Corrected QT Interval and Methadone Dose and Concentrations in Pregnant and Postpartum Women

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ABSTRACT

Background: Methadone is a standard treatment for opioid dependence in pregnancy; however, its impact on maternal corrected QT interval (QTc) has not been evaluated. We studied the association between methadone dose and enantiomer-specific plasma concentrations and QTc among pregnant and postpartum women and newborns. We assessed the relevance of QTc screening guidelines for pregnant women and infants.

Methods: From 2006 to 2008, plasma methadone concentrations were measured during pregnancy, postpartum, and in cord blood in women treated for opioid dependence at a single treatment program. Electrocardiograms (ECGs) were obtained at peak methadone concentrations in mothers and within 48 hours of birth for infants. Pearson correlations were performed at each time point for QTc and *R*-methadone, *S*-methadone, and total methadone concentrations and ratio of *R*-methadone/*S*-methadone concentrations.

Results: Mean (SD) daily methadone dose for the 25 women was 94.2 (39.1) mg during pregnancy and 112.5 (46.6) mg postpartum. During the third trimester, higher methadone dose and *R*-methadone concentration correlated with longer QTc (Pearson $r = 0.67$, $P < .001$ and Pearson $r = 0.49$, $P = .02$, respectively), while *S*-methadone concentration, *R*-methadone/*S*-methadone concentration ratio, and total methadone concentration did not. Postpartum, QTc did not significantly correlate with dose or enantiomer concentrations. Infant QTc did not correlate with maternal dose at delivery or enantiomer-specific cord methadone concentrations. In pregnant and postpartum women, 13% and 17%, respectively, had QTc ≥ 450 ms, as did 19% of infants.

Conclusions: QTc correlated with dose and *R*-methadone concentration during the third trimester. However, longer QTc was common among women during and after pregnancy. Given the relatively high rate of QTc > 450 ms, an ECG before and after methadone initiation is advisable for pregnant and postpartum women.

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The rapid rise in opioid dependence in the United States has not spared pregnant women, for whom the prevalence has quadrupled in the past decade.[1] Methadone is the mainstay of treatment for opioid dependency in pregnancy.[2] In nonpregnant populations, methadone is associated with acquired prolonged corrected QT interval (QTc), torsades de pointes, and sudden death.[3–5] Risk factors for these cardiac events include higher methadone doses,[6] concomitant use of other medications,[7] genetic variations in the hERG gene,[8,9] and cytochrome P450 2B6 poor metabolizing status.[8] Recently published guidelines suggest that patients being initiated onto methadone treatment have an electrocardiogram (ECG) obtained before starting and 30 days later. If the QTc is between 450 and 500 ms, the patient should be counseled about the risk of arrhythmias. If the QTc is greater than 500 ms, the dose should be decreased or the methadone stopped.[10]

Pregnancy requires special consideration because the risks and benefits of treatment for the mother must be balanced with the risks and benefits to the developing fetus. The benefits of methadone treatment in pregnancy include prevention of substance use relapse, lower risk of blood-borne infections, improved pregnancy outcomes, and increased likelihood that infants will be discharged to the mother's care.[11] The risks of treatment to the mother include prolongation of QTc as well as increased probability that the infant will require pharmacologic treatment for neonatal abstinence syndrome and longer hospital stays. The cardiac risks to the infant have not been reported. There are no studies of methadone and QTc in pregnancy, and the literature among exposed infants is also sparse. Hussain and Ewer[12] presented a case report of prolonged QTc and bradycardia in a methadone-exposed neonate that resolved without treatment. The same investigators subsequently conducted a case-control study among methadone-exposed and nonexposed infants in the neonatal intensive care unit. Fifteen percent of exposed infants had a QTc > 460 on day 1, and exposed infants had longer QTc on the first day of life compared to controls. The QTc normalized by day 7 in all exposed infants, and no cardiac events were observed in the infants.[13] No maternal data were collected in the study.

Methadone doses have increased over the past few decades in both pregnant and nonpregnant groups. Higher doses are associated with less illicit substance

Clinical Points

- Methadone is a standard treatment for opioid dependence in pregnancy; however, its impact on maternal corrected QT interval (QTc) has not been evaluated.
- Because this study found that more than 10% of women had QTc ≥ 450 ms during the third trimester of pregnancy and in the 3–6 months postpartum, it is advisable to obtain electrocardiograms at baseline, with dose increases, and, especially, postpartum, when methadone concentrations can increase rapidly.

use and better adherence to treatment programs.[11] Due to physiologic changes in pregnancy (changes to hepatic induction, increased cardiac output, and increased glomerular filtration rate), methadone doses are usually increased each trimester as drug clearance increases and plasma concentrations fall.[14] However, when to lower a woman's dose postpartum is controversial because of the variable rates at which these physiologic changes revert back to nonpregnant state. In a small study of just 3 women,[14] plasma methadone concentrations increased dramatically within a week postpartum. If this is replicated in a larger study, women whose doses are not lowered after delivery may be at particularly high risk for prolonged QTc and excessive sedation.

We evaluated the association between maternal methadone dose and plasma enantiomer-specific methadone concentrations and QTc among pregnant and postpartum women and newborn infants. We examined enantiomer-specific concentrations because the 2 enantiomers are metabolized by different cytochromes and have different (1) activities at the opioid receptor, (2) half-lives, and (3) protein-binding activities.[15–17] We evaluated current screening guidelines for pregnant women and their infants in light of our findings.

METHODS

This longitudinal study included opioid-dependent pregnant women who were treated with methadone at a single community-based treatment program from 2006 to 2008. Eligible women were 18–45 years old, planned to deliver at Magee-Womens Hospital of UPMC (Pittsburgh, Pennsylvania), did not intend to place their baby for adoption, and were at least 20 weeks pregnant at enrollment. There were no limitations on length of time since starting methadone; however, women had to be taking a stable dose for at least 4 weeks at the time of initial blood testing. There were no eligibility restrictions related to concurrent medical and psychiatric conditions or use of other medications. However, because some commonly prescribed medications in pregnancy (diphenhydramine, decongestants, sertraline, fluoxetine, ciprofloxacin, azithromycin, ondansetron)[18] and illicit drugs (eg, cocaine)[19] can also affect QTc, information on medication use was obtained by self-report at each visit and medical record review at delivery. Women were excluded if they had HIV/AIDS because many retroviral medications are associated with changes in methadone metabolism.[20] Women who were unable to provide informed consent or could not speak English were also excluded.

Women were evaluated during the third trimester (27–39 weeks' gestation) of pregnancy and 3 to 6 months postpartum. They had blood drawn at the methadone treatment center immediately prior to their daily dosing time (trough). After being observed taking their methadone, women went to the hospital, where they had an ECG performed. For infants, cord blood samples were obtained at delivery. All blood samples were analyzed for serum enantiomer-specific methadone concentrations. Details of the parent study on peripartum methadone pharmacokinetics were previously reported.[14,21]

Methadone Concentration Samples

All methadone samples were collected by venipuncture into ethylenediaminetetraacetic acid (EDTA) tubes and cold centrifuged within 60 minutes. Plasma was removed using polyethylene Pasteur pipettes into polypropylene vials and frozen at −80°C.

Chiral Methadone Analysis

The plasma samples were analyzed for *R*-methadone and *S*-methadone by the application of a modified chiral high performance liquid chromatography/ultraviolet detection method (HPLC/UV)[22] as previously described.[14]

ECG

During a third trimester visit and a visit 3–6 months after delivery, the women had a 12-lead ECG performed at peak plasma level (2–4 hours after dose). Infants had a 12-lead ECG within 48 hours of birth. All ECGs were interpreted by a single pediatric cardiologist (F.S.) who was blind to maternal methadone dose.

Analysis

Descriptive statistics were used to characterize the study population. Pearson correlations were performed separately at each time point for QTc, *R*-methadone, *S*-methadone, total methadone and the ratio of *R*-methadone to *S*-methadone (*R*/*S*). The University of Pittsburgh Institutional Review Board approved the study.

RESULTS

A total of 26 women were enrolled in the parent study. During the third trimester of pregnancy and postpartum, 23 and 18 women, respectively, had ECGs performed on the same date that plasma methadone samples were obtained. The frequencies of mother and infant ECG and methadone concentrations at pregnancy, delivery, and postpartum are provided in Table 1, and the characteristics of the 25 mother-infant dyads included in the analysis are described in Table 2. The 14 women with complete data did not differ from the 11 women with partial data. Overall, participants were a mean (SD) of 26.8 (6.1) years old, white (88%), insured through

Table 1. Numbers of Participants With Measures at Each Time Point[a]

Maternal Methadone Level and QTc Data	Infant Data[b] None	Methadone Level Only	QTc Only	Methadone Level and QTc	Total
None	0	0	1[c]	0	1
Pregnancy and postpartum	0	4	4	6	14
Pregnancy only	2	2	0	5	9
Postpartum only	1	1	0	0	2
Total	3	7	5	11	26

[a]Methadone levels are plasma concentrations.
[b]One infant had an *R*-methadone but no *S*-methadone or total methadone level.
[c]The 1 infant with QTc only and no maternal data was not included in the analyses.
Abbreviation: QTc = corrected QT interval.

Medicaid (96%), and multiparous (52%). Their mean (SD) daily methadone dose at the time of the pregnancy and postpartum ECG was 94.2 (39.1) mg (range, 22–165 mg) and 112.5 (46.6) mg (range, 26–190 mg), respectively. All women were taking their methadone once daily except for 1 subject who was taking it twice daily during pregnancy. The gestational age of infants ranged from 34.2 to 40 weeks, and mean birthweight was 3.0 kg (range, 1.5–3.8 kg). Sixteen infants (64%) were treated with morphine for neonatal abstinence syndrome.

Pregnancy

During the third trimester of pregnancy, higher maternal methadone dose correlated with longer QTc (Pearson $r = 0.67$, $P < .001$) as did higher trough *R*-methadone concentration (Pearson $r = 0.49$, $P = .02$). However, *S*-methadone concentration, *R*/*S*, and total methadone concentration did not (*S*-methadone: Pearson $r = 0.24$, $P = .27$; *R*/*S*: Pearson $r = 0.33$, $P = .12$; and total methadone: Pearson $r = 0.39$, $P = .07$) (see Figure 1). Three (13%) of 23 women had a QTc ≥ 450 ms (450, 458, and 469 ms), and 12 of 23 had a QTc > 440 ms. Five of the women with a pregnancy QTc between 440–449 ms were prescribed other medications that also may prolong QTc, including prochlorperazine (QTc = 443 ms), prochlorperazine/labetalol/colace (QTc = 450 ms), sertraline (QTc = 444 ms), clonazepam (QTc = 442 ms), and escitalopram (QTc = 446 ms).

Postpartum

Months after birth, QTc values did not significantly correlate with methadone dose (Pearson $r = 0.22$, $P = .38$) or enantiomer concentrations (*R*-methadone: Pearson $r = 0.17$, $P = .53$; *S*-methadone: Pearson $r = -0.06$, $P = .84$; *R*/*S*: Pearson $r = 0.33$, $P = .21$; and total methadone: Pearson $r = 0.05$, $P = .83$). Three (17%) of 18 women had QTc > 450 ms (461, 473, and 495), and 7 of 14 had QTc > 440 ms. None of the women with QTc greater than 450 ms reported exposure to medications other than methadone at that visit, while all of the women with QTc between 440 and 449 ms did, including 3 women each taking either ciprofloxacin, bupropion, or haloperidol and 1 woman taking both nifedipine and hydroxyzine.

Table 2. Characteristics of Mothers and Infants

Characteristic	Total (N = 25) n	%	Complete Data (n = 14) n	%	Incomplete Data (n = 11) n	%	*P* Value[a]
Maternal							
Age of mother, y							.88
18–24	11	44	6	43	5	45	
25–30	8	32	4	29	4	36	
> 30	6	24	4	29	2	18	
Race of mother							.71
White	22	88	13	93	9	81	
Biracial/black	3	12	1	7	2	18	
Partner status							1.00
With partner	8	32	5	36	3	27	
No partner	17	68	9	64	8	73	
Living situation							.96
Lives alone	1	4	0	0	1	9	
With partner	7	28	4	29	3	27	
With parents and no partner	8	32	5	36	3	27	
With parents and partner	1	4	1	7	0	0	
Group home	8	32	4	29	4	36	
Education							.64
< High school	4	16	3	21	1	11	
High school	13	52	6	43	7	89	
> High school	8	32	5	36	3	22	
Methadone dose, mg/d							.17
< 80	9	36	7	50	2	18	
80–120	11	44	4	29	7	63	
> 120	5	20	3	21	2	18	
Urine drug screen at delivery[b]							.47
Positive	4	17	1[c]	7	3[d]	33	
Methadone only	4	17	3	21	1	11	
Negative	15	65	10	71	5	56	
Infant[e]							
Male	18	75	10	71	8	80	1.00
Gestational age, wk							.38
35–36	2	8	2	14	0	0	
37–38	8	33	3	21	5	50	
39–40	14	58	9	64	5	50	
Birth weight, g							1.00
2,000–2,499	4	17	2	14	2	20	
2,500–4,000	20	83	12	86	8	80	

[a]*P* values based on Fisher exact tests.
[b]Only 23 mothers had urine toxicology screens performed at delivery.
[c]Infant was positive for cocaine.
[d]1 infant was positive for morphine, 1 for cocaine, and 1 for cocaine and benzodiazepine.
[e]One infant was delivered at a nonstudy hospital.

Comparing QTc From Pregnancy to Postpartum

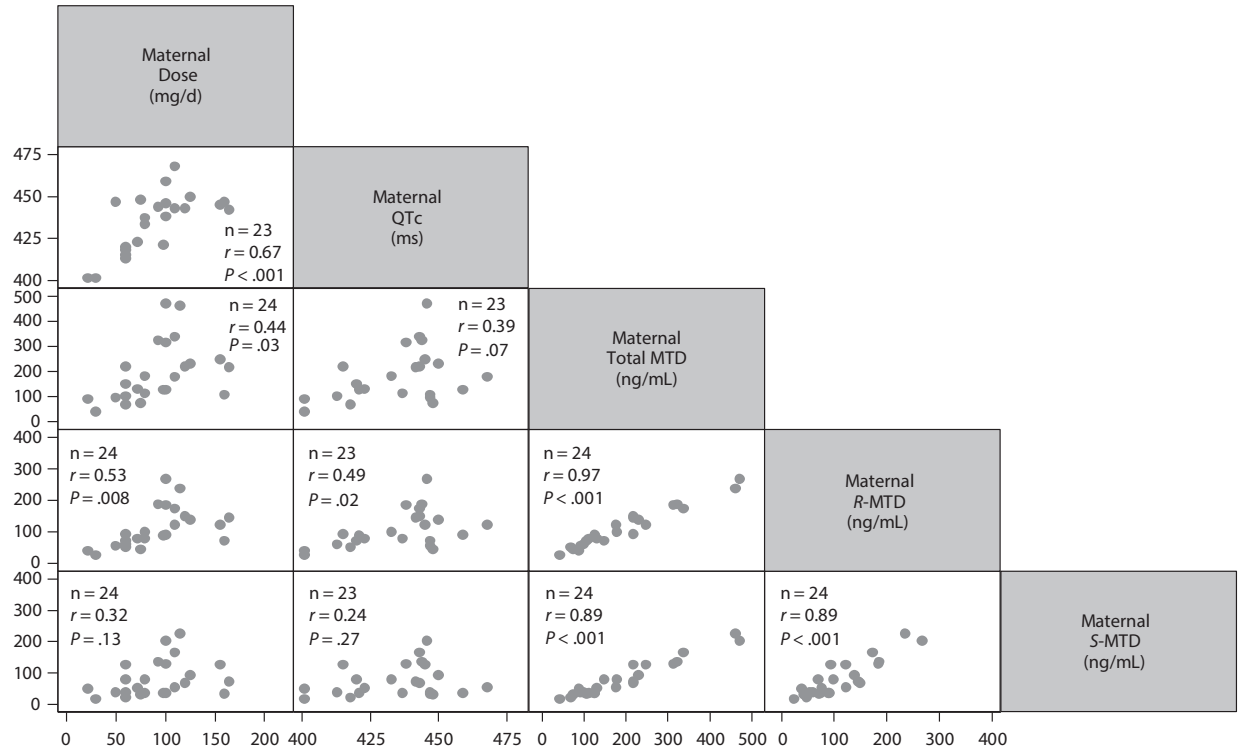
Among the 16 women with ECGs in both pregnancy (mean QTc = 432.3 ms) and postpartum (mean QTc = 440.6 ms), no significant difference in QTc between the 2 time points ($t = -1.64$, $P = .12$) was observed. The 3 women in pregnancy with QTc > 450 did not have high QTc postpartum. However, 3 different women had elevated QTc postpartum.

Infant Results

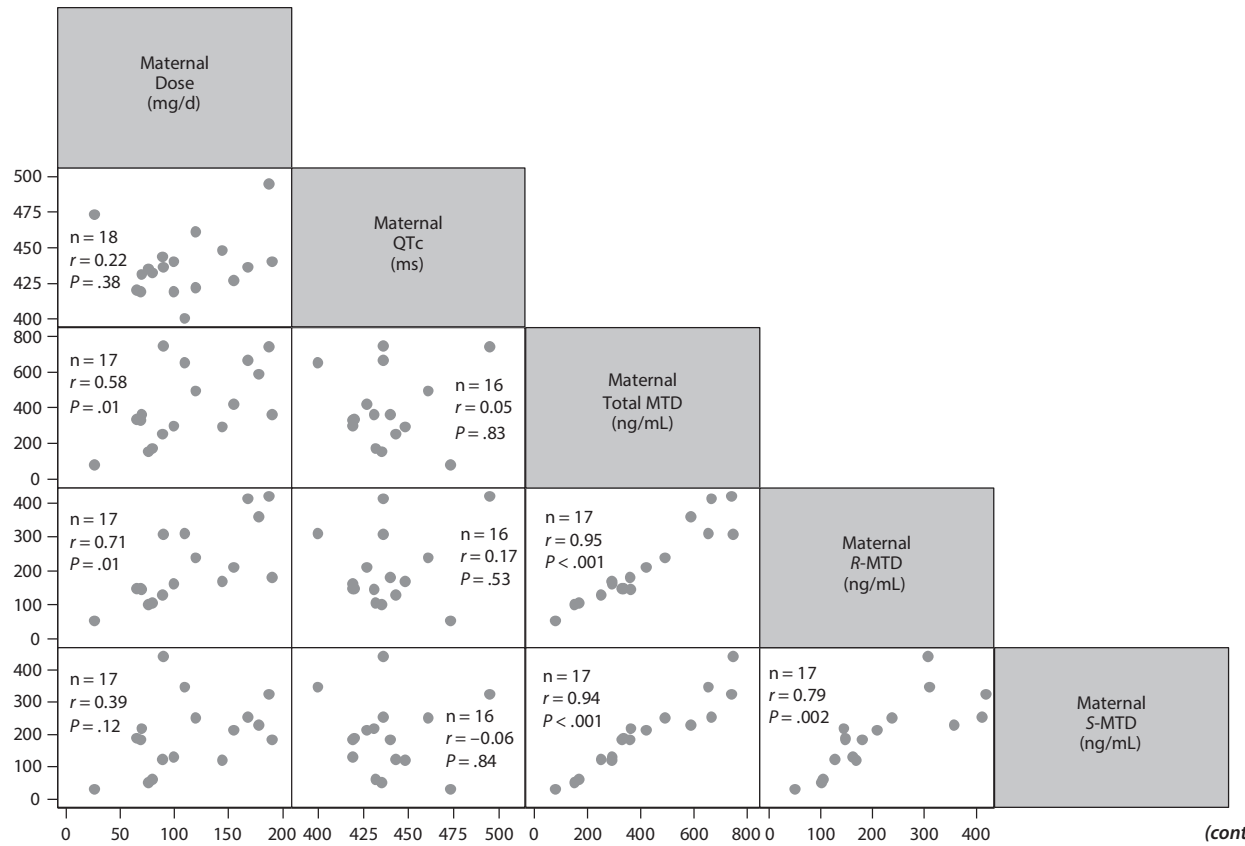
Among the 16 infants with QTc data, 3 (18.7%) had an initial QTc > 450 ms (457, 488, and 519). The mother with the infant with the highest QTc had a toxicology screen at delivery positive for methadone, cocaine, and benzodiazepines. Among the 16 mother-infant dyads with complete information, infant QTc did not significantly correlate with maternal dose at delivery (Pearson $r = 0.34$,

Figure 1. Correlations Between Maternal Methadone Dose, QTc, Total Methadone Concentration, *R*-Methadone Concentration, and *S*-Methadone Concentration During (A) the Mother's Third Trimester of Pregnancy, (B) the 3–6 Months Postpartum for the Mother, and (C) Infant Birth Hospitalization[a]

A. Mother's Third Trimester



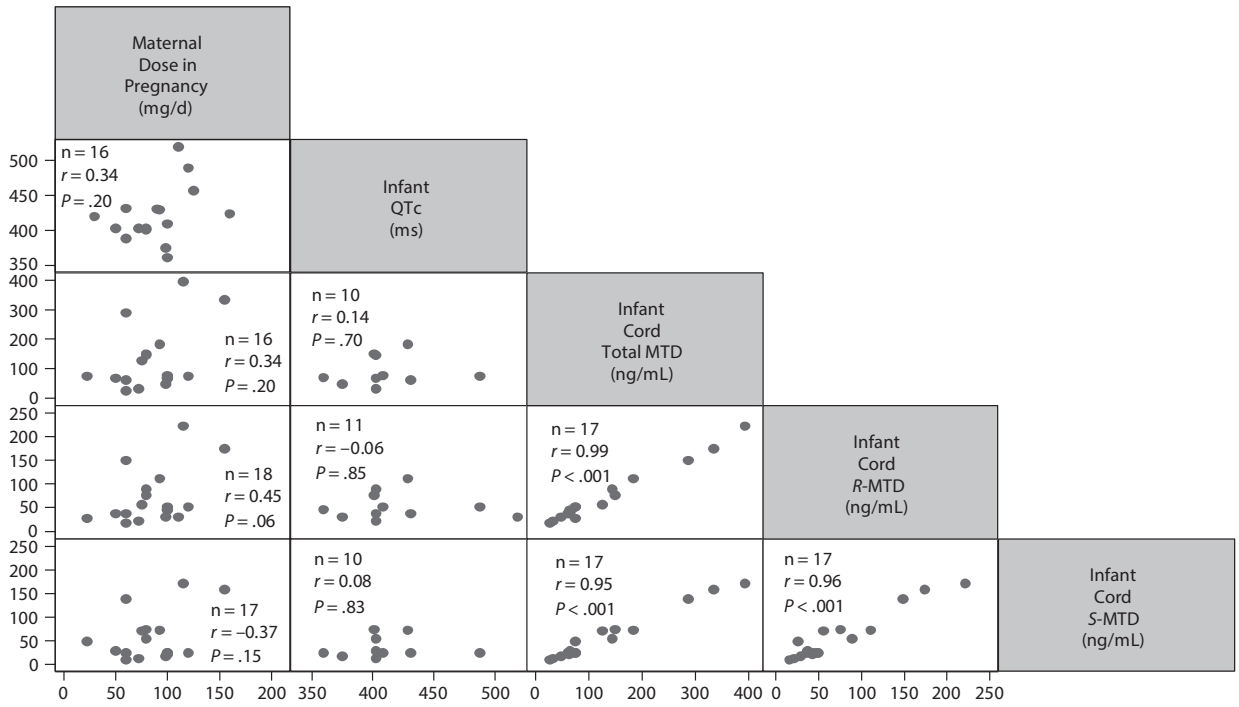
B. Mother at 3–6 Months Postpartum



(continued)

Figure 1 (continued).

C. Infant Birth Hospitalization



[a]Methadone concentrations are plasma concentrations.
Abbreviations: MTD = methadone, QTc = corrected QT interval.

P = .20), cord enantiomer-specific methadone concentrations (*R*-methadone: Pearson *r* = –0.06, *P* = .85; *S*-methadone: Pearson *r* = 0.08, *P* = .83), or third trimester maternal QTc (Pearson *r* = 0.42, *P* = .11). We did not obtain additional ECGs, but infants were observed for withdrawal for at least 5 days, and none had any cardiac events.

DISCUSSION

In this first study to examine the relationships between QTc and methadone dose and concentrations among pregnant and postpartum women, we found that QTc was correlated with higher maternal methadone dose and higher trough *R*-methadone concentrations during pregnancy but not postpartum. At peak plasma methadone concentration, more than 10% of women had a QTc above the range of concern based on recent recommendations[10] during both the third trimester of pregnancy and the months postpartum, and these were not the same women. Among infants, 18% had an initial QTc > 450 ms.

In the United States, all clinically dispensed methadone is a racemic mixture of *R*-methadone and *S*-methadone. However, the *S*-enantiomer is not only a poor μ-opioid receptor agonist, but is also most likely responsible for the prolongation of the QTc interval. The *S*-enantiomer blocks the hERG channel more efficiently than the *R*-enantiomer.[23] In Europe, *R*-methadone is prescribed clinically but it is not available in the United States, at least in part because it would not be profitable for companies to market.

Our finding that 18% of infants had an initial ECG with QTc > 450 ms is consistent with the report by Parikh and colleagues.[13] They found that 15% of infants with methadone exposure in pregnancy had a QTc > 460 ms 1 to 2 days postpartum but that the QTc normalized in all infants in the first week. Most babies exposed to long-acting opioids are observed for at least a few days in the hospital, the time of highest risk of prolonged QTc. Infants may be further exposed to methadone through treatment with the drug or through breastmilk. Methadone is the second most common medication used to treat infants for withdrawal.[24] Also, although only low but variable concentrations of methadone are present in breastmilk, feeding with the mother's own breastmilk is consistently associated with less severe infant withdrawal and lower pharmacologic treatment rates in exposed infants.[25–29] Whether the benefit of breastfeeding for withdrawal results from medication in the milk or other aspects of breastmilk or the act of breastfeeding is not known.[21,30–32] Nonetheless, future studies should include longer term follow-up of infants, particularly among infants being breastfed and those being treated with methadone.

Polypharmacy is a risk factor for prolonged QTc,[33] particularly with benzodiazepines.[5] This is relevant as many women prescribed methadone are also treated with psychotropic medications.[34] If polypharmacy is associated

with longer QTc, we would expect that women with concomitant medication use would have the longest QTc values. However, none of the women with QTc > 450 ms during pregnancy and postpartum were taking concomitant medications; however, those with QTc between 440 and 450 ms were those treated with additional medications. Buprenorphine, which is not associated with prolonged QTc, could be offered as an alternative to women who have a high-risk QTc. Concomitant medication use is also an important consideration for infants. Dubnov-Raz and colleagues[35] found that infants exposed to selective serotonin reuptake inhibitors (SSRIs) had longer QTc in the first day of life compared to unexposed infants (409 vs 392 ms) and that 10% of SSRI-exposed infants had a QTc > 460 ms. We were unable to assess this relationship in the infants, but this observation deserves additional attention in future research.

This is a novel study examining QTc in pregnancy among women prescribed methadone and their infants. However, it has a number of limitations. Given the strong association between opioid receptor genotype and methadone metabolism,[36] the homogeneous population in this study (primarily white) may not be generalizable. Due to practical constraints and the scientific questions, we obtained methadone concentrations at trough and ECGs at peak, which could explain some of the poor correlations. It would have been ideal to have obtained an ECG prior to pregnancy for a baseline QTc as well as electrolyte status (calcium and magnesium) at the time of each ECG, as these can be associated with prolongation of QTc; however, we recruited our subjects during pregnancy. Since we reported that methadone concentration increases soon after delivery, a maternal ECG in the first week postpartum would have been optimal. However, as we discussed in that original report,[14] we collected data on maternal methadone concentrations in the immediate postpartum period in the last 3 study patients because we observed that women appeared to be overmedicated (falling asleep a few hours after dose) in the first weeks postpartum, and we did not obtain additional ECGs.

Our findings support the recent recommendations to obtain an ECG for QTc before and after initiation of methadone treatment.[10] We propose that it is advisable to obtain an ECG after significant dose changes during pregnancy. Dose adjustments are made in pregnancy in response to the active enantiomer, *R*-methadone. Given that women receive racemic methadone and that *S*-methadone is most likely responsible for QTc changes and is metabolized by different cytochromes, when adjustment of *R*-Methadone is made, *S*-methadone is also being adjusted. We found that 10% of women had a QTc above 450 ms in late pregnancy and that longer QTc correlated with higher daily doses. Examination of Figure 1A suggests doses above 100 mg/d are more likely to be associated with QTc above 450 ms. Methadone dose in women is usually increased across trimesters of pregnancy due to faster clearance. Because the dose is not usually lowered quickly postpartum, women have higher methadone concentrations in the early postpartum period,[14] which makes this a vulnerable time for the emergence of QTc prolongation. The effects of higher concentrations include a sudden cardiac event or sedation, both of which can negatively impact a woman's ability to safely care for her infant. The postpartum period is a particularly vulnerable time for women with hereditary long QT syndrome.[37,38] Rashba and colleagues[37] theorized that this postpartum vulnerability could be due to slowing of the heart rate after birth or that stress and altered sleep patterns associated with caring for a newborn infant increase adrenergic-mediated cardiac events during the postpartum interval. Infants should also be observed in the hospital for the first few days after birth and until the mother is on weaning doses of methadone if being treated. Women who are breastfeeding should have their dose lowered if they experience sedation or other signs that their blood levels of methadone are increased. Finally, this study raises awareness of the unique population of pregnant women and their infants and the importance of evaluating the impact of pregnancy physiology on drug concentrations and efficacy.

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Editor's Note: We encourage authors to submit papers for consideration as a part of our Focus on Women's Mental Health section. Please contact Marlene P. Freeman, MD, at mfreeman@psychiatrist.com.