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Changing Outdated Methadone Regulations That Harm Pregnant Patients

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Abstract

Methadone regulations have changed minimally since 1974, despite advances in the understanding of the nature of opioid use disorder (OUD) and the role of medications in its treatment. At that time, most patients with OUD were considered to have anti-social personality disorders and the regulations aimed to exert maximal control over medication access. Six or seven day clinic attendance is required for months, regardless of distance, or childcare and other social responsibilities. Take home medications are not allowed unless rigid and formulaic conditions are met. While addiction medicine has rejected the 'criminal' paradigm in favor of OUD as a treatable medical disorder, methadone regulations have not kept pace with the science.

Pregnancy is characterized by an ultra-rapid metabolic state, but regulations prevent the use of daily divided doses of methadone to maintain stability. This results in repeated episodes of maternal/fetal opioid withdrawal, as well as other fetal physiologic abnormalities. Interference with dose regimen adjustments prevents optimal outcomes.

Further, methadone clinics are mostly urban, leaving patients in rural areas without access. This led to excessive morbidity and mortality when the opioid crisis hit. The response of merely expanding capacity in overcrowded urban clinics created a contagion menace when Covid-19 arrived. Pregnant women (and parents with children) were forced to negotiate dosing in dangerous conditions.

A revised methadone system must provide treatment that is local, flexible, and limited in size to manage viral contagion risks. This regulatory change can most easily be started by changing regulations that adversely affect pregnant women.

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The opioid epidemic in the United States has not spared pregnant women. Opioid use in pregnancy has increased the risk of maternal death and life-threatening health issues by 50%.[1] Opioid use disorder (OUD) is a chronic condition for which methadone and buprenorphine are the evidence-based standards of care. Methadone was the first effective medication developed and has long been available for prescription in primary care clinics in Australia, Canada, and Great Britain, but not the United States.

Pregnancy is a critical opportunity to engage the mother in OUD treatment. Engagement is essential to optimize both short-term outcomes (daily stability that supports abstinence, delivery at term without complications, normal birth weight) and long-term outcomes (children within normal limits of developmental milestones, typical cognitive and emotional development, and patient recovery from substance use).

In 1974, Congress passed the Narcotic Addict Treatment Act requiring patients to attend specifically certified methadone clinics. Methadone is typically administered daily under observation, with required periodic urine drug tests and counseling. These statutory requirements, ostensibly rooted in concern about accidental overdose and diversion, in effect separated methadone treatment from mainstream medicine. Initially, pregnant women were mandated to be withdrawn from methadone, but reports of withdrawal-induced fetal stress and demise quickly reversed that rule.[2] Since then, methadone treatment has been generally indistinct between pregnant and non-pregnant patients. However, pregnant patients have unique needs based on the physiology of pregnancy and their role as mothers with childcare responsibilities.

Unfortunately, federal statutes and regulations have not advanced with the science. This commentary will review how current restrictions on methadone dosing fail to take normal pregnancy-related metabolic changes into account. This failure compromises the safety and well-being of the pregnant woman and her fetus and impedes the function and recovery of the mother. Further, inflexible regulations interfere with maternal responsibilities and childcare duties, which became most apparent with the advent of Covid-19.

Multiple genes code for enzymes of the CYP450 system which metabolize methadone. These genes are induced by elevations of progesterone and estrogens starting shortly after conception. The conversion of methadone to its inactive metabolite, ethylidine-dimethyl-diphenylpyrrolidine (EDDP), is accelerated in the first trimester, with more rapid acceleration in second and third trimesters.[3] The half-life of methadone in later pregnancy has been shown to be reduced by half.[4] Pregnant patients undergo a metabolic shift towards ultra-rapid metabolism which lowers serum levels below what is necessary for stability such that, under standard single dose protocols, mother and fetus will experience daily episodes of withdrawal.

Managing withdrawal by merely increasing the single daily dose, as required by regulations, exposes the mother to high peak serum levels, associated with over-sedation, without solving the problem of later withdrawal.[5] Further, single doses of methadone are associated with fetal physiologic abnormalities: hypoactivity observed on ultrasound at peak levels and hyperactivity at trough levels.[6] Fetal cardiac rhythm abnormalities, demonstrated with single

dose methadone exposure, improve with increasing dose frequency.[7] While increasing doses are part of the response to accelerated metabolism, it is only by also dividing the dose (usually 3-4 times a day) that serum levels can be maintained in a safe, effective, and stable range.[8] The ability of the physician to make dose regimen adjustments, based on changing perinatal pharmacokinetics, is critical for optimal outcomes.

Federal and state regulations define medication not administered directly to the patient as 'take-home doses', which are subject to numerous restrictions intended to limit the risks of diversion. There is an exemption process under which an individual patient can be permitted to take home part of her methadone for administration later in the day in order to accommodate to the metabolic state induced by pregnancy. However, the exemption process requires: (1) requests to state and federal agencies, (2) knowledgeable regulators (especially at state levels) of why the exemption is scientifically legitimate, (3) a physician who is familiar enough with the regulations to request and provide justification for the exception, and (4) a program administrative structure that does not deter requesting exceptions. Taken individually, each requirement could be surmountable. Collectively, these requirements have created and supported an environment where most pregnant women treated with methadone are not managed according to best practices.

Beyond regulatory barriers to appropriate dosing, there are treatment engagement barriers that, while adversely affecting all patients, especially affect pregnant women. Foremost is the requirement for daily clinic attendance. For newly admitted patients (most pregnant patients are new admissions) daily clinic attendance is required for 90 days, with some States allowing Sunday take home dosing. For the next 90 days, if the patient has no illicit drug use, 6 day per week attendance is required. These requirements ignore the challenge of significant travel times for round trips to the clinic that interfere with childcare, employment, school, and other social responsibilities.

Further, methadone clinics are restricted to urban areas with little or no rural availability. For-profit companies, which operate most methadone clinics, have not considered rural clinics economically profitable, and rural counties have not provided these services for their constituents. This was understandable in the distant past when heroin addiction was largely an inner-city problem. It became a major liability with the opioid crisis and the dramatic increase in rural opioid use. There, overdose deaths were escalating at rates comparable to urban areas, while clinics were often hours away.[9] As a response to the opioid crisis, rather than increasing methadone availability in unserved rural areas, existing urban clinics were allowed to increase clinic capacity such that an already crowded 500 patient clinic then became a 1000 patient clinic. When Covid-19 arrived, these clinics became major contagion risks where social distancing became an impossibility.[10] Pregnant women, who often have to bring their young children with them because of lack of options for childcare, are forced to negotiate dosing in these high-risk settings.

When federal methadone regulations were developed 50 years ago, the field of psychiatry considered most patients with heroin addiction to have anti-social personality disorders, and government regulated this approach accordingly. They were to be 'semi-incarcerated' in a rigid program. While addiction medicine has rejected the 'criminal paradigm' and

embraced the concept of addiction as a treatable medical disorder, the regulations have not adapted. Physicians need the flexibility to meet each individual patient's needs without non-scientific barriers that prevent patients from accessing treatment that is both effective and safe. Pregnant patients generally do not engage in criminal activity, including diversion of their medication. On the contrary, to their credit, they show humility and resilience in overcoming a major emotional barrier related to the stigma of being pregnant on methadone. They are motivated to do this because of their wish to be better mothers.[11]

Regulatory restrictions on the use of methadone are the major barrier to treatment for an increasingly fatal disease. While methadone is quite effective in eliminating drug use and reducing mortality and syringe-related diseases for the minority of OUD patients it reaches, pharmacotherapy does not reach 80%-90% of patients, even with the additional option of buprenorphine.[12,13] Thirty-two percent of US counties have no treatment programs.[14] Many of these mostly rural areas have experienced large numbers of overdose deaths which have included pregnant women.

The availability of buprenorphine has certainly increased the total number of patients with OUD who are on medications. However, as of 2017, there were 382,867 patients on methadone in the U.S. vs 112,223 on buprenorphine.[15] While these data do not specify the number of pregnant patients receiving such medications, methadone is a highly prescribed and essential medication. Regulatory change is therefore very important for these patients. While both medications are equally effective for large populations, they have different pharmacologic profiles and this translates into different individual patient appropriateness, effectiveness and acceptability. Therefore, both medications should ideally be available in both urban and rural treatment settings, but that is not currently the case.

The process of regulatory change is most easily started by changing statutes and regulations that adversely affect pregnant women. Immediate federal action is necessary to provide exemption for divided dosing during pregnancy and the early post-partum period from regulations that apply to "take home" medications. Pregnant patients should receive medication at a dose and frequency that is optimized for them at the discretion of the physician, without regulatory limits based on time in treatment, drug test results, or other patient variables. The scientific evidence supports this approach as important for improved maternal/fetal/child outcomes.

A revised system must provide treatment that is flexible, local, and limited enough in size to safely manage viral contagion risks. It should include methadone availability in primary care and obstetrical practices, and in county and community health clinics; and it should also include options for direct pharmacy dispensing to facilitate optimal access to medications. These are effective approaches elsewhere in the world. The opioid epidemic is a complex societal phenomenon that has been relatively resistant to a variety of prevention efforts. With effective treatment still being over-regulated and underutilized, it is not going away in the near future, and our efforts must be guided by this reality.

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