CHAPTER 4
PREGNANCY AND NEONATAL WITHDRAWAL

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4.1. Introduction

4.1.1. Pregnant Patients Need Treatment

Few areas of addiction medicine are as challenging and rewarding as helping a pregnant women recover from opioid use disorder (OUD) through medication assisted treatment (MAT) and having them deliver healthy, drug-free babies. Many physicians have received little to no training in the management of pregnancy complicated by OUD, which makes them understandably reticent to treat this population; they may feel uncertain about the physiologic needs of the fetus and the fetal response to methadone or buprenorphine. Is the fetus dependent? Are medications needed or not? Are the medications beneficial or harmful? Is one medication better than the other? MAT is often misunderstood, and potentially viewed as THE cause of Neonatal Abstinence Syndrome (NAS). However, most women are already physically dependent on an opioid before MAT is started, so the fetus was already at risk of opioid-related NAS. The exception is women who conceive on methadone or buprenorphine. In this situation, the question becomes, "Given that a woman is opioid dependent when she learns she is pregnant, does MAT raise or lower the risk of NAS or other adverse outcomes?"

Decades of research support the safety and efficacy of methadone use in pregnancy in facilitating maternal recovery; maternal recovery rates of over 90% have been reported [94]. Buprenorphine has been implemented for a much shorter time, but the research supports similar efficacy [95]. Methadone and buprenorphine significantly improve perinatal outcomes, reducing maternal and neonatal complications.

There are many treatment issues unique to pregnancy and the postpartum period that will be discussed, but the most important issue when treating a pregnant patient on MAT is understanding adequate and appropriate medication use during pregnancy. Two overriding issues influence all treatment interventions:

1. The fact of fetal dependence with the risk for Neonatal Abstinence Syndrome (NAS);
2. The profound maternal pharmacokinetic changes that occur throughout pregnancy and the perinatal period, which complicate medication use, especially methadone use [96].

These guidelines provide information specific to the medical management of OUD during pregnancy and the postpartum period, focusing on the use of methadone or buprenorphine to optimize treatment of maternal/fetal dependence given the altered physiology and pharmacokinetics associated with the perinatal period. Optimized treatment increases the likelihood of term delivery of a drug-free baby and decreases the risk of NAS.

4.1.2. Pharmacokinetic Changes during Pregnancy

It is not uncommon for mothers maintained on methadone to experience opioid withdrawal between doses soon after conception. For most women, this process of

increased methadone clearance and metabolically-induced withdrawal continues throughout the pregnancy, with significant individual differences in intensity [96]. Increased clearance of buprenorphine is less likely to occur and less pronounced when it does.

Pharmacokinetic science has documented major alterations in drug metabolism secondary to induction of the Cytochrome P450 (CYP) enzyme system by the hormones of pregnancy. Methadone and buprenorphine are both CYP450 substrates whose metabolism is accelerated by pregnancy. However

- Methadone is quickly converted to an inactive metabolite; whereas
- Buprenorphine is a pro-drug, which is converted to three active metabolites.

Pregnancy specifically induces CYP enzymes 34A [97], 2D6 [98], and 2B6 [99]. Methadone is primarily metabolized by CYP 34A, 2B6, and by lesser and variable contributions from 2D6, 2C19, and 1A2. The parent molecule is demethylated into inactive EDDP (2-ethylidene-1,5dimethyl-3,3-dyiphenylpyrrolidine) [100, 101]. Changes in pregnancy can shorten the effective half-life of methadone from its usual 24-hour range to 12 hours, and at times to as short as 4-6 hours [94]. There is a 17-fold variation in methadone serum concentration for a given dosage [102] in large part due to CYP genetic polymorphism.

Alteration in the half-life means that methadone is rarely a once a day medication in pregnancy. Pregnancy changes methadone from a long-acting drug, which can be given once a day, to a short-acting drug that must be given in multiple (divided) doses to maintain stability of maternal/fetal opioid activity and avoid withdrawal. The significant variability in the rate of metabolism during pregnancy creates significant challenges to safe and effective perinatal management. Using divided doses to compensate for the reduced half-life has been associated with a reduced rate of NAS requiring treatment (29% compared to the published rates of 60-80%) [94]. On rare occasions, rapid clearance of methadone may cause the urine drug screen to become negative for methadone or methadone metabolite. The physician must review the situation to determine whether the most likely explanation is a low methadone blood level or diversion of the PM dose.

Despite buprenorphine's accelerated metabolism during pregnancy, once per day dosing is feasible because it is converted to active metabolites, but there is evidence that twice per day may be preferable [103].

Clearly, dose amount and scheduled regimen must be individualized regardless of whether a pregnant woman is prescribed methadone or buprenorphine. Basing the dosing regimen on pharmacokinetics maximizes the desired pharmacodynamic effect, which is stability of mu receptor occupancy by the medication in the maternal and fetal brain. The stability of the opioid system during pregnancy is presumed to be very important for promoting normal fetal brain development.

4.1.3. Medication Selection Considerations: Methadone vs. Buprenorphine

The most important point about the treatment of pregnant women with OUD is that withdrawal puts the woman, the pregnancy and the baby at risk for adverse outcomes. In view of this risk, methadone maintenance is often the treatment of choice. Methadone induction does not require a woman to be in withdrawal at the time of the first dose and poses no risk of precipitated withdrawal. Treatment retention rates are higher with methadone maintenance, and treatment retention correlates strongly with abstinence. The longer a woman remains in treatment, the more likely she is to become and remain drug-free, increasing the likelihood of term delivery of a healthy, drug-free baby that remains in the patient's custody.

There are some cases where buprenorphine may be a better choice:

- Women who meet DSM-5 criteria for OUD, are seeking treatment because they are fearful of relapse, but are **not physically dependent** at the time of presentation for treatment.
- Women who **present for treatment in moderate to severe withdrawal**, because of the time elapsed since the most recent opioid use.

When buprenorphine is used in pregnancy, the mono-product, Subutex, is the recommended formulation. Buprenorphine has several advantages: stabilization on a therapeutic dose may be accomplished in two or three days vs. the weeks or months it takes with methadone. There are no regulatory constraints limiting divided doses. The rate of metabolism of buprenorphine over the course of a pregnancy and post-partum is less variable, so that fewer dose adjustments are required to maintain a therapeutic dose.

Women should be provided with information about both medications and asked which medication they would prefer. Their preference should be honored to the extent possible. They should be informed that the goal of MAT is stabilization on a therapeutic dose to ensure complete suppression of opioid withdrawal. **They should be advised that it is easy to transition from buprenorphine to methadone at any point, but that transition from methadone to buprenorphine is significantly more difficult and should not be attempted in pregnancy.**

A critical question is whether there are differences between methadone and buprenorphine on outcomes, especially NAS severity. A study was done by NIDA (the MOTHER Study) to try to answer this question.

The MOTHER Study (Maternal Opioid Treatment: Human Experimental Research)

The MOTHER Study is the most comprehensive research effort to date on the use of methadone verses buprenorphine for the treatment of OUD in pregnancy. This study examines the safety and efficacy of methadone verses buprenorphine for mothers and babies. The study is well known and widely quoted, so it is important for

physicians treating pregnant women with OUD to be aware of it. The data from this study continues to be analyzed, new questions explored and new articles written to share the findings. There are many important findings from this study. Unfortunately, it did not resolve the question about whether methadone or buprenorphine is more likely to cause NAS.

Perhaps the most important finding is that buprenorphine is a safe and effective alternative to methadone for treating OUD in pregnancy. The rates of pregnancy complications were similar for methadone and buprenorphine. The key indicators of neonatal health and development were also similar. (NIDA Notes 7/6/2012)

There are two reasons that the MOTHER study did not resolve the NAS question. First, during the MOTHER study, methadone was always given as a single daily dose, which means that the women on methadone were not stabilized on a therapeutic dose. A single daily dose of buprenorphine is less problematic because buprenorphine breaks down to active metabolites.

A second reason has to do with different findings at the sites. One of the six study sites, Johns Hopkins Medical Center (an urban U.S. site) found buprenorphine-exposed neonates to have shorter treatment durations for NAS and lower medication (morphine) requirements than methadone-exposed neonates [104]. None of the other sites showed this, but the findings at this site were so pronounced that cumulative scores (from all the sites) favored buprenorphine. Furthermore, morphine use at the Johns Hopkins site was 7 times greater, and the number of days of medication use was 2-3 times longer than at the rural U.S. or European sites [105]. This would suggest that the treatment location, and other non-pharmacologic variables, seem to be more significant determinants of outcome than medication used.

One important difference between sites was that the Vienna site, which found no medication differences in NAS severity and used significantly lower mean morphine doses for both medications, was the only site to use a rooming-in model of post-natal care. This suggests that methadone-exposed neonates who are separated from the mother may be more vulnerable to increased NAS severity, but methadone-exposed neonates that are not separated are not.

The drop-out rate due to medication dissatisfaction was significantly greater for buprenorphine than for methadone, indicating that a mixed partial agonist/antagonist medication is not optimal for many pregnant women.

Methadone vs. Buprenorphine – Other Considerations

The major known differences between the two medications are pharmacokinetic (see Table 4.1). However, there are no studies comparing methadone and buprenorphine using dosing based on pregnancy pharmacokinetics. Therefore, it is not clear if there is an advantage to one or the other medication in terms of neonatal outcomes. However, the major known differences between the two medications are pharmacokinetic (see Table 4.1). Metabolic clearance is the major determinant of fetal exposure and a source of potential differences in outcomes.

As Grossman et al. (2017) stated [106]: "None of the published articles on NAS comparing different drug therapies control for non-pharmacologic interventions, nor are these interventions routinely documented. When a child has a [Finnegan] score of 8 or greater, we do not make sure that the mother is at the bedside or review other non-pharmacologic interventions to ensure they are maximized. We just give morphine."

Whatever the actual differences are between medications, they appear to be relatively minor compared to recent studies demonstrating that the standard policy of separating mothers and babies to monitor or treat NAS in newborn intensive care units (NICUs) actually worsens the NAS symptoms. Four studies of increasing sophistication have demonstrated that a rooming-in model that relies on intensive maternal care (prolonged skin to skin contact, nursing, other normal maternal soothing) to minimize NAS symptoms was associated with dramatic reductions in the need for treatment, shorter length of stay, and major cost reductions vs. traditional management in a NICU [106-109].

Table 4.1

Advantages of Buprenorphine vs. Methadone

Buprenorphine	Methadone
■ More rapid stabilization on a therapeutic dose and a narrower dosing range (2mg-24mg) ■ Relative ease of medication management with less frequent episodes of withdrawal requiring dose increases ■ No regulatory restrictions on divided dosing regimens ■ Availability of medication through regular MD offices/ pharmacies, allowing for treatment of patients who need to travel or relocate to a remote area	■ Safety of induction with no risk of precipitated withdrawal ■ Greater rates of retention in treatment, the best marker of treatment success

4.1.4. Risks of Withdrawal vs. MAT During Pregnancy

With the epidemic of opioid dependence nationally, the rate of women delivering babies with NAS requiring treatment has risen dramatically [110]. In response, there has been public pressure to withdraw mothers from opioids during pregnancy. However, this is not a good solution because the risk of relapse to illicit opioid use is very high when MAT is discontinued. NAS that is related to withdrawal from multiple substances (alcohol, benzodiazepine, marijuana, cigarettes, etc.) may have different long-term outcomes than that related to methadone or buprenorphine alone. There is a growing literature that raises concern about long-term neurodevelopmental problems for babies treated for NAS. The MOTHER Study and the Developmental Follow-up Study is the only randomized controlled trial of infants and children who were exposed in utero to methadone or buprenorphine with minimal to no concomitant illicit drug use. The findings from this study are encouraging. "Children exposed to methadone or buprenorphine before birth followed a three-year path of normal physical and mental development. Children who required treatment for NAS did not differ in developmental outcome from children who did not require treatment." (Addiction Treatment Forum 4/17/2018, Jones 2012, Kaltenbach 2017)

In light of this study, NAS appears to be a short-term problem that does not pose a long-term risk; babies treated generally do not differ in long-term outcomes from babies not treated. If NAS does occur, it is far safer to treat significant NAS in a fully grown, term baby with an appropriate pharmacologic agent (methadone, buprenorphine or morphine) than to allow a small, incompletely developed baby to withdraw under blind conditions in utero by trying to taper the pregnant mother. Long-term safety should be the critical determinant of approach to dependence and pregnancy.

The most documented risk of maternal opioid withdrawal is miscarriage in the first trimester. After the first trimester, fetal mu opioid receptors are fully functional, so maternal withdrawal is associated with fetal withdrawal. Mothers in withdrawal often feel uterine cramping and fetal hyperactivity. Risks from maternal opioid withdrawal during the second trimester and after are less visible but may have significant consequences.

Withdrawal causes a physiologic stress reaction in maternal and fetal brains. An intrauterine abstinence syndrome (IAS) has been described, supported by clinical studies and animal model research [111, 112]. Gross measures of fetal distress may not accompany withdrawal because routine clinical measures are not sensitive to fetal stress symptoms unless they are life-threatening. Although it is not possible to use routine fetal monitoring to clinically diagnose fetal withdrawal or to quantify short- and long-term consequences of fetal withdrawal stress, there is an expanding literature on the adverse effects of in-utero stress on fetal development. The effect of maternal withdrawal stress carries an adrenergically-mediated risk for fetal hypoxia, as well as a corticosteroid-medicated risk of epigenetic alterations of the fetal genome and the potential for long-term developmental problems.

4.1.5 Admission Criteria

Under current federal and California regulations, any pregnant woman with a past history of OUD who is determined by the admitting physician to be physically dependent on opioids is qualified for methadone maintenance treatment (MMT). Federal regulations allow for MMT for a pregnant woman who is not currently physically dependent, if she has a past history of OUD and is at risk for relapse. In California, an exception request must be submitted to and approved by the Department of Alcohol and Drug Programs (ADP) prior to admitting a pregnant woman who is not currently physically dependent.

A history, physical examination and records documenting prior treatment episodes or opioid dependence while hospitalized or incarcerated are sufficient to comply with these regulations. Observation of signs of opioid withdrawal is the usual way of documenting physical dependence. However, withdrawal should be minimized during pregnancy because of the risk of fetal stress and the potential for precipitating premature labor. Women should be told to time their last opioid use so that the earliest stages of withdrawal will begin within a few hours of presentation to the clinic. They should be cautioned that if they come to clinic when intoxicated, it will not be safe to start medication.

4.1.6. Pregnant Patients and Polysubstance Abuse

Pregnant women who are physically dependent on alcohol, benzodiazepine, barbiturates or other sedatives, in addition to opioids, must be evaluated by the admitting physician to determine whether inpatient detoxification with fetal monitoring is necessary. Methadone treatment should be initiated prior to hospitalization, so opioid withdrawal does not complicate the sedative detoxification.

A DSM-5 diagnosis of OUD and a waiver to prescribe or dispense buprenorphine is needed to qualify for admission to buprenorphine treatment. For pregnant women who are physically dependent on opioids, induction must be delayed until the patient is in moderate opioid withdrawal. Initiating treatment before this poses the risk of precipitated withdrawal.

4.1.7. Pregnancy and Patient Assessment

The most important task during the admission interview is to establish nonjudgmental rapport with the patient on the mutual, primary issue of fetal safety. If this is not accomplished, the patient may decline treatment altogether, provide an incomplete history or drop out of treatment. As the pregnancy progresses, she may be reluctant to request dose increases or for a higher level of care when/if needed.

In addition to the usual patient history queries, prior pregnancies should be noted, specifying whether patient

was opioid dependent at the time, whether treatment was received, the outcome of the pregnancy, and the current status of the child. If the patient received treatment during a prior pregnancy, it is helpful to understand whether she had a positive or negative experience with treatment in general and with treatment around delivery in particular. If the experience was a negative one, an effort should be made to address the issue(s) raised, in an effort to ensure that patient's experience during the current pregnancy will be a positive one.

Review of the patient's non-opioid substance use history is essential, including other illicit drugs, alcohol, marijuana, nicotine, prescription and over-the-counter medications. If another physician is prescribing medication(s), the OTP physician should confirm that the medication(s) are still indicated and are compatible with pregnancy and with methadone/buprenorphine treatment. For example, lithium and valproate are contraindicated in pregnancy because of the risks of birth defects. Certain TB medications (e.g. Dilantin, Phenobarbital, Tegretol, Rifampin) will severely complicate methadone stabilization by inducing CYP450 metabolism of both methadone and potentially buprenorphine (see sections on Dosing and Pharmacokinetics). Sedating medications like benzodiazepines pose risk of maternal/fetal dependence. Written authorization should be obtained to allow coordination of care with the prescribing physician to ensure the baby's safety.

An obstetrical history including complications during prior pregnancies/deliveries should be recorded. Equally important are the patient's feelings about the current pregnancy, whether the father is involved and whether the father and patient's family are supportive of patient, the pregnancy, treatment and recovery, especially recovery with MAT. Conjoint sessions with the father or other concerned family members may be critical to patient participation. Asking whether the father is using alcohol or drugs will allow the program to assist and expedite getting him into treatment if desired.

Mental health problems are a particularly important area for inquiry, as mental illness can adversely affects neonatal and long-term outcomes. Women with OUD have a very high incidence of both childhood and adult traumas, including molestations, rapes, and physical violence. PTSD and other anxiety disorders are common, as are mood disorders (depression and bipolar disorder). Patients should be asked if they feel safe in their current living situation and whether there is a history of domestic violence with the baby's father or current partner; they should be advised and assisted accordingly.

4.1.8. Pregnancy and Initial Testing

Routine laboratory testing including a metabolic panel, hemogram, confirmation of pregnancy, medical urinalysis, liver function tests and screens for syphilis, hepatitis B and C should be included in the record. All women should receive HIV counseling and be offered testing. The physician should encourage all pregnant women with known risk factors (e.g. IV drug use, multiple sexual partners) to be tested for HIV in view of the data that treatment has been shown to reduce the risk of perinatal HIV transmission [113-115]. If the patient has risk factors within the preceding year, the HIV test and/or syphilis screening should be repeated in each trimester and at delivery. Many of these tests will be offered by the prenatal care provider, so it is reasonable to check to see what has already been done to avoid unnecessary phlebotomy.

A PPD (tuberculosis) skin testing should be done unless the patient has a history of a prior positive result, in which case the physician should conduct a symptom review and investigate whether a chest X-Ray (CXR) was done. If there was no CXR, or no copy may be obtained, referral for a CXR should be considered. If the patient is asymptomatic and low risk, the chest x-ray may be delayed until the second trimester.

In 2012, because of the increased prevalence of pertussis in the U.S., the ACIP recommended that every pregnant woman be given Tdap during the third trimester to protect her from pertussis around the time of delivery and to provide passive immunity to the newborn. Maternal antibodies are short-lived, so re-vaccination is required during each pregnancy. Infants are at highest rate of death from pertussis.

Women who express the intention to terminate the pregnancy should be provided with support and appropriate resources and referrals. Until reliable documentation of termination has been obtained, the patient must continue to receive the same care as other pregnant women. Some women express a desire to terminate the pregnancy but do not follow through.

4.1.9. Medical Counsel Regarding MAT during Pregnancy

Many pregnant women seeking MAT for OUD feel guilty and fearful. These feelings stem from a variety of beliefs and misconceptions, many promoted and endorsed by society or medical providers unfamiliar with substance use disorders and treatment. Patients may believe that they cannot genuinely be in recovery while on opioid medication. They may think that they should be able to achieve and maintain abstinence on their own, fearing that friends, family, and society will not accept them if they are on methadone or buprenorphine. They may fear that methadone or buprenorphine is bad for their health or bad for the baby, and that withdrawing from methadone or buprenorphine is worse than withdrawing from heroin or the prescription opioids they were using. The physician should be very sensitive to the fear these mothers have of having their baby taken away from them and the anxiety about how their participation in MAT will be perceived.

Pregnant women often present for admission to MAT after being advised that detoxification is contraindicated during pregnancy. Despite this, many pregnant women feel they are pursuing a mode of treatment that will ensure their own comfort, assuming that it is at the baby's expense.

The admitting physician should explain the risks of continued use of heroin or other illicit drugs during

pregnancy, including small-for-gestational-age infants, increased incidence of SIDS, prematurity, and low birth weight. If needles are shared, the risks expand to include infection with HIV, HTLV I/II, hepatitis and soft tissue infections. The lifestyle associated with drug use increases the risk of trauma, STDs, lack of prenatal care, and loss of custody of the baby. The consequences of opioid withdrawal during pregnancy should be discussed, including:

- The baby experiences the stress of cyclical withdrawal states, which compromises growth and may have long-term "epigenetic" consequences.
- The uterus may become hyperactive resulting in miscarriage or preterm labor and delivery.
- Cravings for opioid may make it difficult for the woman to avoid illicit use.
- Nausea may suppress the appetite resulting in malnourishment and maternal depletion.
- Vomiting may lead to dehydration and loss of part of the methadone or buprenorphine dose.

This information needs to be re-visited during on-going physician/patient meetings. Discussing the research that indicates that infants exposed to methadone in utero have normal physical and mental development is very important to convey to the mother, the partner and concerned family members. (Rattleback & Finnegan 1987; Kaltenback & Finnegan 1984; Kaltenback, Graziani & Finnegan 1979; Kaltenback & Finnegan 1989).

NAS is a critical issue for detailed discussion as it is the major contributor to maternal fear of MAT and problematic desires to withdraw or suffer through withdrawal to minimize exposure of the baby to the medication (see NAS section). Women should be counseled about the risk of NAS, the symptoms, the timing of onset, the treatment, the things she can do during and after pregnancy to decrease the risk/minimize the symptoms. Above all, mothers should be reassured that NAS is treatable and much safer than a growing baby undergoing in utero withdrawal.

Not all hospitals and pediatricians are equally experienced in the treatment of NAS. It is helpful if the OTP physician is familiar with local hospitals and with the level of comfort of the medical staff in managing babies with NAS.

4.2. MAT Induction during Pregnancy

The physician's objective should be to stabilize the pregnant woman on a therapeutic dose of medication as quickly as is safely possible in order to minimize withdrawal and/or ongoing drug use. To ensure that the initial dose of medication is given as soon as possible, the patient should see the physician early in the admission process. Medication may be started after the physician has confirmed the diagnoses of opioid use disorder and pregnancy, evaluated for current physical dependence and observed for signs of withdrawal. In the event the patient presents in an intoxicated state, induction must be delayed.

Table 4.2

Dosing Guidelines for Pregnant Women

1. An initial dose of 2 mg is given in the clinic under observation. Should any precipitated withdrawal occur, another 2 mg should be repeated immediately. If no withdrawal is precipitated, the patient should be observed for 1-2 hours, monitoring vitals and COWS every 30-60 minutes. Decisions about further dosing are made on the basis of the presence of withdrawal. If present 1-2 hours after the initial dose, another 2-4 mg dose should be given.
2. The patient is sent home once symptoms of withdrawal have been suppressed. If the patient appears sedated after a dose, vitals should be monitored to ensure stability of the pulse, blood pressure and respirations until the peak has passed (2 hours).
3. The patient should be sent home with a 2 mg dose for the PM, to be taken if symptoms of withdrawal return and a dose to be taken the following morning prior to coming to clinic for day 2 of induction. The AM dose taken at home on day 2 should be the total dose from day 1 (dose in clinic + dose taken at home). The patient should be advised to bring in any unused buprenorphine on day 2. Instructions should be provided verbally and in writing.
4. When the patient presents on day 2, the physician will be able to observe the patient after the home dose. If symptoms of withdrawal returned at home on day 1 and were not completely suppressed by the PM dose, or returned again before the morning dose, an additional dose of 2-4 mg should be given in clinic and the patient sent home with 2-4 mg to be taken in the PM should withdrawal return. The patient should be provided with a dose to be taken at home before coming to clinic on day 3 (the total dose from day 2).
5. For patients that appear unable to follow these instructions or to secure medication, the next morning's dose may be omitted. The patient should be scheduled to return to clinic first thing in the morning for evaluation and the next day of induction.
6. Most patients will stabilize on a therapeutic dose within a few days. Patients using ½ gram of heroin per day, or equivalent, often stabilize on 16 mg per day. Patients with pain complicating addiction or using high amounts of heroin, may need up to 24 mg/day.

4.2.1. Pregnancy and Buprenorphine Induction

Buprenorphine, because it is a mixed mu receptor partial agonist/antagonist, carries special risks during induction that are not a problem with methadone, which is a full mu receptor agonist. If there are significant amounts of an opioid agonist on maternal/fetal mu receptors when buprenorphine is started, precipitated withdrawal will occur, which may result in acute onset of labor and acute fetal distress. Therefore, women **MUST** be in some level of withdrawal before buprenorphine can be started.

The research on buprenorphine induction during pregnancy was done in-patient and involved a complicated protocol of transitioning from heroin to morphine to buprenorphine (the MOTHER study). This induction protocol is not practical, and at this time, there are no research-supported protocols for safe induction of pregnant women who are physically dependent on opioids. Inductions are currently being done in the outpatient setting, but without any formal reporting in the literature.

Note that the transition from methadone to buprenorphine during pregnancy is absolutely contraindicated. Methadone's length of action makes precipitated withdrawal very likely and is therefore too dangerous to be recommended. Transitioning from buprenorphine to methadone is not a problem; methadone will not displace buprenorphine from mu receptors, but rather, will gradually gain access to receptors as they are vacated by buprenorphine.

Prior to the first dose of buprenorphine, physical dependence on short-acting opioids should be established. The date, time and amount of the last opioid use should be documented. Objective signs of early withdrawal should be present, meaning a COWS of at least 10 (moderate or higher), not including subjective symptoms. The patient should be advised that precipitated withdrawal is more likely to occur if she has used a long-acting opioid or used any opioid within the last few hours. Special care should be taken to ask about use of opioids not detected by the on-site urine drug test used in clinic.

Although buprenorphine metabolism during pregnancy is not as impacted as methadone, and buprenorphine can be administered once a day, the principle of avoiding peaks and troughs of fetal exposure applies. A strong case can be made for divided dosing, usually twice per day, except for patients who have pain, when three to four times per day is more effective. It should be noted that when the dose is divided, the patient may stabilize on a lower total daily dose.

Patients who are being treated to prevent a relapse, meaning they have a history of opioid use, but are not currently dependent, are given a 2 mg dose on day 1 and observed for signs of sedation. A PM dose may be added if once per dosing does not control craving. The dose should be adjusted gradually, every couple of days, to avoid sedation.

4.2.2. Pregnancy and Methadone Induction

It is a misconception that methadone induction should be done in an inpatient setting. This is unnecessary, as methadone induction is very safe once opioid dependence has been established and may cause delays posing increased risk to the fetus. Once opioid dependence has been established, the patient may be safely given 15 mg of methadone provided there are no signs of intoxication. Then the rest of the usually long admission process can be completed without exposing the maternal/fetal dyad to withdrawal.

The patient should be re-evaluated 3-4 hours later to determine the response to the first dose. Another 15 mg is usually given at that time, unless there is uncertainty about the degree of dependence or signs of sedation from the first dose. A usual starting dose for a woman who reports using ½ gram of heroin or more daily is 30-40 mg. The same is true for heavy users of prescription opioids. Women who are using relatively low doses (1.5x maximum therapeutic dose) of weaker prescription opioids, such as hydrocodone, codeine, or tramadol are started on 10-20 mg methadone per day. Daily evaluation and dose assessment should occur until the patient reports 24-hour stability.

Under California regulation, no more than 30 mg may be legally administered at one time on the first day of dosing. Additional methadone may be given on the first day but must be administered after a physician-specified observation period. The physician must note the rationale for a dose above 40 mg on the first day. Doses >40 mg may be necessary for patients who have an established dependence on higher doses of methadone, such as pain patients. The patient should be advised that the total dose given in clinic on day 1 will not normally relieve all symptoms for a full 24 hours. Symptoms that begin as the methadone blood level falls (about 5 hours after dosing) will usually subside after the blood level of methadone has stabilized (about 5 days).

The first step in establishing a therapeutic dose is to completely suppress symptoms of withdrawal at the time of the methadone peak, meaning 5 hours after dosing. When symptoms of opioid withdrawal are present at the peak, it is safe to increase the dose daily. Doses are generally increased in 5-10mg increments. By the time the dose is 50 – 60 mg, 10mg increases are generally required. It may be necessary to have the patient remain in clinic or return to clinic 5 hours after dosing for a face-to-face evaluation to ensure that it is safe to increase the dose.

Once a patient is comfortable at the time of the peak, the duration of complete suppression will last longer every day for 3-5 days. Dose increases are made at 3-5-day intervals, to allow the patient to experience the full effect of the current dose before adding to it. Increasing the dose more frequently may cause sedation or overdose. Once symptoms of withdrawal are completely suppressed between doses, the dose should be raised if the woman reports cravings or ongoing illicit opioid use. Peak and

trough methadone blood levels (PTR) or methadone/metabolite ratios (MMR) may be helpful in determining a therapeutic dosing schedule.

If the patient experiences sedation after dosing, the dose must be decreased promptly to avoid overdose over the next few days. A person who metabolizes methadone at a normal rate will find that as the dose is increased, it suppresses withdrawal for longer and longer periods of time. When the right dose is reached, withdrawal remains suppressed for the entire 24-hour period between doses. A person who metabolizes methadone at a more rapid rate, which includes most pregnant women, may find that they begin to feel sleepy at the time of the methadone peak while continuing to experience withdrawal between doses. Merely increasing the dose in rapid metabolizing pregnant patients would unnecessarily increase the peak, while having a minimal effect on the trough [116, 117]. In this situation, a divided dose is required for stabilization.

Federal and California regulations do not allow a daily take-out dose of methadone for the PM until a patient meets the "8-point criteria" (42 CFR 8.12 – Federal Opioid Treatment Standards and Title 9, 10370 California Code of Regulations) for take-out doses[7]. Federal regulations also require that a patient be in treatment long enough to qualify for 6 take-home doses/week, which is 270 days. It is therefore necessary to submit a SAMHSA/CA exception request to allow a daily take-out dose for the PM prior to initiating split dosing. The rationale for the request is the fetal need for stability of opioid exposure. SAMHSA/CA will generally approve these exception requests, except in the case of a woman who is using non-opioid substances. Approval is generally contingent on the patient becoming abstinent from illicit opioids on the divided dose and remaining abstinence from all illicit drugs.

As soon as regulatory requirements are satisfied, a second dose should be added to be taken 10-12 hours after the AM dose. The PM dose is increased in 5-10 mg increments every 3-5 days. The AM and PM doses may or may not be the same. Some patients require a higher dose during the day, when they are more active. In the event that a woman experiences sedation after dosing and withdrawal between doses on a twice/day dosing schedule, the dose will need to be divided three or even four times/day. Computerized dosing systems do not allow for more than two doses/day. The patient should be advised to make a line or lines on the take-out bottle to allow them to take the dose in 2 or 3 parts as directed. This is precise enough to be effective and reduces the risk of spilling that could occur if the dose is poured into a separate container.

When a divided dosing regimen is used, the use of "high" doses (average 152mg/day) has not been associated with high serum levels, but with average serum levels in the mid-therapeutic range: 275 ng/mL [94]. It should be noted that when the dose is divided, the patient may stabilize on a lower total daily dose.

Risks of Once a Day Methadone Dosing Regimens for Rapid Metabolizers

Peak/trough extremes are likely to be associated with daily episodes of maternal/fetal withdrawal in the late PM and early AM. Use of single doses of methadone in pregnant women has been associated with adverse effects on fetal physiology. Depressed fetal movement and decreased fetal heart rate have been documented at the time of elevated methadone peak levels, and fetal hyperactivity and cardiac rhythm irregularities have been observed at the time of sub-therapeutic methadone trough levels [118, 119]. In one study, blinded radiologists were able to identify pregnant patients on single daily methadone doses because of the observation of reduced fetal movements in the hours following dosing and increased fetal movements in the evening [118]. These findings suggesting over sedation of the baby at peak blood levels and withdrawal-related hyperactivity as methadone blood levels fell in the evening. Split dose patients had ultrasound exams with fetal movements similar to controls.

It has been postulated that the fetus may become "sensitized" to repeated withdrawal [111]. Sensitization may be associated with the increased risk of NAS found in many single-dose studies. NAS may be partly a learned fetal response, one that may occur during erratic opioid misuse or under dosing conditions that disrupt normal fetal physiology.

There is compelling research to support giving all but the most impaired pregnant patients divided doses (BID – QID schedules) based on fetal and maternal needs. For all patients, the physician must weigh the clinical benefits and risks of take-home doses, especially for emotionally unstable patients or those in an unstable home environment. If at all possible, patients who are too unstable to be considered for a daily take-home for the PM, should be offered referral to a higher level of care, where daily doses are delivered and a PM dose can be secured.

The Importance of a Therapeutic Dose of Methadone

Some obstetricians continue to advocate low doses of methadone or even methadone tapers to avoid the risks of NAS [120]. However, the literature on the relationship of dose to NAS is inconclusive (see also the Etiology of NAS below), and it has not been established that babies exposed to higher doses of methadone in utero are at greater risk of adverse outcomes. (McCarthy, Leamon, Parr, Anania 2005). It is well established that therapeutic doses of methadone are associated with decreased illicit drug use, increased participation in prenatal care and longer retention in treatment. It is clear that babies exposed to ongoing illicit drug use are at greater risk of adverse outcomes.

The current recommendation is to treat pregnant women according to the same dosing guidelines as non-pregnant patients, meaning to use a dose sufficient to eliminate withdrawal, drug use, and drug cravings, without arbitrary limits on the dose. Clinical experience has shown that after initial stabilization many women require dose increases as pregnancy progresses to maintain a therapeutic methadone dose and to suppress re-emergence of signs and symptoms of withdrawal. The pharmacokinetic changes play a significant role and there is an increasing volume of distribution during pregnancy (see Pharmacokinetic Changes during Pregnancy).

Serum methadone levels and metabolic ratios are important tools to help physicians to stabilize pregnant patients on methadone during pregnancy and to ensure that doses remain therapeutic throughout the pregnancy and the post-partum period.

Peak and Trough Methadone Levels

Serial serum methadone levels are a well-established, readily available, and effective way to follow a pregnant patient's changing metabolic rate during and after pregnancy. Serum levels correlate very well with the clinical picture during pregnancy and provide reassuring, objective evidence for the OTP physician and patient. Seeing that the serum level has gone down in spite of dose increases helps a pregnant patient to feel comfortable requesting and accepting dose increases as necessary to prevent withdrawal between doses. Trough serum levels done every 4-6 weeks during pregnancy and for up to 8 weeks post-partum give an accurate assessment of changing maternal metabolism and fetal exposure.

Serum levels are the only way of scientifically assessing fetal exposure. Fetal cord blood has about half the concentration of methadone as maternal blood. It is helpful for the mother to understand that it is not her oral methadone dose that determines fetal exposure; it is her serum methadone level, which counters the common sense, but very inaccurate idea, that the more methadone a mother takes, the more her baby is exposed to.

Serum levels do not predict dosing needs. A relationship between methadone serum concentration and therapeutic effect is not precisely defined [121]. Some patients stabilize with low serum levels and some need levels at the upper end of the therapeutic range, related largely to individual pharmacogenetics. A trough concentration range of 200-600 ng/mL serves as a guide to effective treatment [122]. This range is clinically safe and effective for pregnant patients [94].

Peak to trough serum ratios (PTR) are used to evaluate the rate of methadone metabolism. They are somewhat invasive and inconvenient, requiring two blood draws on the same day, one before dosing and another four hours after dosing. A ratio greater than 2 indicates more rapid clearance than the usual 24-hour norm [116, 117] and the necessity for a multiple dose regimen. Serial peak to trough ratios are useful for monitoring the dynamic changes in a mother's metabolic rate throughout pregnancy and post-partum.

Serum methadone levels may change dramatically in the postpartum period. Checking serum levels within the first week after delivery should be the standard of care, as they provide a clear measure of individual changes to guide safe dosing, especially when late third trimester levels are used for comparison. Monitoring postpartum levels is important for patient safety, as escalating serum levels can cause over-sedation and impair mothering. In one study, 4 of 13 post-partum patients (31%) had serum levels that exceeded the therapeutic range of 600 ng/mL, one going as high as 1020 ng/mL. The postpartum period may be the most dramatic period of pharmacokinetic change in adult human physiology.

For most patients in the immediate postpartum period, dose reductions should occur. This is especially true for patients who required higher doses. Split dosing should be continued postpartum to maintain maternal opioid stability and avoid even more dangerous peak methadone levels. Further, it is important that the mothers not become dependent on high, clinically unnecessary, serum levels. There is evidence from a study of midazolam (a3A4 substrate) metabolism in pregnancy that the return to a pre-partum metabolic state may take longer than 10 weeks, making serial serum level monitoring advisable [123].

Methadone/Metabolite Ratio

A newer test, called the methadone/metabolite ratio (MMR), measures methadone, the EDDP metabolite, and the methadone to EDDP calculated ratio with a single blood draw. This is more practical and provides a more dynamic picture of metabolism than simple serum levels, with the important ability to categorize individuals based on their ratios. This test has not been as widely used and may not be available at/familiar to all labs. Individuals may be categorized, based on their ratios as poor metabolizers (PM), ratio >16, intermediate metabolizers (IM), ratio 12-15, extensive metabolizers (EM), ratio 5-11, and ultra-rapid metabolizers (URM), ratio 4 or less [124]. The MMR gives information regarding the net effect of the multiple enzymes involved in methadone metabolism. A lower ratio indicates more rapid metabolism, and accordingly less opioid activity at a given dose. MMRs have been studied in MMT populations, and a study of 32 non-pregnant methadone maintenance patients measured ratios at peak and trough and found that the mean ratios were virtually identical.

A study using MMRs in pregnancy estimated a mean 6.1 for all pregnant patients [96]. Even pregnant patients in the first trimester had ratios well below that in non-pregnant patients, with an average of 7.2. Ratios changed significantly over time. Average ratios decreased from 7.2 in the first trimester to 5.9 in the second trimester, to 5.1 in the third trimester. Equally important, ratios increased to 7.2 post-partum. The percent of pregnant women that had ratios of 4 or less, indicating ultra-rapid metabolism, increased from 8% (N=1/13) in the first trimester, to 30% (N =9/13) in the second, to 38% (N=9/24) in the third and decreased to 5% (N=1/22) postpartum. Forty-four percent (N=10/23) of individual patients had at least one pre-partum ratio of 4 or less. The number of ultra-rapid metabolizers by trimester was N=1 (9%) in the first trimester, N=7 (44%) in the second trimester, N=5 (31%) in the third trimester, and N=1 (9%) postpartum. Postpartum ratios increased rapidly, by 41%, compared with third trimester values, making the post-partum period, arguably, the most dramatic period of pharmacokinetic change in adult human physiology.

While this pilot study focused on pregnancy as an inducer of methadone metabolism, the MMR may have important use in other clinical situations. Foremost is the potential use of MMRs to monitor drug-drug interactions, such as may occur with co-administration of some antidepressants, anticonvulsants, and antifungals. The effect of these interactions of methadone concentration is poorly predicted by current studies. Further, there is not yet full consensus on the involvement of the various CYP450 enzymes known to metabolize methadone [125], and it has been suggested that

guidelines warning of CYP3A4-mediated drug interactions may be incorrect [126]. The metabolic ratio, representing the net effect of the specific CYP enzymes involved in a particular patient, could provide a quantitative alert to the clinician of the effect of such medications on methadone metabolism, provided a baseline ratio is obtained before starting the new medication. One could even make a case for establishing a baseline ratio on all patients treated with methadone. The MMR is a unique identifier for an individual patient, based on his/her genetic polymorphisms for the enzymes that are involved with the kinetic conversion of methadone. Ratios identify ultra-rapid metabolizers who are at risk for poor treatment response, as well as poor metabolizers who are at risk for unusually high serum levels at routine doses with potential for sedation, overdose [127] and arrhythmias [98].

4.3. Considerations for Pregnant Patients on MAT

4.3.1. Prenatal Considerations

It is important for NTP physicians to be aware that there are specific regulatory requirements when treating pregnant patients on Medication Assisted Treatment. These regulations are listed below.

Regulatory Requirements for Pregnant Patients on MAT

- Clarification of pregnancy within 2 weeks of the possibility of pregnancy being raised
- Documentation of prenatal care within 2 weeks of confirmation of pregnancy
- Weekly urine drug testing
- Monthly follow up visits with the OTP MD
- OTP MD visit within 60 days of delivery to document whether a woman remains "Fit for MAT"
- Documentation that a copy of the hospital delivery summary including urine drug screening results for mother and baby have been requested
- Verification of pediatric care and immunizations after baby is born

Per California Code of Regulation, Title 9, Section 10285, the following specific information must be provided to all female patients of childbearing age:

1. Knowledge of the effects of medications used in replacement narcotic therapy on pregnant women and their unborn children is presently inadequate to guarantee that these medications may not produce significant or serious side effects**
2. Abrupt withdrawal from medications used in replacement narcotic therapy may adversely affect the unborn child,
3. The use of other medications or illicit drugs in addition to medications used in replacement narcotic therapy may harm the patient or unborn child,
4. The patient should consult with a physician before nursing,
5. For a brief period following birth, newborns exposed to medications used in narcotic replacement therapy may show irritability or other ill effects from the patient's use of these medications.
6. Provisions for patient acknowledgement of orientation shall be a part of the patient record.

***While regulations require that women be given this specific statement, NIDA Factsheet on MAT, Section 1: Factsheet 2 states, "Healthcare professions may want to reassure women that, to date, research has not shown that buprenorphine and methadone can cause an increase in birth defects (Committee on Healthcare for Underserved Women, ASAM, & American College of Obstetricians and Gynecologists, 2017; Holbrook & Rayburn, 2014) and has minimal long term neurodevelopmental impact (ASAM, 2015)."*

Prenatal Care

Regular prenatal care has been shown to improve outcomes for patients on MAT, and participation in regular prenatal care is one of the best-documented effects of MAT. Barriers to accessing care and keeping appointments need to be identified and addressed. The name and location of the prenatal care provider and the hospital of delivery should be documented in the record and written authorization obtained to allow coordination of care. Patients should be informed under what circumstances the prenatal care provider and/or hospital staff will be contacted including:

- To provide assistance to schedule/reschedule prenatal care provider appointments or access care for urgent conditions
- To obtain verification of participation in prenatal care
- To answer questions/concerns raised by the prenatal care provider about continuation on MAT or the dose of methadone/buprenorphine
- To inform of ultra-rapid methadone metabolism requiring an unusually high dose
- To advise of ongoing use of drugs or alcohol putting the pregnancy/baby at increased risk of adverse outcomes and necessitating a higher level of care
- To advise of multiple missed doses of methadone or buprenorphine or discontinuation of treatment
- To provide information regarding pain management (particularly around delivery) or breastfeeding
- To verify the current dose of methadone or buprenorphine during hospitalization
- To inform that if IV methadone dosing is required, half the oral dose is equivalent
- To ensure the prenatal care provider is aware of the absolute contraindication to the use of mixed agonist/antagonist analgesics, such as Nubain (nalbuphine), which will immediately precipitate severe withdrawal in the MAT dependent mother and baby, which will require high doses of pure opioid agonists to reverse.

Attachment 4.1

Letter to Hospital Obstetrical Staff Regarding Pregnant Patients in Treatment at Bi-Valley

To Hospital Obstetrical Medical Staff

Re: Bi-Valley Medical Clinic Pregnant Patient

This letter is an explanation of treatment with methadone during pregnancy at our clinic, explaining the unique aspects of methadone dosing during pregnancy and at the time of delivery.

During pregnancy, methadone metabolism is accelerated, such that what is normally a long acting, once-a-day medication becomes shorter acting, requiring divided methadone doses for the stability of the mother and to avoid withdrawal in the fetus. Some mothers become ultra-rapid metabolizers during pregnancy (documented by methadone serum levels done routinely during the pregnancy) and require unusually high doses for stability. Their doses do not translate into high fetal exposure because the methadone is rapidly metabolized into an inactive metabolite and excreted. Serial methadone serum levels allow us to monitor fetal exposure to be sure that exposure is within a strict therapeutic range.

In many pregnant patients, the half-life of methadone is shortened to 6-8 hours requiring TID or QID dosing to avoid withdrawal. Our research indicates that reducing risks of maternal/fetal withdrawal during pregnancy will reduce risks of neonatal withdrawal. That is the goal of our approach. On the day of delivery, the patient may be instructed to take a greater portion of their dose (if possible) before delivery. This is done because the severity of neonatal abstinence has been correlated with how rapidly the neonatal methadone level falls.

After delivery, methadone metabolism returns to the "normal" (non-pregnant state) and the methadone serum level can increase, sometimes rapidly, so the mother is instructed to report any signs of over-sedation immediately. Even in the hospital, a mother may require dose reduction, and will have serum levels and dose reductions when she returns to the clinic.

Please call the clinic if there are any questions regarding our mutual care of these patients. Patients are given the doctor's cell phone number to facilitate ease of communication.

Sincerely,

Dr. John McCarthy

A detailed published description of the dosing science employed in our program can be found in: The Effect of Methadone Dose Regimen on Neonatal Abstinence Syndrome. McCarthy JJ, Leamon ML, Willis NH, Salo R. Journal of Addiction Medicine 2015. A copy can be requested from the clinic.

Table 4.3.1

Subjective Opioid Withdrawal Scale (SOWS) Augmented for Pregnancy

Withdrawals Symptoms*	
■ Restlessness	■ Muscle twitching
■ Bone/muscle aches	■ Tearing
■ Hot flushes	■ Goose bumps
■ Anxious	■ Stomach cramps
■ Nausea	■ Shaking
■ Perspiring	■ Feel like using
■ Lacrimation	■ Uterine cramping
■ Vomiting	■ Increased fetal movements
■ Cold	

* Severity Range: (0) "Not at all" to (4) "Severe"

See Attachment 4.1 for a sample letter used by Bi-Valley Medical Clinic to provide information to Obstetrical staff regarding methadone in pregnancy.

Monthly Follow-up Visits with the OTP Physician

While monthly physician visits are a regulatory requirement, this is a minimal requirement, and the dynamic nature of pregnancy often requires more frequent assessments, especially regarding adjusting the dose of medication as pregnancy progresses.

The first follow-up visit should be scheduled within a few days of the patient's admission because of the high likelihood that she will have questions and the dose of medication (especially methadone) will need to be raised. Weekly physician visits may be needed until the patient is stabilized on a therapeutic dose of methadone. The Subjective Opioid Withdrawal Scale (SOWS) Augmented for Pregnancy may be particularly helpful as it includes symptoms specific to pregnant patients [94]. Patients and clinic staff need to be aware that uterine cramping and fetal hyperactivity are symptoms of opioid withdrawal.

The patient should be encouraged to request dose adjustments between physician visits as needed and advised of the procedure to accomplish this. It may be helpful to designate one of the program's counselors and/or one of the dispensing nurses to track monthly physician visits, prenatal care visits and to ensure that barriers to care are identified and addressed. The patient should be encouraged to request dose adjustments between physician visits as needed and advised of the procedure to accomplish this. All program staff need to be alerted that when a pregnant or newly delivered mother raises a concern about her dose, this needs to addressed promptly, on the day it is raised, not delayed until the next physician visit.

At the first follow-up visit, the physician should keep in mind that the patient may have been sufficiently anxious and uncomfortable during the admission interview that she may remember little. The basic information about methadone use during pregnancy should be reviewed and the patient encouraged to ask any questions she may have. Questions about drug use or urine drug test results are important but must be asked in a neutral fashion, so that the patient does not feel she is being accused of being bad if she reports ongoing use. The physician should provide assurance that with a therapeutic (and, if necessary, blocking) dose of methadone/buprenorphine, coupled with good psycho-social counseling, abstinence is not only achievable, but is the norm.

Monthly follow up visits provide an opportunity to discuss the importance of regular prenatal care, to verify that the patient is attending prenatal care consistently, and to discuss any issues or concerns the prenatal care provider has about the pregnancy. Other topics discussed over the course of pregnancy may include: necessity of informing all treating MDs about MAT, necessity of verifying that all medications, including OTC medications, are safe during pregnancy, the effects of various substances (including alcohol, cigarettes, cannabis, prescription and illicit drugs) on the body, pregnancy and the baby, issues around delivery and post-partum including dose verification when hospitalized and upon release, pain management, breastfeeding, postpartum depression, NAS, contraceptive choices, risk of relapse after delivery, medication monitoring and postpartum adjustment. Be sure to give the patient the opportunity to ask questions.

Comorbid Conditions

STI surveillance data from the California Department of Public Health shows a dramatic increase in cases of syphilis among women of childbearing age (7-fold in 2017 compared with 2012). Mother to child transmission can occur at any state of syphilis infection. In 2017, 278 babies in California were born with congenital syphilis, which can cause premature birth, low birth weight, birth defects, blindness, hearing loss and even death. The number of infants born with congenital syphilis has increased every year for the past 5 years. Prenatal screening and prompt

Table 4.3.2

Child Protection — Mandatory Reporting

It is important for pregnant women and mothers on MAT to be aware that physicians and other treatment program providers are mandatory CPS reporters. Some of the issues that could arise requiring a report include:

- Clinic staff observing a child left unattended in a car
- Patient presenting to clinic with a child while under the influence of alcohol or drugs
- Patient driving with a child while under the influence of alcohol or drugs
- Patient exposing a child to hazardous situations, such as domestic violence, drug use or being present while drugs are being obtained
- Clinic staff observing a child who appears to be physically or medically neglected or abused
- Clinic staff becoming aware that a woman is breastfeeding while using alcohol or drugs
- Clinic staff becoming aware of a child accessing a patient's methadone or buprenorphine

treatment for pregnant women is essential to prevent devastating birth outcomes. Treatment must be completed 28 days before delivery. Women at risk may need repeated screening throughout the pregnancy and at delivery.

Women who are HIV positive can reduce the incidence of HIV transmission to the infant by taking anti-virals during pregnancy. The OTP physician and staff are in a position to support compliance with this prophylaxis and may even be able to dispense the medications at the dosing window. Women with risk factors for HIV should be offered screening during each trimester of pregnancy and at delivery.

When a pregnant woman is hepatitis C positive, the risk of virus transmission to the child is up to 5%. Pregnant women who screen positive for hepatitis C should be counseled about this risk and advised to make sure the child's pediatrician is aware, so that the child may be screened for hepatitis C at twelve to eighteen months of age, sooner if there are any indications of illness. Antibody in the child prior to one year of age may be maternal. The natural history of hepatitis C virus acquired in the perinatal period is not completely known, but disease appears to be less severe with slower and less frequent progression to cirrhosis.

Hepatitis B screening provides the opportunity to offer immunization to women not already immune and to protect the infants of women who are hepatitis B carriers.

Advocacy

The physician should be available to intervene with medical staff around issues of pain management and/or breastfeeding. The physician should be prepared to provide information to social workers or CPS staff who are not familiar with MAT or have biases against this treatment. The physician may need to educate the protection system and/or the courts on the critical role of MAT in long term recovery, the complete compatibility of MAT with good mothering, and the assistance that participation in treatment provides to women in their parenting role. The physician should assure the patient of assistance with these issues.

Within the program, the physician should ensure that women are provided with exception take-home doses when they are medically necessary and pose greater benefit than risk. Women put on bed rest for obstetrical complications, such as pre-term labor or who are recovering from C/S or traumatic delivery may be better served by take-home doses. It will be necessary to obtain a waiver from SAMHSA/CA if the woman does not meet regulatory requirements for take-home doses. When ongoing use or an unsuitable home environment makes take-home doses too risky, car dosing may be considered.

Inadequate Level of Care

Pregnant women who continue to use or are unable to dose daily due to impaired functioning should be offered a more intensive level of care, either Intensive Outpatient Treatment or Residential Treatment, while on MAT, to enable them to stabilize and achieve a sustained abstinence.

Patients should be cautioned that they and their baby will be drug tested at the time of delivery and counseled that participation in treatment is viewed favorably. Women who are not in treatment and/or test positive at delivery are at increased risk of losing custody of their children.

Voluntary Withdrawal during Pregnancy

Despite overwhelming evidence of the multiple advantages of MAT during pregnancy, MAT is voluntary. A patient's choice about how and when to withdraw from methadone or buprenorphine must be honored. If a pregnant patient is adamant in her desire to withdraw from MAT, after education and discussion of risks of fetal stress, relapse, and potential developmental problems, the physician should obtain an informed consent for withdrawal and help the patient to plan a very slow taper with obstetrical monitoring. The taper should be reversible upon request, and the patient should be directed to seek obstetric evaluation promptly in the event of symptoms of premature labor. Every effort should be made to help mothers view tapering off MAT as secondary to maintaining long term abstinence and protecting the baby. A decision to discontinue tapering and to stabilize on a therapeutic dose should be reinforced as a commitment to recovery, not a failure.

Involuntary Discharge

Involuntary discharge and discontinuation of MAT during pregnancy should be avoided if at all possible. Acts of violence/threats of violence by the patient towards other patients or program staff may necessitate immediate discharge. Transfer to another program should be facilitated if at all possible. Multiple missed doses of methadone or buprenorphine, such that it is never possible to achieve a stable medication blood level, may necessitate discontinuation of treatment. Every effort should be made to identify barriers and salvage treatment. Pregnant patients should not be withdrawn from MAT for issues such as sporadic attendance at program services (other than dosing), or failure to remain free of illicit drug use, provided use is not putting them at high risk of overdose. Methadone maintenance is associated with a significant reduction in drug use and high-risk behavior as well as an increased likelihood of receiving prenatal care, even when some illicit drug use continues. These benefits provide significant protection to the fetus. Pregnancy and delivery can be life-changing experiences, so ongoing attempts to engage these patients in treatment are often successful. Programs that provide parent education, childcare and transportation facilitate participation, especially when a patient has young children.

4.3.2. Postpartum Considerations

Breastfeeding

Breastfeeding should be encouraged. It promotes maternal-infant bonding, provides the ideal neonatal nutrition and has been shown to ameliorate NAS symptoms. Nursing is the cornerstone of the "rooming-in" model of NAS

management, which dramatically reduces NAS intensity, the need for NAS treatment and the length of hospital stay. All mothers should be educated about these benefits and encouraged to hold the baby skin-to-skin and to begin breastfeeding their babies immediately after birth and on demand. Nursing may provide some protection against SIDS, which is more prevalent in drug-exposed infants [128].

Contraindications to breastfeeding include abuse of illegal drugs and maternal HIV infection or risk factors. Any woman whose risk factors for HIV are recent (within the past year) should be advised of the risk of transmission of HIV to the baby through breastmilk. The Center for Disease Control has concluded that HCV infection in not a contraindication to nursing as there is no evidence to date of an increased incidence of HCV infection in nursing infants (CDC). A woman who is infected with HCV should be counseled to pump and discard if she experiences nipple trauma, until she has healed, to avoid the baby ingesting HCV infected blood. Smoking is a relative contraindication to breastfeeding [129].

MAT is not a contraindication to breastfeeding. The amount of methadone passed in breast milk has been found to be very low, an average of 0.05mg/day in a newborn ingesting about 500 mL/day [130], and certainly far less than in-utero exposure. At least 8 studies since 1974 have confirmed this [128]. The American Academy of Pediatrics has determined that maternal methadone maintenance, with no dose restrictions, is compatible with breastfeeding [131]. Buprenorphine appears to be equally safe for nursing, although less well studied.

Divided MAT doses should be continued while the mother is breastfeeding to assure a more constant level of neonatal ingestion. Due to reversal of accelerated metabolism after delivery, significant serum methadone level increases have been documented in the postpartum period [94, 96]. This increased serum level will result in increased methadone exposure for the neonate. Continuing to monitor serum methadone levels post-partum will alert the OTP physician to the magnitude of change in maternal metabolism, so that the maternal dose may be adjusted.

Breastfeeding while on buprenorphine is normally considered safe. In a single case of a woman allowing her baby to routinely suckle all night, disruption of breastfeeding at 6 months resulted in acute withdrawal symptoms (author personal communication). It was postulated that "pooling" of buprenorphine in the baby's mouth allowed for absorption of unusual amounts of buprenorphine, which is absorbed from contact with the buccal mucosa, but not after swallowing. It is probably best to advise mothers on buprenorphine to avoid this type of nursing.

The nursing mother may need support and assistance to get breastfeeding successfully established. Involvement of a lactation specialist may be necessary as drug exposed babies may experience logistical problems with nursing. Neonatal over-sedation from high serum methadone levels or single dose regimens may make it difficult for the baby to achieve the necessary alert and aware stage; hypertonicity may make positioning awkward; nasal stuffiness may frustrate a baby's efforts to remain latched [128].

Neonatal Abstinence Syndrome (NAS): The Etiology

NAS has a complicated, multi-factorial etiology that includes risks primarily related to chronic maternal opioid use (licit or illicit), but exacerbated by co-occurring alcohol, benzodiazepine, or tobacco use. It also involves the baby's genetics, meaning how quickly an individual neonate clears methadone or buprenorphine post-partum. Symptoms of neonatal abstinence usually begin within the first 24-36 hours after birth and may be so mild as to be indistinguishable from normal newborn behavior or may be moderate in severity. On very rare occasions, withdrawal might intensify after hospital discharge, and this must be evaluated in person by an experienced neonatologist or pediatrician.

Many older studies purported to find an association between higher methadone doses and the need for NAS treatment, with an equal number refuting this association. Justification for attributing any adverse outcome, like NAS, to high doses of methadone, relies on documentation of actual higher fetal exposure, i.e. unusually high serum levels. No study has shown such an association. In fact, the literature on dose, serum levels, and potential side-effects is compromised by nearly universal failure to document actual dosing conditions and serum levels.

A large meta-analysis found no relationship between methadone dose and NAS severity [132]. Two studies of "high dose" treatment, up to 200 mg/day, have shown no association between severity of neonatal withdrawal and methadone dose or maternal serum level [133, 134]. A study of 100 mother/infant pairs on doses above and below 80 mg daily compared the rates of illicit drug use before delivery, the NAS score, the need for treatment of NAS and the duration of treatment [134]. Findings indicated that the NAS score, the need for treatment of NAS, and duration of treatment were similar for the two groups. However, the women on doses below 80 mg had a trend toward a higher incidence of illicit drug use before delivery. McCarthy et al. (2005) studied 81 mother/infant pairs looking at the effect of high (>100 mg with a mean of 132 mg) vs. low (<100 mg with a mean of 62 mg) methadone during pregnancy, looking particularly for differences in the rate of medication treatment for NAS symptoms, the days of infant hospitalization and the number of women using illicit drugs at delivery [133]. They found that high doses of methadone were not associated with higher rates of NAS symptoms or more days of infant hospitalization.

The idea that higher doses would be correlated with increased fetal exposure, and adverse outcomes like NAS, ignores the known pharmacokinetic science of pregnancy. Higher doses would only be needed in the context of *increased* methadone clearance and the resulting *decrease* in fetal exposure. Higher doses may be needed to treat maternal/fetal withdrawal in an effort to compensate for increased clearance, without increasing fetal exposure.

Studies have shown that NAS can be exacerbated by separation of the baby from his/her mother and further exacerbated by an overstimulating NICU environment and care by multiple strangers [107, 108].

In a prospective study of long-term effects of different post-delivery mother-infant separation practices (in a normal population), the practice of skin-to-skin contact, early suckling, or both, during the first 2 hours after birth positively affected maternal sensitivity, infant self-regulation, dyadic mutuality and reciprocity at one year after birth, compared to neonates exposed to various separation practices [135]. The negative effect of a two-hour separation was not compensated for by the practice of rooming-in. Swaddling decreased the mother's responsiveness to the infant and decreased the mutuality and reciprocity in the dyad. The study suggests an early "sensitive period" during which close contact between mother and infant induced long-term positive effects on mother-infant interactions. The authors state that, "Newborn babies should not be separated from their mothers except for significant medical reasons but be placed skin-to-skin as soon as possible after birth" [135].

A further study of maternal-neonate separation found an 186% increase in autonomic activity (a sign of anxious stress) and an 86% decrease in quiet sleep duration, compared with infants provided skin-to-skin contact [136]. While this study was in "normal" neonates, it clearly demonstrates that symptoms on the Finnegan scale can be worsened by maternal-neonate separation. The NAS scoring should be done in the room with the mother, to eliminate maternal separation as a cause of neonatal distress.

The neonate needs its mother to assist with warmth, nutrition, cardiac and respiratory regulation, oxygen saturation, sleep, pain relief, neurobehavioral development, mental/motor skills, and attachment. NAS vulnerability affects many of these basic functions, and to deprive the neonate of its mother under these vulnerable circumstances compounds the problem. NAS severity from this perspective may be largely iatrogenic, due to a misplaced emphasis on medicalization at the expense of physiological and psychological needs of the maternal/neonatal dyad. The frequency and severity of NAS are likely to be reduced markedly if doses of methadone/buprenorphine are optimized during pregnancy and neonates routinely placed in the room with their mothers.

Management of NAS

The traditional approach has been to put neonates at risk of NAS in the NICU for observation, using a standardized scoring tool, like the Finnegan NAS scoring system, to evaluate infants every 8 hours and assign a score. Moderate symptoms, as reflected by 2 or 3 scores on the Finnegan scoring system of 8 or above, may require medication (usually morphine). Medication use in no way precludes rooming-in. The medication dose is titrated until NAS is controlled, then gradually tapered as tolerated. This approach has been challenged by research showing that nonpharmacologic intervention may be more effective.

A study at Yale New Haven Children's Hospital [106] showed that the babies who "roomed-in" and remained close to their mothers after birth, rather than being taken to the NICU for observation, were significantly less likely to need treatment with morphine (14% vs 98%) and had much shorter hospital stays (5.9 days vs 22.4 days), which decreased the average cost ($10,289 vs $44,824). This study developed a different approach to assessing babies, focusing on babies' crying, feeding and sleeping habits. This method of assessment was less intrusive and less likely to aggravate symptoms of NAS. When symptoms of NAS increased, the first intervention provided was to increase the comfort measures by the infant's mother and father. If these measures were ineffective, morphine was used as needed to ensure that infants could feed well, sleep well, and be easily consoled.

Holmes et al. (2016) described implementation of a "Family-Centered Care" model [109] using rooming-in on a pediatric unit instead of the NICU, and an "infant-centered" scoring system based on scoring with the mother present with minimal infant disruption. They found NAS treatment rates were reduced from 46% to 27%, including reduced length of stay and reduced costs. They found no medications differences in NAS outcomes.

Grossman et al. (2017) [106] in an extension of the rooming-in concept, found a treatment rate of 16% of methadone exposed neonates, compared to rates at the same institution (Yale New Haven's Children's Hospital) of 98% of methadone exposed neonates in the period (2003-2009) before implementing a rooming-in model, and compared to the 57% rate of treatment for methadone and 47% for buprenorphine in the MOTHER study [104, 106]. Furthermore, the treatment rate for methadone exposed neonates was only 6% when babies who were transferred to an NICU for problems other than NAS excluded.

The "rooming-in" model of NAS management allows intensive maternal nurturing, avoids NICU separation, and has been associated with dramatic reductions in NAS symptoms that are of far greater magnitude than the effects of medication. Hospital policies that support maternal/infant bonding, physical closeness, and reduced neonatal stimulation will reduce NAS severity. Policies that limit maternal-infant contact—by post-delivery separation for assessment, interventions, and care in a Newborn Nursery, or by a low threshold for placing the baby in the NICU—worsen NAS severity.

In light of the above, medical counsel to prepare the expectant mother for her role in the management of NAS is crucial. Mothers need to understand the benefits of "rooming-in" and the role of intensive maternal nurturing of baby in the prevention/treatment of NAS for methadone/buprenorphine exposed neonates. They need to be familiar with the Finnegan NAS scoring system in general use, so they will be prepared for the range of symptoms that may emerge and understand the criteria for starting medication. This knowledge empowers the mother to be active in the process of interacting with hospital staff.

Education about the important role of the mother in assuring normal bonding to her baby must be stressed, especially because this bonding is also beneficial for NAS symptom mitigation. Mothers should be strongly advised to request immediate undisturbed time with their newborn after birth without unnecessary medical interventions, like taking the baby away to wash, weigh or to do NAS scoring.

Postpartum Changes

After delivery, many women find they are exhausted, achy, and more emotional. Some experience frequent and severe episodes of diaphoresis. These symptoms remind many opioid dependent women of opioid withdrawal. A careful history, focusing on the nature of the symptoms, the time of onset of symptoms and whether they are relieved by the morning dose of methadone will help to clarify the source. Post-partum withdrawal, when a mother was on a therapeutic dose at the time of delivery, is extremely rare given post-partum pharmacokinetics.

Preparing a woman for postpartum changes before delivery can help prevent her from becoming anxious, assuming she is in withdrawal and relapsing, to manage the symptoms. For many women, being pregnant provides strong motivation to avoid use. Post-delivery, some women experience a return of cravings and drug dreams that may be aggravated by coping with a demanding infant. Discussing these issues prior to delivery gives mothers a chance to think through how they will handle them in a healthy way. Postpartum depression puts a woman at increased risk of relapse. Women should be counseled regarding the symptoms and provided early assessment and treatment if depressive symptoms occur.

The dramatic pharmacokinetic changes that occur post-partum have been discussed in other sections of this document (see sections on Pharmacokinetics and Dosing and on Breastfeeding). Women should be counseled prior to delivery that serial methadone troughs will be necessary starting within a week of delivery and that methadone dose reductions are necessary for most women in the very early post-partum period to address rapidly rising serum levels. The clinical picture can be confusing, as mothers may not experience sedation with rising methadone levels, and post-delivery fatigue is common for new mothers. Women should be advised to let clinic staff know promptly if they experience sedation after dosing.

The Post-Delivery Visit

According to California Regulation, each woman who qualified for methadone maintenance treatment due to pregnancy must be seen within 60 days of delivery or termination of pregnancy to determine whether she remains an appropriate candidate for continued methadone maintenance treatment. Practically speaking, continued MAT is critical for all new mothers. Opioid withdrawal is a relapse risk and a physiologic stress and should be avoided in the postpartum period when the focus needs to be on adjusting to a newborn baby, to major post-partum physiologic changes, and often, to care of other children. Post-delivery, women will normally require more than one visit. Monitoring serial methadone levels, making dose reductions as needed, observing for post-partum depression, and other psychosocial stressors, usually requires visits every 1-3 weeks during the first 60 days.

During these visits with the NTP physician, a primary focus will be ensuring that the dose of methadone or buprenorphine continues to be appropriate, but the physician should explore the patient's progress in recovery generally. It is important to revisit the patient's status with regard to substances that were stopped due to pregnancy, which may include cigarettes, marijuana, alcohol, prescription sedatives/stimulants or illicit drugs, and screen for cravings, drug dreams, lapse or relapse. New mothers should be strongly encouraged to participate consistently in group or individual counseling to support ongoing abstinence. Continued treatment is the best assurance that relapse will not compromise a mother's ability to provide appropriate care for her new baby. In the event of relapse, women should be assisted to access the appropriate level of care (residential with baby and doses of methadone delivered if available).

The physician should ensure that the patient is aware of contraceptive choices and that follow-up OB care occurs. Women should be reminded of and encouraged to follow up with medical issues that were delayed due to pregnancy such as INH prophylaxis for PPD converters, TwinRix vaccination, Hepatitis C evaluation/treatment, abnormal PAPs, dental procedures, etc.

The physician should inquire about how the baby is doing and ensure that the baby has a pediatric care provider and is being followed for normal newborn care and other medical concerns. A referral to public health nursing may be offered if there are particular concerns. On very rare occasions, NAS can be delayed and occur 3-4 weeks post-partum. The reasons are not clear but may relate to unusually slow infant clearing of methadone. The baby's pediatrician needs to monitor for delayed NAS and be prepared to treat the baby if it occurs. If the mother is Hepatitis C positive, the baby will need to be screened after 12-18 months. A copy of the baby's immunization record should be included in the mother's file to document that the baby is receiving routine well child care.

Conceiving while on Methadone

Many opioid dependent women of childbearing age will conceive on methadone. While it is not an ideal situation for a pregnancy to be complicated by opioid dependence, outcomes for women maintained on methadone throughout pregnancy have been found to be better than for women with shorter periods of methadone exposure during pregnancy, referring to women entering treatment partway through pregnancy while actively addicted. In a study of 83 women who delivered babies in a specialized methadone pregnancy program, 26 (31%) were in treatment at the time of conception [133]. These 26 women had the best drug treatment and obstetrical outcomes, with lower levels of drug use, higher birth weights, and lower rates of NAS that required treatment with medication, (40%) compared with those admitted to the program acutely addicted. The importance of this observation is that in spite of a much greater total methadone exposure throughout the entire pregnancy, there were better outcomes and less risk for NAS. This information should be conveyed to women to relieve some of the concerns about conceiving on methadone.

While there have been decades of research "speculation" about adverse developmental consequences of methadone exposure, no rigorous study has supported this. Studies

on this issue have usually been based on retrospective assessments of babies with NAS without controlling for other confounding variables, such as drug use during pregnancy (Kaltenback and Finnegan, Jones et al MOTHER). Although there is an association between OUD and negative postpartum outcomes, these outcomes often stemmed from continued drug use problems or family dysfunction rather than methadone exposure [137].

All women of childbearing age who enter MAT should be advised that conceiving on methadone or buprenorphine will result in the complication of fetal dependence. While such dependence may not occur until the fetus is 10-12 weeks, when mu receptors are fully functional, withdrawal in the first trimester presents a significant risk of miscarriage. In Dr. McCarthy's clinical experience, 4 miscarriages occurred among 6 buprenorphine patients who abruptly discontinued buprenorphine (on their own or on advice from a non-addiction medicine physician) when they discovered they were pregnant. While not a controlled study, no miscarriages were noted in a small group of women who maintained buprenorphine after conception.

Contraceptive counseling should be provided to all women on methadone and buprenorphine. Women can be assisted to try to taper off MAT prior to a planned pregnancy to see if such a plan can successfully avoid the complication of methadone or buprenorphine dependence without jeopardizing the woman's recovery.

See Attachment 4.2 below for an informational document developed by Bi-Valley Medical Clinic and given to women of childbearing age at admission to provide appropriate information and informed consent.

Attachment 4.2

Considerations Before Pregnancy – Letter Provided to Women of Childbearing Age at Admission to Bi-Valley Medical Clinic

You are being given this letter because you are on methadone and have the potential to become pregnant. We want our female patients to understand that conceiving on methadone means that your baby will be dependent on methadone and subject to opioid withdrawal.

Although there is a possibility that a woman could withdraw from a low dose of methadone during pregnancy, any withdrawal attempt must be very slow and carefully monitored to assure that the baby is not experiencing withdrawal distress in the womb. Also, there is risk of causing a miscarriage or premature labor if the withdrawal is too fast. Finally, there is a risk to the mother of relapsing to drug use during a withdrawal attempt. Most mothers who conceive on methadone remain on the medication for the duration of the pregnancy as the best option for a healthy baby.

At the time of delivery, the baby will be assessed in the hospital for signs and symptoms of withdrawal, which is called neonatal abstinence. Most babies will have some mild symptoms of withdrawal. But some will have symptoms that require treatment with medication. The mother's dose does not determine the withdrawal severity. Many mothers will need high doses because their body gets rid of methadone more rapidly. This is a normal physiologic change in pregnancy.

When methadone is given in divided doses adequate to prevent maternal withdrawal during pregnancy, most babies will have withdrawal that is mild enough that it will not need to be treated with medications. These babies go home with the mother, usually within the first 2-4 days. In a recent research at Bi-Valley, only 29% of babies required medications. If the baby has withdrawal symptoms that are severe enough to require medications, the baby will likely be kept in the hospital for between 3-6 weeks to be tapered slowly off opioids.

We recognize that some women may feel that methadone treatment provides the best way to remain drug-free, healthy and prepared to parent. There is no evidence that babies exposed to methadone have any long-term problems, beyond the short-term problem of neonatal withdrawal. There is no increased risk of withdrawal in the newborn from exposure to methadone for the entire pregnancy, compared to shorter periods of methadone exposure. Also, you can nurse your baby while on methadone, which we strongly encourage.

For these reasons we respect a woman's decision to conceive on methadone, and we certainly understand that unplanned pregnancies may happen on methadone. We will provide our unequivocal support to any woman who does conceive on the medication and will provide counseling to you about things you can do to minimize the risks of withdrawal in your baby.

In summary, conceiving on methadone carries a risk of withdrawal with the potential for up to 6 weeks of hospital treatment after delivery. For this reason, we cannot recommend conceiving on methadone, but we respect a woman's right to make her own decision about this. Please inform your counselor as soon as you think you are pregnant, so that our specialized care for you and your baby can begin as soon as possible. If you have any questions, please contact our medical staff for more information.

Sincerely,

John J. McCarthy, MD