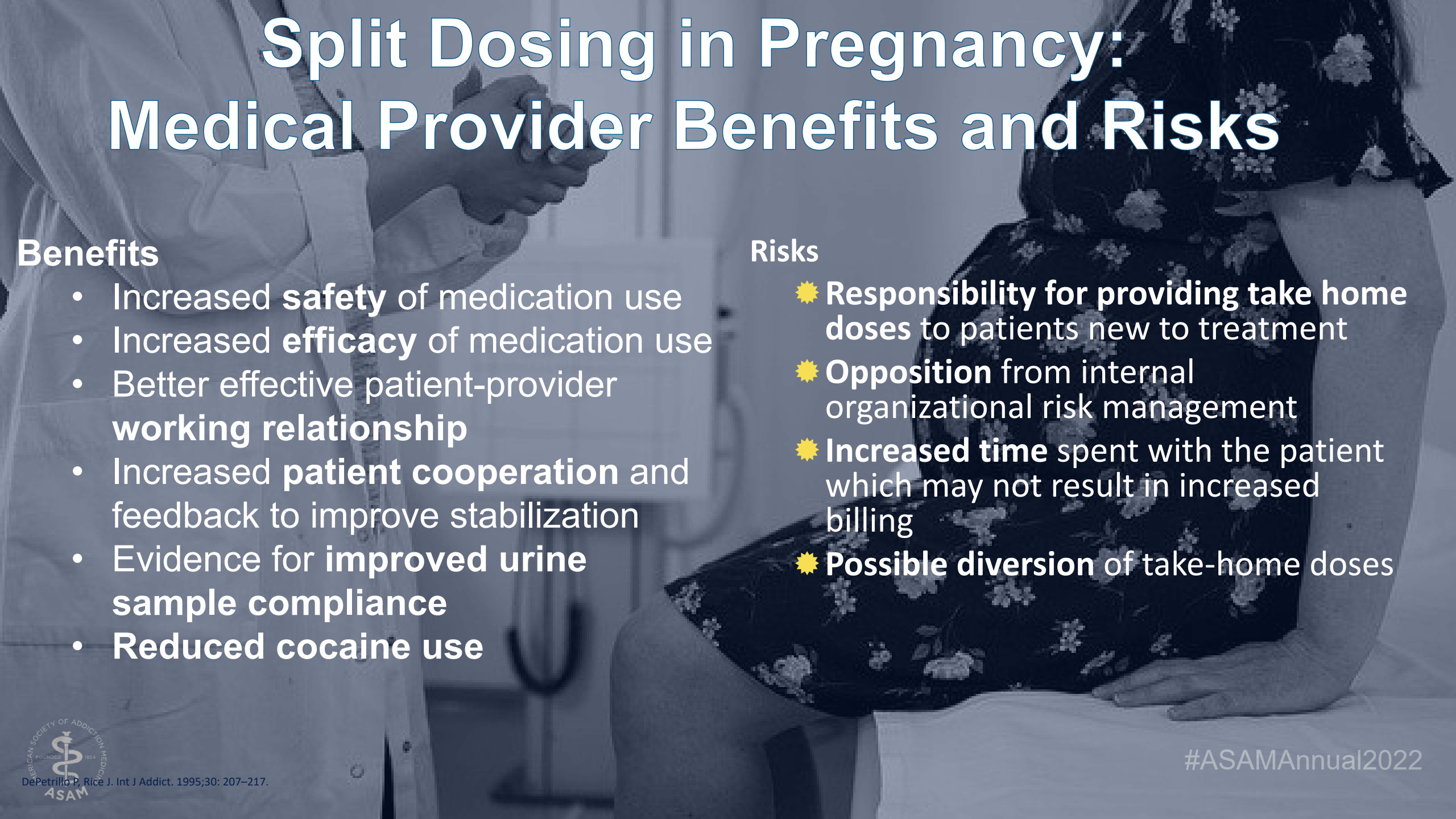
- Normalizes fetal movement
- Normalizes cardiac rhythm

Risks

- No risks to the fetus of divided doses, per se.
- If the mother's take home dose was taken from her, the fetus could experience some withdrawal (intrauterine withdrawal syndrome)

vectors/scales-balance-symbol-justice-36417/ Jansson LM, Dipietro JA, J Matern Fet

Split Dosing in Pregnancy: Medical Provider Benefits and Risks



Benefits

- Increased **safety** of medication use
- Increased **efficacy** of medication use
- Better effective patient-provider **working relationship**
- Increased **patient cooperation** and feedback to improve stabilization
- Evidence for **improved urine sample compliance**
- **Reduced cocaine use**

Risks

- **Responsibility for providing take home doses** to patients new to treatment
- **Opposition** from internal organizational risk management
- **Increased time** spent with the patient which may not result in increased billing
- **Possible diversion** of take-home doses

DePetrillo P, Rice J. Int J Addict. 1995;30: 207–217.

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Washington Pilot:
Standardize split dose for birthing and postpartum people

Offer compassionate and trauma-informed care to appreciate patient's substance history, to provide education on opioid use disorder (OUD) and to offer information on available pharmacotherapy

Discuss Methadone daily vs split dose options, safe home environment/storage and diversion risk assessment.

Prioritize whole person, patient-centered care

Washington Pilot:
Standardize split dose for birthing and postpartum people

- Validate birthing people's "voice and choice" for pharmacotherapy, dose preference, recovery and treatment engagement.
- Emphasize the split dosing flexibility to manage methadone stability under conditions of increasing clearance
- Initiate stabilization with Methadone BID and continue in postpregnancy x 12 weeks

Methadone Split Dose Initiation

Mild-moderate opioid use

- Day#1: 20mg x1 + 10mg Q4H prn
- Day#2: 15mg Q12H + 10mg Q4H prn
- Day#3: 20mg Q12H + 10mg Q4H prn
- Day#4: 25mg Q12H + 10mg Q4H prn
- Day#5: 30mg Q12H + 10mg Q4H prn

Moderate-severe opioid use

- Day#1: 30mg x1 + 10mg Q4H prn
- Day#2: 20mg Q12H + 10mg Q4H prn
- Day#3: 30mg Q12H + 10mg Q4H prn
- Day#4: 40mg Q12H + 10mg Q4H prn
- Day#5: 50mg Q12H + 10mg Q4H prn

Washington Pilot:
Standardize split dose for birthing and postpartum people

Warm hand-off and care coordination with OTP team; overdose prevention/Narcan, safe storing medication, recovery and treatment engagement.

Option for medically-shared group zoom visits for pregnant and postpartum birthing people

Peer-to-peer provider support line: 1833-YesWeCan (1833-937-9326); WAG/WSAM hotline

Final Takeaways/Summary

- Provider education and state rules facilitate safe care and evidence-based medication regimens
- Pregnant people deserve compassionate care that responds to changing pharmacokinetic needs
- Offering split Methadone dose treatment is the standard of care, not the exception
- Methadone split dose facilitates healthy outcomes for birthing people and newborns
- We can empower positive change for patients and providers, Yes We Can!

https://pixabay.com/photos/mother-son-family-mom-baby-love-5469312/

References

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