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Pharmacokinetics of Antidepressants in Pregnancy

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Abstract

Depression is common in pregnant women. However, the rate of antidepressant treatment in pregnancy is significantly lower than in nonpregnant women. Although some antidepressants may cause potential risks to the fetus, not treating or withdrawing the treatment is associated with relapsing and adverse pregnancy outcomes such as preterm birth. Pregnancy-associated physiologic changes can alter pharmacokinetics (PK) and may impact dosing requirements during pregnancy. However, pregnant women are largely excluded from PK studies. Dose extrapolation from the nonpregnant population could lead to ineffective doses or increased risk of adverse events. To better understand PK changes during pregnancy and guide dosing decisions, we conducted a literature review to catalog PK studies of antidepressants in pregnancy, with a focus on maternal PK differences from the nonpregnant population and fetal exposure. We identified 40 studies on 15 drugs, with most data from patients taking selective serotonin reuptake inhibitors and venlafaxine. Most of the studies have relatively poor quality, with small sample sizes, reporting concentrations at delivery only, a large amount of missing data, and not including times and adequate dose information. Only four studies collected multiple samples following a dose and reported PK parameters. In general, there are limited data available regarding PK of antidepressants in pregnancy and deficiencies in data reporting. Future studies should provide accurate information on drug dosing and timing of dose, PK sample collection, and individual-level PK data.

Keywords

antidepressants, fetal exposure, obstetrics, pharmacokinetics, special populations

Women, especially those of childbearing age, disproportionately suffer from mental health conditions such as depression and anxiety.[1,2] The overall prevalence of depression ranges from 6.9% to 20% in pregnant women[3–8] and is often associated with co-occurring anxiety or other mental health problems.[9] In the United States, 39.6% of pregnant women with major depressive episodes were treated with prescription drugs from 2005 to 2009.[10] However, the 2001−2002 US National Epidemiologic Survey on Alcohol and Related Conditions reported that the rate of pharmacotherapy use for mood disorders in pregnant women (14.3%) was significantly lower than in nonpregnant women (25.5%).[9] Reduced treatment during pregnancy may be due to the perception that pharmacologic treatments for mental health disorders lead to adverse fetal outcomes.[11,12] Practitioners may also reduce doses of drugs to decrease fetal exposure.

Pharmacokinetic (PK) studies provide information to guide clinical dosing. Pregnancy-related physiologic changes such as increased hepatic and renal blood flow, decreased plasma albumin concentration, changes of body composition, and altered metabolic enzyme activity lead to changes in PK.[13] However, data are limited due to small sample sizes and practical and ethical concerns with conducting clinical studies in pregnant women.[14] As pregnant women are largely excluded from clinical trials, dosing is based on extrapolation from nonpregnant populations, which could lead to ineffective doses or higher risk of adverse reactions.

This issue is particularly important for the treatment of mood disorders in pregnancy. Whereas some antidepressants have been associated with postnatal adaptation syndrome or increased risk of malformation,[12,15–18] other studies have shown that associations with neurodevelopmental disorders and

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cardiac defects are not significant after adjusting for confounding factors.[19,20] Additionally, withholding or withdrawing antidepressant treatment also poses a threat to maternal and fetal health. The discontinuation of antidepressants during pregnancy is associated with a significantly higher risk of relapsing to major depression during pregnancy compared to women who continue therapy (68% vs. 26%).[21] Untreated mood disorders have been associated with higher rates of adverse pregnancy outcomes such as preterm birth.[22] To balance fetal safety and maternal mental health, an understanding of PK changes during pregnancy is critical to guide dosing decisions.

The objective of this review is to catalog PK studies of antidepressants in pregnancy with a focus on maternal PK changes during pregnancy and fetal exposure. We also identify limitations of published literature and gaps in current knowledge. While safety of medications in mother and fetus is also important to guide antidepressant dosing in pregnant women, it is out of the scope of this review. Interested readers are referred to recent reviews regarding neonatal outcomes following antidepressant therapy.[23–25]

Methods

Search Strategy

The entire PubMed database (search date May 20, 2020; updated on October 24, 2022) was queried for studies using the search terms "pharmacokinetic, pregnancy" and individual drug names or classes for antidepressants including sertraline, fluoxetine, paroxetine, citalopram, escitalopram, fluvoxamine, selective serotonin reuptake inhibitor, venlafaxine, desvenlafaxine, duloxetine, milnacipran, viloxazine, levomilnacipran, serotonin–norepinephrine reuptake inhibitor, trazodone, nefazodone, serotonin antagonist and reuptake inhibitor, clomipramine, nortriptyline, imipramine, amitriptyline, desipramine, doxepin, amoxapine, maprotiline, protriptyline, trimipramine, tricyclic antidepressant, bupropion, mirtazapine, vilazodone, esketamine, vortioxetine, isocarboxazid, phenelzine, tranylcypromine, and monoamine oxidase inhibitor. The search was limited to humans and English language. Titles and abstracts of identified studies were screened by two authors, and potentially relevant articles were retrieved in full text for review. Exclusion criteria included in vitro studies, animal models, or placental perfusion models; studies specific to lactation; those that did not contain primary PK data in pregnancy; and review articles. Additionally, relevant articles identified in reference lists of retrieved papers but not flagged in the initial search were added.

Data Extraction

Relevant study information was extracted from each article including drug(s) and dosage(s) studied, number and characteristics of the study population, and any reported PK parameters including individual plasma or cord blood concentrations, maximum plasma concentration (C_{max}), area under the concentration–time curve (AUC), half-lives, apparent clearance (CL), apparent volume of distribution (V), or cord blood/maternal plasma (C/M) ratios. Study data are generally reported with summary descriptive statistics. Where possible, similarly reported PK data were synthesized or reported together. Drugs were classified by their mechanisms of action and ranked by the number of available studies. Information on individual drugs is summarized in text and tables in chronological order. Data relating to concentrations of drug in breast milk were not included.

Results

Forty publications on 15 antidepressants studied in 961 pregnant women were identified (Tables S1 and S2). Seventeen manuscripts contained PK data for multiple drugs.[26–42] No information was found regarding PK of desvenlafaxine, milnacipran, viloxazine, levomilnacipran, nefazodone, desipramine, doxepin, amoxapine, maprotiline, protriptyline, trimipramine, vilazodone, esketamine, vortioxetine, isocarboxazid, phenelzine, and tranylcypromine in pregnancy. Tables 1 and Table S3 summarize findings for each drug. Only six studies reported PK parameters such as AUC, CL, or V. Four studies collected samples at multiple time points following a single dose. Ten studies reported information at delivery only. Eight studies were case reports with only one patient for each drug. Below, we provide detailed findings for individual antidepressants.

Selective Serotonin Reuptake Inhibitors

Sertraline. Eight studies determined cord and maternal plasma concentrations of sertraline at time of delivery, and six also reported N-desmethylsertraline concentration (Table 2).[28,29,31,36,38] C/M ratios for sertraline ranged from 0.1 to 1.6, and N-desmethylsertraline C/M ratios ranged from 0.1 to 4.

Maternal plasma and amniotic fluid concentrations were reported in three studies.[28,33,43] Hostetter et al.[28] measured sertraline and N-desmethylsertraline serum and amniotic fluid concentrations in a 40-year-old patient at 17 weeks' gestation treated with 150 mg/day sertraline monotherapy. The patient underwent an amniocentesis 1 h after sertraline administration. Serum concentrations of sertraline and N-desmethylsertraline were 53 and 349 ng/mL, respectively. Amniotic fluid concentrations of drug and metabolite were less than 5% of serum concentrations:

Table 1. Pharmacokinetic Data on Antidepressants and Observed Changes in Pregnancy.

Drug name	Primary active metabolite	Primary metabolic route	Nonpregnant elimination half-life	Dose linearity	Plasma protein binding	Excreted unchanged in urine	General conclusions
Sertraline[76,77]	N-desmethylsertraline	CYP2B6, 3A4, 2C19, 2D6, 2C9	22–36 h	Linear	98%	Minor	Weak evidence that sertraline exposure and parent/metabolite ratio decrease during pregnancy compared to postpartum; one study showed CYP2C19 genotype dependency
Fluoxetine[78,79]	Norfluoxetine	CYP2D6, 2C9, 2C19	1–4 days	Nonlinear (>40 mg)	94.50%	<10%	Decreasing fluoxetine concentration throughout pregnancy and lower parent/metabolite ratio compared to postpartum
Paroxetine[80]		CYP2D6, 3A4	21 h	Nonlinear	93%	2%	Decreasing paroxetine concentration throughout pregnancy; one study showed CYP2D6 genotype dependency
Citalopram[81,82]	N-desmethylcitalopram	CYP2C19, 3A4, 2D6	35 h	Linear	80%	10%	Weak evidence of decreasing citalopram concentrations throughout pregnancy and lower parent/metabolite ratio compared to postpartum
Escitalopram[83,84]	N-desmethylescitalopram	CYP2C19, 3A4, 2D6	27—32 h	Linear	56%	8%	Inconsistent results
Fluvoxamine[85]		CYP2D6, 1A2	15–20 h	Nonlinear	77%	2%	Limited data showing decrease of fluvoxamine concentration during pregnancy and compared to postpartum
Venlafaxine[86,87]	O-desmethylvenlafaxine	CYP2D6, 2C19, 3A4, 2C9	5 h	Linear	27%	5%	Decrease of venlafaxine concentration and metabolic ratio during pregnancy
Duloxetine[88]		CYP1A2, 2D6	10–12 h	Linear	>90%	<1%	Limited data
Trazodone[89]	M-chlorophenylpiperazine	CYP3A4	7.1 h	Linear	89%–95%	<1%	Limited data
Clomipramine[90,91]	N-desmethylclomipramine	CYP2D6, 2C19, 3A4, 1A2	19–37 h	Nonlinear	97%	0.80%	Weak evidence of decreasing clomipramine exposure and increasing parent/metabolite ratio during pregnancy
Amitriptyline[92]	Nortriptyline	CYP2C19, 3A4, 2D6	25 h	Linear	95%	2%	Limited data showing decrease of amitriptyline concentration during pregnancy and compared to postpartum
Nortriptyline[93,94]	10-hydroxy-nortriptyline	CYP2D6	18–35 h	Linear	93%	2%	Decreasing nortriptyline concentrations throughout pregnancy
Imipramine[95]	Desipramine	CYP1A2, 3A4, 2D6, 2C19	12 h	Linear	60%–96%	<5%	Limited data showing decrease of imipramine concentrations during pregnancy and compared to postpartum
Mirtazapine[96,97]	N-desmethylmirtazapine	CYP2D6, 1A2, 3A4	20–40 h	Linear	85%	4%	Limited data showing decrease of mirtazapine concentrations during pregnancy and compared to postpartum
Bupropion[98,99]	Hydroxybupropion (OHBUP), threohydroxybupropion (TB) and erythrohydroxybupropion (EB)	CYP2B6, 2C19, 3A4	21 h	Linear	84%	0.50%	No significant change of bupropion exposure and apparent clearance; significantly higher EB/BUP ratio in second trimester, but not significant for OHBUP/BUP and TB/BUP

Abbreviation: CYP, cytochrome P450.

Table 2. Maternal Plasma/Serum and Cord Blood Concentrations of Sertraline and N-Desmthylsertraline at Delivery.[a]

				Sertraline			N-desmethylsertraline		
Study	*N*	Dose (mg/day)	Study location	Maternal concentration at delivery (ng/mL)	Cord concentration at delivery (ng/mL)	Cord/Maternal ratio	Maternal concentration at delivery (ng/mL)	Cord concentration at delivery (ng/mL)	Cord/Maternal ratio
Hostetter et al. (2000)[28]	1	175	USA	45	21	0.47	320	194	0.61
Rampono et al. (2004)[31]	4	50	Australia	10.5 (9–64)	10 (5–24)	0.7 (0.4–1.2)	37.5 (21–189)	26.5 (13–93)	0.63 (0.46–0.81)
Sit et al. (2011)[38]	9	Corrected to 50 mg/day (50–200)	USA	8.1 (3.9–16)	2.7 (1.5–6.7)	0.3 (0.19–0.99)	25.9 (10.8–48.5)	8.2 (3.4–19)	0.38 (0.28–0.60)
Rampono et al. (2009)[36,b]	6	50 (44–100)	Australia	15 (11–45)	6 (4–11)	0.33 (0.29–0.36)	45 (35–91)	16 (12–26)	0.40 (0.34–0.50)
Hendrick et al. (2003)[29]	11	Corrected to 50 mg/day (25–100)	USA	10 (3–44)	7 (1–7)	0.27 (0.1–1)	51 (5–148)	15.4 (6–36)	0.28 (0.1–4)
Paulzen et al. (2017)[43,b]	6	75 (43.75–100)	Germany	15.4 (11.88–20.88)	5.7 (4.52–7.05)	0.36 (0.28–0.49)	–	–	–
Colombo et al. (2020)[40]	24	75 (50–150)	Italy	12 (6.1–42.6)	6 (5–35.5)	0.4 (0.18–1.6)	–	–	–
Heinonen et al. (2021)[45]	9	75 (50–100)	Sweden	14.38 (3.64−24.17)	4.28 (1.22−6.12)	0.33 (0.14− 1.17)	33.60 (7.01−31.36)	9.93 (4.96−17.23)	0.29 (0.24−1.42)

[a] Median (range).
[b] Median (interquartile range).

less than 2.0 and 19 ng/mL, respectively. At 37.6 weeks' gestation, increased depressive symptoms led to a dose increase to 175 mg daily. Loughhead et al.[33] reported this case along with five additional cases of women receiving an average daily dose of 130 mg (50–250 mg). At gestational ages of 14.7–21.7 weeks ($n = 4$), the mean maternal serum concentration corrected to a 50-mg daily dose was 39.78 ± 13.26 ng/mL for sertraline and 71.12 ± 15.27 ng/mL for desmethylsertraline. The mean amniotic fluid/maternal serum ratio was 11.78 ± 15.11% for sertraline and 14.18 ± 12.38% for N-desmethylsertaline. Maternal serum parent and metabolite concentrations (corrected to 50 mg) in one subject measured at 36.4 weeks were 33.33 and 68 ng/mL, respectively, with an amniotic fluid/maternal serum ratio of 4% for sertraline and 2% for the metabolite. Paulzen et al.[43] reported higher amniotic fluid ratios (median [interquartile range (IQR)] 0.57 [0.28–0.75]) of sertraline at delivery in six mother–infant pairs, with median (IQR) sertraline concentrations of 8.9 (4.38–11.0) ng/mL in amniotic fluid.

Colombo et al.[40] studied 24 pregnant women treated with sertraline (50–150 mg/day). Maternal plasma samples were collected in the third trimester, and both maternal and umbilical plasma samples were collected at delivery (Table 2), approximately 12 h after dosing. The median concentration/dose (C/D) ratios were 0.26 (0.11–0.43) (ng/mL)/(mg/day) in the third trimester and 0.19 (0.08–0.71) (ng/mL)/(mg/day) at delivery. They also assessed the effect of cytochrome P450 (CYP) 2C19 phenotype, finding median C/D ratio of sertraline at delivery in CYP2C19 intermediate ($n = 4$) and poor metabolizers ($n = 2$) (IM/PMs; 0.31 [ng/mL]/[mg/day]) to be nonsignificantly higher than in ultra-rapid ($n = 4$) and extensive ($n = 9$) metabolizers (UM/EMs; 0.26 [ng/mL]/[mg/day]). Campbell et al.[41] collected serial maternal plasma samples up to 4.5 h after dosing from two patients taking 125 and 200 mg of sertraline at 36 weeks' gestation. Dose-corrected maximum plasma concentrations were 0.73 and 1.5 (ng/mL)/(mg/day).

Several longitudinal PK studies have been conducted for sertraline. Sit et al. studied six women receiving 50−200 mg/day sertraline.[35] S-sertraline and N-desmethylsertraline plasma concentrations were determined at 20, 30, and 36 weeks' gestation, at delivery, and at 2 and 12 weeks postpartum. C/D ratio of S-sertraline decreased between 20 weeks' gestation (0.5 ± 0.4 [(ng/mL)/[mg/day]) and 30 weeks' gestation (0.3 ± 0.2 [ng/mL]/[mg/day]). Dose-corrected concentrations remained low through 2 weeks postpartum (0.3 ± 0.1, 0.2 ± 0.1, and 0.2 ± 0.2 [ng/mL]/[mg/day]) at 36 weeks' gestation, delivery, and 2 weeks postpartum), increasing to 0.6 ± 0.2 (ng/mL)/(mg/day) and 0.4 ± 0.3 (ng/mL)/(mg/day) at 4−6 and 12 weeks postpartum, respectively. A corresponding increase in N-desmethylsertraline C/D (0.6 ± 0.3 and 0.8 ± 0.3 [ng/mL]/[mg/day], at 20 and 30 weeks' gestation) was observed. However, dose-corrected metabolite concentrations remained high through 12 weeks postpartum (0.9 ± 0.7 [ng/mL]/[mg/day]).

Freeman et al.[44] reported a 15.7% mean increase in oral clearance of sertraline but no significant difference in dose-corrected sertraline AUC in six patients between the second (10.34 ± 6.19 ng/mL• h/mg) and third (9.41 ± 4.98 ng/mL• h/mg) trimesters. Postpartum dose-corrected AUC was 13.5 ± 8.61 ng/mL• h/mg ($n = 3$). Similarly, dose-corrected desmethylsertraline AUC was not significantly different between the second and third trimesters (26.48 ± 24.8 and 29.94 ± 23.55 ng/mL• h/mg; $P = .38$) or postpartum (29.93 ± 20.96 ng/mL• h/mg).

Westin et al.[39] fitted serum concentration data of sertraline from 34 women from a routine therapeutic drug monitoring service in Norway to linear mixed-effects models to assess changes of serum antidepressant concentrations and metabolic ratios across pregnancy. While authors did not note the actual dose taken, all concentrations were corrected to a 50-mg daily dose. The model-predicted baseline (nonpregnant) serum sertraline concentration was 9.0 ng/mL and increased across gestation to 9.8, 12.2, and 15.1 (95% confidence interval [CI], 12.3–18.5) ng/mL at 6, 20, and 34 weeks' gestation. During the third trimester (week 34), sertraline concentrations were 68% ($P < .001$) higher than the baseline nonpregnant state. The ratio of sertraline/desmethylsertraline was significantly lower at 34 weeks' gestation compared to nonpregnant (0.4 vs. 0.5, $P < .001$).

A subset of nine mothers and seven infants enrolled in a double-blind placebo-controlled randomized clinical trial (MAGDALENA) studying the short-term and long-term effects of sertraline exposure during pregnancy on infants were included in a PK analysis.[45] The daily dose started at 25 mg and increased on the basis of treatment response. The median (IQR) C/D ratios of sertraline trended lower in the second and third trimesters, and the morning after delivery (0.15 [0.12–0.24], 0.19 [0.12–0.23], and 0.19 [0.15–0.25] [ng/mL]/[mg/day]) than at 1 month postpartum (0.25 [0.17–0.29] [ng/mL]/[mg/day]). Similar trends were observed for desmethylsertraline C/D ratios (0.49 [0.45–0.65] [ng/mL]/[mg/day] in the second trimester; 0.70 [0.47–0.74] [ng/mL]/[mg/day] in the third trimester; 0.46 [0.37–0.62] [ng/mL]/[mg/day] the morning after delivery; and 0.69 [0.43–1.05] [ng/mL]/[mg/day] 1 month postpartum).

Stika et al.[46] evaluated sertraline and its metabolite concentrations across pregnancy and postpartum in

47 women. Maternal sertraline trough C/D ratios and parent-to-metabolite (S/DS) ratios were reported every 4 weeks, from 4 to 8 weeks' gestation to greater than 36 weeks' gestation, and before and after 8 weeks postpartum. The sertraline C/D ratio at greater than 36 weeks' gestation (0.24 ± 0.13 [ng/mL]/[mg/day]) was significantly lower than the within and after 8 weeks postpartum ratios, 0.39 ± 0.23 ($P < .0001$) and 0.32 ± 0.2 (ng/mL)/(mg/day) ($P = .0012$). The sertraline C/D ratios throughout pregnancy were not significantly different from those greater than 36 weeks' gestation, with the exception of 24−28 weeks' gestation (0.32 ± 0.2; $P = .004$). There was a trend of decreasing S/DS ratio during pregnancy from 0.49 ± 0.22 to 0.32 ± 0.1 with the highest S/DS ratio within 8 weeks postpartum (0.53 ± 0.22). Genotypes of CYP2C19, CYP2C9, CYP2D6, and CYP3A5 were obtained from 46 subjects. The mean (95% CI) sertraline C/D ratio in CYP2C19 IM/PMs was higher than those in EMs and UMs after 8 weeks postpartum, while lower than or similar to EMs and UMs during pregnancy. No other difference was observed among CYP2C9 and CYP2D6 phenotypes.

Leutritz et al.[42] also reported a decreased exposure of sertraline in 11 patients during pregnancy. The daily dose of each patient was not reported. The mean C/D ratio was 0.56 in the first trimester ($n = 1$), 0.29 in the second trimester ($n = 4$), and 0.39 in the third trimester ($n = 4$). The mean ± standard deviation (SD) C/D ratio was 0.43 ± 0.02 within 2 weeks postpartum ($n = 2$) and 0.8 ± 0.79 after 2 weeks postpartum ($n = 8$).

O'Brien et al.[37] used a novel hair segmental analysis to assess the changes in metabolic ratios during pregnancy and the postpartum period. In a woman taking sertraline (75 mg/day) the S/DS ratio was 5.8 in the first trimester and 3.5 in the third trimester.

Sertraline is metabolized by multiple enzymes, which are altered in different ways during pregnancy (e.g., increased CYP2B6, CYP3A4, and CYP2D6 activity but decreased CYP2C19 activity),[13] making it difficult to predict the overall effect on sertraline concentrations. Four studies reported lower sertraline concentrations in late pregnancy compared to postpartum, though only one study demonstrated statistical significance.[42,44–46] In contrast, one study reported a significant increase in maternal sertraline concentrations during pregnancy and higher concentrations in the third trimester than in nonpregnant individuals.[39] Lower metabolic ratios in late pregnancy were reported in two studies, one also showing a trend of decreasing metabolic ratios throughout pregnancy.[39,46] One study reported lower or similar sertraline concentrations in CYP2C19 IM/PM during pregnancy compared to postpartum than in UM/EM, suggesting decreased CYP2C19 activity among UM/EM during pregnancy.[46]

Fluoxetine. Maternal plasma and cord blood fluoxetine concentrations were reported in seven studies, and six of them also reported norfluoxetine concentrations (Table 3). The C/M ratio ranged from 0.32 to 1.36 for fluoxetine and from 0.12 to 1.6 for norfluoxetine.

Loughhead et al.[33] studied 12 women taking a mean daily dose of 39 (20–80) mg of fluoxetine. All samples were collected between 14.1 and 19 weeks' gestation, except one at gestational week 38.6. The mean maternal serum concentration corrected to a 40-mg daily dose was 237.28 ± 126.93 ng/mL for fluoxetine and 236.78 ± 137.38 ng/mL for norfluoxetine in the second trimester. The amniotic fluid concentration as a percentage of maternal serum was 9.01 ± 7.02% for fluoxetine and 12.88 ± 11.6% for norfluoxetine.

Several studies reported fluoxetine and norfluoxetine concentrations in the third trimester. Loughhead included one subject measured at gestational week 38.6 whose maternal serum parent and metabolite concentrations (corrected to a 40-mg daily dose) were 128 and 288 ng/mL for fluoxetine and norfluoxetine, respectively.[33] The amniotic fluid as a percentage of maternal serum was 17.2% for fluoxetine and 18.1% for norfluoxetine.

Heikkinen et al. reported trough plasma concentrations of fluoxetine and norfluoxetine in 11 women receiving 20−40 mg/day of fluoxetine at 36−37 weeks' gestation, at delivery, and postpartum.[47] Plasma fluoxetine concentrations were lower during pregnancy (152 ± 107 nmol/L at 36−37 weeks' gestation) and during the first week postpartum (154 ± 109 nmol/L on Day 2 and 183 ± 122 nmol/L on Day 4) than at 2 weeks (338 ± 166 nmol/L; $P < .05$) and 2 months (388 ± 190 nmol/L; $P < .05$) postpartum. In contrast, norfluoxetine concentrations were not significantly different between pregnancy and postpartum: 364 ± 73 nmol/L during pregnancy, 310 ± 102 nmol/L at delivery, 274 ± 85 nmol/L postpartum Day 2, 281 ± 87 nmol/L postpartum Day 4, 365 ± 109 nmol/L 2 weeks postpartum, and 310 ± 161 nmol/L 2 months postpartum ($P > .05$). However, concentrations were not dose-corrected, and it is unclear whether doses were adjusted during or after pregnancy.

Laine et al.[30] conducted a prospective study in 10 women taking 20−40 mg of fluoxetine daily. They reported the sum of fluoxetine and norfluoxetine concentrations. Trough concentrations in the third trimester had a mean (range) of 468 (317–692) nmol/L. The mean umbilical vein concentration was 278 (209–366) nmol/L at delivery. Infant plasma concentrations were 319 (151–573) nmol/L 2 days postpartum and 153 (58–345) nmol/L 2 weeks after delivery.

Kim et al.[48] evaluated the plasma concentrations of R- and S-fluoxetine and norfluoxetine in nine

Table 3. Maternal Plasma/Serum and Cord Blood Concentrations of Fluoxetine and Norfluoxetine.

				Fluoxetine			Norfluoxetine		
Study	*N*	Dose (mg/day)	Study location	Maternal concentration at delivery (ng/mL)	Cord concentration at delivery (ng/mL)	Cord/Maternal ratio	Maternal concentration at delivery (ng/mL)	Cord concentration at delivery (ng/mL)	Cord/Maternal ratio
Rampono et al. (2004)[31,d]	4	20–40	Australia	96 (56–199)	65(52–149)	0.67 (0.61–0.75)	110 (20–252)	81 (8–252)	0.72 (0.4–1)
Sit et al. (2011)[38,d]	4	10–40[a]	USA	51.7 (31.3–162)	26.7 (20–89.1)	0.55 (0.50–0.64)	94.7 (12.7–127.5)	54.9 (8.7–76)	0.43 (0.48–0.7)
Rampono et al. (2009)[36]	2	30	Australia	52; 192	37; 141	0.71; 0.73	126; 52	99; 226	0.77; 0.79
Hendrick et al. (2003)[29,d]	15	10–60[a]	USA	45.3 (13–274)	26 (6–262)	0.54 (0.32–1.36)	126 (30–388)	62 (18–213)	0.6 (0.12–1.6)
Kim et al. (2006)[48,b]	9	10–30	British Columbia	38.5 (15.1, 62.1)	41.3 (16.9, 59.8))	0.91 (0.60, 1.02)	74.6 (41.7, 107.4)	78.5 (42.3, 114.6)	1.04 (0.93, 1.15)
Heikkinen et al. (2003)[47,c]	11	20–40	Finland	56.9 ± 37.8	34.6 ± 23.2	0.61	91.5 ± 30.1	61.7 ± 23.3	0.67
Colomboet al. (2020)[40,d]	4[e]	25 (20–30)	Italy	147; 216.8	152; 108.6	1.03; 0.5			

[a] Concentrations are dose-corrected to 20-mg dose.
[b] Reported as mean (95% confidence interval).
[c] Reported as mean ± standard deviation (range).
[d] Reported as median (range).
[e] Concentration at delivery available from only three subjects, with one below the limit of quantitation.

women taking 10−30 mg of fluoxetine daily during the third trimester and at delivery. Mean (95% CI) R-fluoxetine concentrations were 20 (7.3–32.7) μg/L and 10.9 (6.3–15.5) μg/L during the third trimester and at delivery, respectively. S-fluoxetine concentrations were reported as 41.0 (13.7–68.3) and 27.7 (8.4–47) μg/L; R-norfluoxetine concentrations were 32.6 (19.8–1.19) and 22.4 (15.8–29.0) μg/L; and S-norfluoxetine concentrations were 80.6 (41.8–119.3) and 52.2 (24.4–80.0) μg/L.

Colombo reported the fluoxetine concentration following 30-mg daily dosing in the third trimester in a patient genotyped as a CYP2D6 IM to 346.8 ng/mL.[40]

Campbell described PK of three patients treated with fluoxetine at doses of 20, 60, and 80 mg daily.[41] The mean ± standard error SE AUC from time zero to 4.5 h ($AUC_{0–4.5h}$) was 3221 ± 1919 (ng/mL) • h, and C_{max} was 613 ± 342 ng/mL following dosing at 36 weeks' gestation. However, fluoxetine had not reached C_{max} by 6−8 h after dosing.

Three studies assessed PK of fluoxetine longitudinally across pregnancy. Westin et al.[39] studied 41 pregnant women receiving fluoxetine (dose not reported). Serum concentrations were dose corrected to 20 mg/day and reported as a sum of fluoxetine and norfluoxetine concentrations. No trend was observed in the summed serum concentrations of fluoxetine and norfluoxetine at baseline and 6, 20, and 34 gestational weeks (167.1, 163.2, 154.4, and 146.1 ng/mL [95% CI, 107.4–198.8]; $P = .39$). The ratio of fluoxetine/norfluoxetine at gestational week 34 was 0.6, which was significantly lower than that at baseline (1.0; $P = .01$).

Sit et al.[49] studied 17 pregnant women taking a stable dose of fluoxetine (10–80 mg daily) for at least 4 weeks. Maternal plasma was collected 15−23 h after dosing at weeks 20, 30, and 36; delivery; and postpartum. Two analytical methods were used: a chiral method capable of separating R- and S-fluoxetine and R- and S-norfluoxetine ($n = 9$), and a racemic method ($n = 8$). Total drug concentrations (bound plus unbound) were assessed. The authors provided individual dose and plasma fluoxetine and norfluoxetine (racemic or individual enantiomers) for each woman in a supplemental table. Racemic norfluoxetine C/D ratios decreased from 30 weeks' gestation (4.7 ± 2.0 [ng/mL]/[mg/day]) to delivery (2.1 ± 0.9 [ng/mL]/[mg/day]; $P = .0491$). C/D ratios of S-fluoxetine and total chiral fluoxetine increased significantly between 36 weeks' gestation (2.7 ± 3.7 and 3.5 ± 4.9 [ng/mL]/[mg/day]) and 12 weeks postpartum (5.7 ± 2.7 and 7.0 ± 2.9 [ng/mL]/[mg/day]; $P = .016$ and .0255). When measured using the chiral assay, the S/DS ratios indicated that fluoxetine clearance increased during pregnancy (1.0 ± 0.7 at week 20, 0.9 ± 0.8 at week 30, 0.6 ± 0.8 at week 36, 1.4 ± 0.7 at 12 weeks postpartum; $P = .001$). However, this increase was not observed in subjects in which racemic fluoxetine was measured.

Carvalho et al.[50] investigated the PK and placental transfer of a single 20-mg oral dose of racemic fluoxetine in nine subjects. In the third trimester, the median (IQR) oral clearance (CL/F) was 0.66 (0.52–1.16) L/h • kg for R-fluoxetine and 1.45 (0.63–3.24) L/h • kg for S-fluoxetine. The median (IQR) elimination half-life of R- and S-fluoxetine was 24.72 (18.07–34.56) h and 17.19 (9.73–22.20) h. The AUC of S-norfluoxetine was significantly greater than for R-norfluoxetine (942.7 vs. 498.6 ng • h/mL; $P < .05$). At delivery, fluoxetine and norfluoxetine enantiomers were measured in the maternal vein plasma, umbilical vein plasma, intervillous space, and amniotic fluid. Samples were collected, on average, 198 min after fluoxetine administration. The umbilical vein/maternal vein ratio of R-fluoxetine was significantly lower than that of S-fluoxetine (0.33 vs. 0.44; $P = .0039$). The intervillous space/maternal vein ratio and amniotic fluid/maternal vein ratio were 1.28 and 0.08 for R-fluoxetine and 1.30 and 0.08 for S-fluoxetine, respectively. There were no significant differences between norfluoxetine enantiomers.

In the O'Brien[37] study evaluating metabolic ratios of antidepressants in hair, one patient was taking fluoxetine. At a fluoxetine dose of 30 mg/day, the ratio of fluoxetine/norfluoxetine was 14 in the first trimester and decreased to 5.4 in the third trimester.

While no study found a significant effect, fluoxetine concentrations tended to decrease during pregnancy compared to postpartum or nonpregnant individuals.[39,47,49] The metabolic ratio also decreased during pregnancy, indicating increased metabolism, which may be related to an increase of CYP2D6 activity.[37,39,49] The disposition and metabolism of R- and S-enantiomers were different, as expected, due to differential metabolism.[48–50]

Paroxetine. Four studies of paroxetine reported maternal plasma and cord blood concentrations at delivery (Table 4). The range of paroxetine C/M ratio was 0.05–0.91.

First-trimester concentrations of paroxetine in plasma and amniotic fluid were reported by Loughhead et al.[33] In a woman receiving a 20-mg daily dose studied at 16.7 weeks' gestation, the paroxetine concentration was 39 ng/mL in maternal serum. The amniotic fluid paroxetine concentration was below the limit of quantification (less than 2 ng/mL). Another woman who was taking a 40-mg daily dose was studied at 16.1 weeks' gestation. The concentration of paroxetine was 14 ng/mL in maternal serum and 3 ng/mL in amniotic fluid.

Oberlander et al.[51] reported paroxetine concentrations in maternal plasma and cord blood in patients

Table 4. Maternal Plasma/Serum and Cord Blood Concentrations of Paroxetine.

				Paroxetine		
Study	*N*	Dose (mg/day)	Study location	Maternal concentration at delivery (ng/mL)	Cord concentration at delivery (ng/mL)	Cord/Maternal ratio
Rampono et al. (2004)[31]	2	20	Australia	13; 10	7; not detected[b]; 5	0.54; 0.5
Rampono et al. (2009)[36]	1	30	Australia	13	2	0.15
Hendrick et al. (2003)[29,a]	11	Corrected to 20 mg/day (10–40 mg)	USA	29 (8–118)	12 (3–48)	0.56 (0.05–0.91)
Oberlander et al. (2004)[51,c]	3/14	22.5 ± 10.3/20.0 ± 7.7	Canada	4.4 ± 3.3/8.4 ± 8.6	1.5 ± 1.0/3.32 ± 4.6	

[a] Median (range).
[b] Study included a woman with nonidentical twins; paroxetine was not detected in one twin's cord.
[c] Data stratified by exposed infants with/without transient neonatal symptoms, reported as mean ± SD.

treated with paroxetine alone or in combination with clonazepam. The authors reported that infant withdrawal symptoms were associated with higher concentrations of paroxetine in maternal plasma during the third trimester and at delivery in patients cotreated with clonazepam. Mean infant cord blood concentrations were less than 40% of maternal delivery concentrations for all groups. However, the evaluation of PK of paroxetine are limited by the wide range of doses administered (5–40 mg/day) and lack of information on when blood draws were obtained after dosing.

Two studies evaluated concentrations of paroxetine in the third trimester. Colombo et al.[40] studied 11 women taking paroxetine with a median daily dose of 20 mg (10–25 mg). Maternal paroxetine plasma concentrations were measured in four subjects during the third trimester. Only two of them were above the limit of quantification (LOQ; 5 ng/mL) at 10.3 and 41.9 ng/mL. For the four out of 10 quantifiable maternal plasma concentrations at delivery, the mean ± SD was 23.73 ± 17.55 ng/mL. Only three of eight umbilical plasma concentrations were above LOQ, with mean ± SD of 7.3 ± 4.2 ng/mL and C/M ratio of 0.265 ± 0.108. CYP2D6 genotype and phenotype information were available from eight women, including one PM, two IMs, and five EMs. The median C/D ratio was 2.56 (ng/mL)/(mg/day) for IM and PM, and 0.37 (ng/mL)/(mg/day) for EM at delivery. Campbell et al.[41] reported PK in two women at 36 weeks' gestation, taking 20 and 30 mg of paroxetine daily. The mean ± SE $AUC_{0–4.5h}$ was 125 ± 66 (ng/mL) • h and C_{max} was 24 ± 5.2 ng/mL.

Only two studies captured longitudinal data on paroxetine concentrations throughout pregnancy, both demonstrating significantly decreased dose-corrected plasma concentrations. Ververs et al.[52] collected plasma samples longitudinally throughout pregnancy from 74 women. A total of 190 plasma paroxetine concentrations were included in a linear mixed effects model including CYP2D6 genotype, gestational age, dose, and interaction terms for genotype with gestational age and dose. In CYP2D6 EMs, the plasma concentrations of paroxetine significantly decreased as gestational age increased (−0.3 μg/L per week; $P = .014$). Conversely, in IMs and PMs, plasma concentrations increased with increasing gestational age (0.57 μg/L per week; $P < .001$). However, in both groups the Edinburgh Postnatal Depression Scale scores increased during pregnancy, indicating a worsening of depression symptoms, with IM/PMs having higher Edinburgh Postnatal Depression Scale scores than the EM group. Westin et al.[39] found a significant decrease in paroxetine concentrations across pregnancy in 19 women. After dose-correcting to 20 mg, the serum paroxetine concentrations were 33.5, 29.6, 22.1, and 16.5 (95% CI, 11.5–23.6) ng/mL when nonpregnant, at 6, 20, and 34 gestational weeks ($p \leq .001$). Paroxetine concentrations were 51% lower in the third trimester compared to nonpregnant.

Overall, it is clear that paroxetine concentrations are significantly decreased during pregnancy, which may be attributed to the increased clearance through CYP2D6.[39,52] One study showed that this effect depends on CYP2D6 genotypes, with decreased exposure in EMs and increased in IMs and PMs.[52]

Citalopram. The results of five studies reporting maternal and cord plasma concentration at delivery of citalopram are summarized in Table 5. The average C/M ratio was 0.56–0.83. Three studies measured the concentration of the active metabolite, finding an average C/M ratio of N-desmethylcitalopram of 0.57–0.86.[29,36,38]

Loughhead et al.[33] studied a patient at 17 weeks' gestation taking 50 mg/day of citalopram with a serum citalopram concentration of 262 ng/mL. The amniotic fluid citalopram concentration was 94 ng/mL, 35.9% of the maternal serum concentration.

Laine et al.[30] determined citalopram concentrations in 10 pregnant women taking 20−40 mg daily during pregnancy. The mean maternal plasma trough citalopram concentration was 99.8 (58–214) nmol/L in the third trimester. The average duration of pregnancy

Table 5. Maternal Plasma/Serum and Cord Blood Concentrations of Citalopram.

				Citalopram			N-desmethylcitalopram		
Study	*N*	Dose (mg/day)	Study location	Maternal concentration at delivery (ng/mL)	Cord concentration at delivery (ng/mL)	Cord/Maternal ratio	Maternal concentration at delivery (ng/mL)	Cord concentration at delivery (ng/mL)	Cord/Maternal ratio
Heikkinen et al. (2002)[53,a]	11	20–40 (dose corrected to 20)	Finland	31.8 ± 10.4	20.2 ± 7.2	0.64			
Rampono et al. (2009)[36,b]	9	20–30	Australia	33 (24–51)	27 (20–50)	0.83 (0.77–0.86)	14 (10–18)	12 (9–23)	0.86 (0.82–1.06)
Sit et al. (2011)[38]	1	50	USA	41.4	23	0.56	14.7	10.5	0.71
Hendrick et al. (2003)[29,c]	4	20–40 (dose corrected to 20)	USA	37.5 (12–64)	22 (5–36)	0.62 (0.17–1.42)	10 (9–20)	10 (5–11)	0.57 (0.5–1.0)
Paulzen et al. (2017)[65,c]	12	20 (10–40)	Germany	32.75 (7–84.7)	25.15 (5.1–61.7)	0.78 (0.46–1.66)			

[a]Mean ± standard deviation.
[b]Median (interquartile range).
[c]Median (range).

was 39.1 (35.9–41.6) weeks. At delivery, the mean cord blood concentration of citalopram was 82 (35–217) nmol/L. The mean infant plasma trough citalopram concentration was 50.7 (23–95) nmol/L on Day 2 postpartum and 8.5 (0–20) nmol/L 2 weeks after delivery.

Two women taking 20 mg/day of citalopram were included in the Colombo et al.[40] study. One was a CYP2C19 EM with maternal citalopram plasma concentration in the third trimester of 90.2 ng/mL. The other was a CYP2C19 IM with a plasma concentration of 14.9 ng/mL in the third trimester and 9.3 ng/mL at delivery. The umbilical plasma concentration of citalopram was 5.5 ng/mL, and the C/M ratio was 0.59.

Five subjects took 40−60 mg of citalopram daily at Gestational Week 36 in the Campbell et al.[41] study. The mean ± SE $AUC_{0-4.5h}$ was 906 ± 271 (ng/mL) • h, and C_{max} was 274 ± 92 ng/mL.

Heikkinen et al.[53] measured trough concentrations of citalopram and its metabolites desmethylcitalopram and didesmethylcitalopram corrected to a 20-mg daily dose in 11 pregnant women taking 20−40 mg of citalopram once daily. Maternal plasma concentrations remained stable from 20 to 37 weeks' gestation: 25.3 ± 6.8 μg/L at 20−24 weeks; 24.4 ± 5.9 μg/L at 28−32 weeks; and 25.0 ± 8.1 μg/L at 36−37 weeks. Dose-corrected citalopram concentrations obtained 2 weeks and 2 months after delivery were 45.8 ± 8.1 μg/L and 42.9 ± 16.2 μg/L, respectively. The desmethylcitalopram/citalopram ratio was 23% higher ($P = .008$), and didesmethylcitalopram/desmethylcitalopram ratio was 54% higher ($P < .001$) during pregnancy compared to 2 months postpartum. C/M ratios of citalopram, desmethylcitalopram, and didesmethylcitalopram were 0.64, 0.66, and 0.68, respectively. No significant differences were found between umbilical artery and umbilical vein concentrations.

Sit et al.[35] studied three women taking 20−40 mg of racemic citalopram daily. The C/D ratios of S- and R-citalopram were 0.7 ± 0.1 and 1.4 ± 0.2 (ng/mL)/(mg/day) at 20 weeks' gestation, 0.7 ± 0.4 and 1.2 ± 0.4 (ng/mL)/(mg/day) at 30 weeks, 0.4 ± 0.1 and 0.8 ± 0.1 (ng/mL)/(mg/day) at 36 weeks, and 0.3 and 0.5 (ng/mL)/(mg/day) at delivery. C/D ratios increased postpartum to 1.4 and 2.5 (ng/mL)/(mg/day) at 2 weeks postpartum and 0.5 ± 0.2 and 1.3 ± 0.8 (ng/mL)/(mg/day) at 12 weeks postpartum. The primary metabolites, S- and R- desmethylcitalopram, followed similar trends, decreasing during pregnancy and then increasing after delivery. The C/D ratios of S- and R- desmethylcitalopram were 0.3 ± 0.1 and 0.4 ± 0.1 (ng/mL)/(mg/day) at Week 20, 0.4 ± 0.2, and 0.4 ± 0.1 (ng/mL)/(mg/day) at Week 30, 0.2 ± 0.02 and 0.3 ± 0.03 (ng/mL)/(mg/day) at Week 36,

0.1, and 0.1 (ng/mL)/(mg/day) at delivery, 0.4 and 0.5 (ng/mL)/(mg/day) at 2 weeks postpartum, and 0.3 ± 0.1 and 0.4 ± 0.2 (ng/mL)/(mg/day) at 12 weeks postpartum.

Westin et al.[39] analyzed therapeutic drug monitoring data of 58 women who took citalopram during pregnancy. The serum concentration, corrected to 20-mg doses, was 30.4 ng/mL at baseline (nonpregnant) and decreased to 28.9, 25.8 and 23.0 (95% CI, 18.7–28.2) ng/mL at 6, 20, and 34 gestational weeks ($P = .007$). The citalopram/desmethylcitalopram ratio was not significantly different between baseline and Gestational Week 34 (2.6 vs. 2.3; $P = .16$).

Leutritz et al.[42] reported citalopram C/D ratios in four women during and after pregnancy. The mean C/D ratio was 1.71 in the first trimester ($n = 1$), 1.75 in the second trimester ($n = 2$), and 1.76 in the third trimester ($n = 1$). After 2 weeks postpartum, the C/D ratio in one of the patients was 2.63.

O'Brien et al.[37] measured the metabolic ratio of citalopram in the hair of four pregnant women receiving 30–60-mg daily doses. The mean citalopram/desmethylcitalopram ratios were significantly lower in the first (0.89 ± 0.26; $P = .022$) and third (0.9 ± 0.14, $P = .048$) trimesters than postpartum (1.4 ± 0.24).

Citalopram concentrations were generally lower during pregnancy compared to postpartum or nonpregnant individuals. However, only one study reported this as statistically significant.[39] The trend throughout pregnancy and alteration of metabolic ratio were not consistent between studies.

Escitalopram. Escitalopram maternal plasma and cord blood concentrations at delivery were reported in three studies (Table 6). Two studies also reported N-desmethylescitalopram concentrations (Table 6). The range of C/M ratio was 0–0.91 for escitalopram and 0.66–0.8 for the metabolite.

One woman was taking escitalopram (5 mg daily) in the Loughhead et al.[33] study. At 15.4 weeks' gestation, the amniotic fluid concentration of escitalopram was 17.6% that of serum escitalopram concentration (3 ng/mL vs. 17 ng/mL).

Colombo et al.[40] reported plasma concentrations from patients in the third trimester. Two were below the LOQ (5 ng/mL). The other two were 21.8 and 68.8 ng/mL. Among the five women with CYP2C19 genotype and phenotype information, there were two EMs and three IMs. The median C/D ratios at delivery were 0.63 (ng/mL)/(mg/day) for EMs and 3.63 (ng/mL)/(mg/day) for IMs.

Sit et al.[35] reported decreased concentrations of escitalopram in two women studied during pregnancy. One subject taking a 10-mg daily dose had escitalopram

Table 6. Maternal Plasma/Serum and Cord Blood Concentrations of Escitalopram.

				Escitalopram			N-desmethylescitalopram		
Study	*N*	Dose (mg/day)	Study location	Maternal concentration at delivery (ng/mL)	Cord concentration at delivery (ng/mL)	Cord/Maternal ratio	Maternal concentration at delivery (ng/mL)	Cord concentration at delivery (ng/mL)	Cord/Maternal ratio
Rampono et al. (2009)[36,a]	8	20 (10–28)	Australia	21 (12–52)	17 (10–36)	0.73 (0.71–0.91)	13 (9–16)	10 (7–16)	0.70 (0.66–0.80)
Sit et al. (2011)[38]	2	10	USA	5.6; 13.5	0; 6.7	0; 0.5	5.4; 2.6	3.6; 2.0	0.67; 0.77
Colombo et al. (2020)[40,b]	7	10 (5–10)	Italy	9.5 (5–36.5)	7.7 (5–15.9)	0.491; 0.865[c]			

[a] Median (interquartile range).
[b] Median (range).
[c] Only two subjects with data above the limit of quantification (5 ng/mL).

Table 7. Maternal Plasma/Serum and Cord Blood Concentrations of Fluvoxamine

				Fluvoxamine		
Study	*N*	Dose (mg/day)	Study location	Maternal concentration at delivery (ng/mL)	Cord concentration at delivery (ng/mL)	Cord/Maternal ratio
Rampono et al. (2009)[36]	1	150	Australia	27	21	0.78
Sit et al. (2011)[38]	1	200	USA	62.7	4.9	0.08
Hostetter et al. (2000)[28]	1	150	USA	7	5	0.71

plasma concentrations of 17, 10, and 13 ng/mL of escitalopram at 20, 30, and 36 weeks' gestation; 14 ng/mL at delivery; and 24 ng/mL at 2 weeks postpartum. Another subject received a 20-mg daily dose with escitalopram concentrations of 58, 70, and 67 ng/mL at 20, 30, and 36 weeks' gestation; 95 ng/mL at 2 weeks postpartum; and 63 ng/mL at 12 weeks postpartum.

In the Westin study, 95 women took escitalopram during pregnancy.[39] After correcting to a 10-mg daily dose, the estimated serum escitalopram concentrations were 9.3, 9.4, 9.7, and 9.9 (95% CI, 8.0–12.3) ng/mL when nonpregnant and at 6, 20, and 34 gestational weeks. The trend of increase throughout pregnancy was not significant ($P = .55$). The escitalopram/desmethylescitalopram ratio at gestational week 34 was significantly higher than that at baseline (2.5 vs. 1.8; $P = .012$).

In the Leutritz study, eight women were taking escitalopram but only one serum escitalopram concentration was reported in each trimester.[42] The C/D ratio was 1.93, 1.47, and 0.6 in the first, second, and third trimester. Serum concentrations were available for five women after 2 weeks postpartum with mean ± SD C/D ratio of 1.91 ± 1.35.

One study reported a significantly higher escitalopram metabolic ratio in late pregnancy than at baseline, while no trend was observed for escitalopram or desmethylescitalopram concentrations.[39] Other studies had limited sample size and showed no clear trend.

Fluvoxamine. Fluvoxamine PK in pregnancy have been reported in only six women.[28,36,38,39] Two of these evaluated only maternal and cord blood concentrations at delivery in a single woman, with the C/M ratio ranging from 0.08 to 0.78 (Table 7). Hostetter et al.[28] reported a case of a 34-year-old White woman taking fluvoxamine. At 16 weeks, the maternal serum fluvoxamine concentration was 41 ng/mL 18 h after a 100-mg dose. Amniotic fluid obtained 20 h after dosing contained 4 ng/mL of fluvoxamine. At 29 weeks' gestation, the daily dose of fluvoxamine was increased to 150 mg due to increased anxiety. Following a vaginal delivery at 40 weeks' gestation, maternal serum and cord blood concentrations of fluvoxamine obtained 30 h after a 150-mg dose were 7 ng/mL and 5 ng/mL, respectively.

Westin et al.[39] reported concentrations in three women taking fluvoxamine from a therapeutic drug monitoring service. After dose correcting to 100 mg/day, the average concentration of fluvoxamine observed in the nonpregnant state was 117.9 ng/mL and decreased throughout gestation: 101.9, 72.5, and 51.6 (95% CI, 29.3–91.1) ng/mL in Gestational Weeks 6, 20, and 34 ($P = .004$).

Although the sample size was small, fluvoxamine concentrations showed trend of decreasing throughout pregnancy.[28,39]

Serotonin and Norepinephrine Reuptake Inhibitors

Venlafaxine. Plasma concentrations at delivery have been reported in 15 women taking venlafaxine.[36,31,38] A large variability in C/M ratio is noted between individuals and studies (range, 0.14–2.41 for venlafaxine and 0.56–3.35 for O-desmethylvenlafaxine) (Table 8).

Loughhead studied three women taking venlafaxine at a mean daily dose of 200 mg (150–225 mg).[33] Maternal serum samples were collected within 14 days of amniocentesis (16–36.6 weeks' gestation). The average maternal serum concentrations of venlafaxine and O-desvenlafaxine were 50 ± 16.4 and 270.7 ± 126.3 ng/mL. The average venlafaxine and O-desvenlafaxine concentrations in the amniotic fluid were 90 ± 70.24 and 777.67 ± 773.91 ng/mL. The average amniotic fluid/maternal serum ratio of venlafaxine and its metabolite were 1.73 ± 0.91 and 3.00 ± 2.3.

Paulzen et al.[54] reported venlafaxine and O-desmethylvenlafaxine concentration in nine mother–infant pairs on therapeutic drug monitoring (Table 8). The median (range) daily dosage was 75 (37.5–225) mg and the time of measurement after the last dose was 5 (2.5–22) h. The maternal C/D ratios of venlafaxine and O-desmethylvenlafaxine at delivery were 0.13 (0.03–0.89) and 1.39 (0.6–3.75) (ng/mL)/(mg/day). Amniotic fluid samples were available from five subjects. The amniotic fluid/maternal plasma ratio was 2.01 (0.79–3.2) for venlafaxine and 2.81 (1.27–4.82) for O-desmethylvenlafaxine. There was no

Table 8. Maternal Plasma/Serum and Cord Blood Concentrations of Venlafaxine.

				Venlafaxine			O-desmethylvenlafaxine		
Study	*N*	Dose (mg/day)	Study location	Maternal concentration at delivery (ng/mL)	Cord concentration at delivery (ng/mL)	Cord/Maternal ratio	Maternal concentration at delivery (ng/mL)	Cord concentration at delivery (ng/mL)	Cord/Maternal ratio
Rampono et al. (2009)[36,a]	11	225 (150–300)	Australia	45 (23–64)	20 (9–53)	0.72 (0.41–1.11)	256 (151–294)	184 (123–348)	1.08 (0.68–1.17)
Sit et al. (2011)[38]	2	75	USA	100; 28.3	79.9; 46.4	0.8; 1.64	56.4; 188	44.7; 105	0.79; 0.56
Rampono et al. (2004)[31]	1	150	Australia	220	232	1.1	392	406	1
Hostetter et al. (2000)[28]	1[b]	150	USA	335	584; 554	1.74; 1.65	97	304; 325	3.13; 3.35
Paulzen et al. (2020)[54,c]	9	75 (37.5–225)	Germany	18.2 (2–201)	23.4 (2–157)	1.00 (0.78–1.77)	190 (31.9–281)	204 (19.1–425)	1.07 (0.60–2.16)
Colombo et al. (2020)[40,c]	7	75 (37.5–150)	Italy	179.9 (76.8–199.8)	184.8 (78.9–234.7)	0.40 (0.14–2.41)			

[a]Median (interquartile range).
[b]Twins.
[c]Median (range).

significant correlation between venlafaxine daily dose and total concentration of venlafaxine and metabolite in maternal plasma, cord blood, or amniotic fluid.

Seven pregnant women taking extended-release venlafaxine were included in the Colombo study.[40] The median (range) daily dose was 75 mg (37.5–150 mg) and the maternal plasma venlafaxine concentration was 86.1 (37.6–245) ng/mL at the third trimester. Maternal and umbilical plasma concentrations at delivery are reported in Table 8. Genotype and expected phenotype were available from six women with one I/EM whose C/D ratio was 2.06 (ng/mL)/(mg/day) and five EMs whose median C/D ratio was 1.15 (ng/mL)/(mg/day).

Campbell et al. reported venlafaxine PK in 11 women at 36 weeks' gestation.[41] The daily dose ranged from 75 to 262.5 mg. The mean ± SE $AUC_{0\text{-}4.5h}$ was 621 ± 314 (ng/mL) • h and C_{max} was 163 ± 74 ng/mL.

Six studies reported longitudinal changes of venlafaxine PK throughout pregnancy. Hostetter et al.[28] reported a case of a 40-year-old woman with a twin pregnancy taking 100 mg of venlafaxine twice daily. At 17 weeks' gestation, the venlafaxine and O-desmethylvenlafaxine concentrations were 16 and 313 ng/mL 3 h after maternal dose in the amniotic fluid. Venlafaxine dose was increased to 150 mg twice daily because of increased depression and irritability at 30 weeks' gestation. At 36 weeks' gestation, the patient had a cesarean section delivery of twins. The maternal and cord concentrations of venlafaxine and its metabolite at delivery (36 weeks' gestation, 20 h after maternal dose) were 335 and 97 ng/mL, respectively (Table 8).

Klier et al.[34] reported a case of a 17-year-old woman taking 300 mg of quetiapine, 75 mg of extended-released venlafaxine, and 150 mg of extended-released trazodone daily for bipolar disorder and sleep disorder. The plasma concentrations of the three drugs were closely monitored, and AUC and elimination half-life in each trimester were reported. For venlafaxine, the AUC (2.5–11.5 h) was 147, 180, and 204 (ng/mL) • h in the first, second, and third trimesters, respectively. Venlafaxine dose was increased to 150 mg daily immediately postpartum and returned to 75 mg 4 months postpartum. The AUC (2.5–11.5 h) at 6 months postpartum was 600 (ng/mL) • h. Elimination half-life of venlafaxine was calculated to be 8.7, 7.3, 3.2, and 6.5 h in the first, second, and third trimesters and at 6 months postpartum, respectively.

Venlafaxine and O-desmethylvenlafaxine plasma concentrations during pregnancy and in the postpartum period were determined in seven women treated with venlafaxine (37.5–225 mg daily).[55] The median venlafaxine/O-desvenlafaxine ratios were 1.5 (0.44–3.08), 2 (0.85–7.6), 3.3 (2.44–8.0), and 2.2 (0.57–9.20) in the first, second, and third trimesters and 3 months

postpartum, respectively. A significant decrease of venlafaxine concentration ($P = .028$) and significant increase of O-desmethylvenlafaxine/venlafaxine ratio ($P = .018$) were observed during pregnancy compared to postpartum.

In the Westin study, 33 women received venlafaxine during their pregnancy (daily dose corrected to 100 mg).[39] The total serum concentration of venlafaxine and O-desmethylvenlafaxine was 141.8, 135.8, 122.9, and 111.2 (95% CI, 79.6–155.4) ng/mL at baseline and gestational weeks 6, 20, and 34, respectively. The trend of decline was not significant ($P = 0.16$). The metabolic ratio of venlafaxine/O-desmethylvenlafaxine was not significantly different in nonpregnant women compared to pregnant women at 34 weeks' gestation (0.4 vs. 0.3 [95% CI, 0.2–0.5]; $P = .16$).

Venlafaxine maternal serum concentrations were reported in the second and third trimesters and postpartum in the Leutritz study from eight women.[42] The mean C/D ratio was 1.26 in the second trimester ($n = 3$) and 0.96 in the third trimester ($n = 3$). The mean ± SD C/D ratio was 1.9 ± 0.72 within 2 weeks postpartum ($n = 3$) and 2.71 ± 0.08 after 2 weeks postpartum ($n = 2$).

O'Brien et al.[37] measured the metabolic ratio of venlafaxine in hair samples of three women taking 75−300 mg venlafaxine daily. The ratio of venlafaxine to norvenlafaxine (also known as N-desmethylvenlafaxine) was 1.1 ± 0.4 in the first trimester, 0.8 ± 0.2 in the third trimester, and 1.03 ± 0.06 in the postpartum period. The metabolic ratio in neither the first nor third trimester was significantly different from the postpartum period.

One study reported a significantly decreased venlafaxine concentration and increased metabolite/parent drug ratio during pregnancy as compared to postpartum, indicating increased metabolism of venlafaxine.[55] This finding is supported by other studies, which reported similar trends in case reports or small sample sizes.

Duloxetine. Three case reports of duloxetine concentrations in pregnancy were identified. Boyce et al.[56] presented a case of a 31.4-year-old woman taking 60 mg of duloxetine daily for depression throughout pregnancy and while breastfeeding. The maternal and cord serum duloxetine concentration at delivery were 151 and 18 μg/L, resulting in a C/M ratio of 0.12. On Day 18 postpartum, duloxetine concentrations measured 7.6 h after the maternal dose were 245 μg/L in the maternal serum and 2 μg/L in the infant serum, indicating a low transmission of duloxetine through breast milk. In a second case report of a mother taking 60 mg of duloxetine daily, the cord blood concentration at delivery was 65 μg/L.[57] Maternal plasma concentration at delivery was not reported. On Day 32 postpartum, the maternal plasma trough concentration was 24 μg/L 40 min after the dose, and a concentration of 53 μg/L was observed about 6 h after the dose. Leutritz et al.[42] reported maternal duloxetine serum C/D ratio in one person of 1.17 during the first trimester and 0.17 during the second trimester. While evidence is weak, it appears that duloxetine concentrations may be decreased in the third trimester.

Serotonin Antagonist and Reuptake Inhibitors

Trazodone. Trazodone PK data in pregnancy come from two case reports. The first is a 17-year-old woman taking quetiapine, venlafaxine, and 150 mg of extended-release trazodone once daily.[34] The AUC (17.5–26.5 h) of trazadone were 3480, 2469, and 4362 (ng/mL) • h in the first, second, and third trimesters, and elimination half-lives were 12, 12, and 13 h in the first, second, and third trimesters, respectively. A second case is of a 44-year-old woman treated with etizolam and 50 mg trazodone once daily from 28 weeks' gestation.[58] Maternal plasma concentrations of trazodone and its metabolite m-chlorophenylpiperazine (mCPP) were recorded following the last dose before delivery and one dose 4 days postpartum. At delivery, the maternal trazodone and mCPP concentration were 256.1 and 20.1 ng/mL at 6.4 h after dosing, 23.5 and 1.3 ng/mL at 30.5 h after dosing, and below the limit of quantification (BLQ) at 77 h after dosing. Umbilical cord blood trazodone and mCPP concentration were 255.3 and 19.8 ng/mL 7 h after the maternal dose. At 14.2, 41.6, and 83 h after the maternal dose, the trazodone infant serum concentration was 156.6, 7.0, and 4.0 ng/mL, respectively, and the mCPP concentration was 9.8 ng/mL, 0.6 ng/mL, and BLQ, respectively. On Day 4 postpartum, maternal concentrations at 7.4 and 21 h after dosing were 267.6 and 69.3 ng/mL for trazodone, and 22.8 and 7.3 ng/mL for its metabolite.

Tricyclic and Tetracyclic Antidepressants

Clomipramine. Schimmell et al.[59] reported one case of a 27-year-old woman, taking 125 mg of clomipramine daily throughout pregnancy. Maternal and neonatal plasma samples were obtained 10−14 h after the mother's daily dose at delivery and on Days 4, 6, 10, 14, and 35 postpartum. At delivery, the maternal plasma concentration was 474.4 ng/mL, and the neonatal plasma concentration was 266.6 ng/mL. Maternal plasma concentration decreased to 211.0 and 208.4 ng/mL on Days 4 and 6, respectively. The daily dose of clomipramine was increased to 150 mg on Day 8. Maternal plasma concentrations were 355.0, 364.8, and 509.8 ng/mL on Days 10, 14, and 35 postpartum, respectively. The neonate was not breastfed during

the first week of life. Clomipramine concentration in neonatal plasma decreased with a half-life of 92.8 h.

Wisner et al.[26] compared the dose and serum tricyclic antidepressant concentrations in eight women during their third trimester and when they were not pregnant. Serum samples were collected 12−18 h after the dose. One woman in the study was taking clomipramine at a daily dose of 175 mg prior to pregnancy and gradually increased to 275 mg at Gestational Week 30. The dose of 275 mg was maintained through delivery. The C/D ratio of clomipramine plus desmethylclomipramine was 1.71 (ng/mL)/mg clomipramine prior to pregnancy and decreased to 0.98 (ng/mL)/mg during the third trimester.

Loughhead et al.[32] studied seven pregnant women taking clomipramine at a median daily dose of 100 mg (50–175 mg). The mean maternal serum concentrations of clomipramine and desmethylclomipramine at delivery were 76.4 ± 39.3 ng/mL and 103.3 ± 50.1 ng/mL, respectively. The mean C/M ratio of clomipramine was 0.53 ± 0.49 and 0.75 ± 0.52 for the metabolite.

An observational study by Ter Horst et al.[60] included 12 women and 13 pregnancies (one mother had two pregnancies during the study period) who took clomipramine throughout pregnancy. The median daily dose at delivery was 50 mg (25–125 mg). CYP2D6 (fast/normal/intermediate/poor metabolizers, n = 0/5/4/1) and CYP2C19 (fast/normal/poor metabolizers, n = 2/7/1) phenotypes were also reported. Trough concentrations of clomipramine and desmethylclomipramine at steady state were measured in each trimester and postpartum. The median maternal clomipramine C/D ratio decreased from 0.89 (0.03–1.44) (μg/L)/mg to 0.7 (0.03–1.99) (μg/L)/mg from the first to the third trimester and was 0.7 (0.33–1.29) (μg/L)/mg postpartum. The median metabolite concentration also decreased from 0.51 (0.03–1.87) (μg/L)/mg to 0.1 (0.03–1.72) (μg/L)/mg during pregnancy and was 0.58 (0.38–2.78) (μg/L)/mg postpartum. The metabolite/parent ratio was 0.96 (0.07–3.79), 0.77 (0.04–2.50), 0.23 (0.04–2.00), and 1.29 (0.35–3.08) during the first, second, and third trimesters and postpartum, respectively.

One clomipramine concentration was reported at the second trimester, one at the third trimester and two postpartum in the Leutritz et al.[42] study. The C/D ratio was 2.29 and 2.16 at the second and third trimesters, respectively. After 2 weeks postpartum, the mean ± SD C/D ratio was 2.26 ± 0.11.

Clomipramine is metabolized by multiple enzymes (i.e., CYP2D6, CYP2C19, CYP3A4, and 1A2) and shows nonlinear PK at doses above 150 mg, making it difficult to predict the alteration of its PK during pregnancy. Both clomipramine and desmethylclomipramine concentrations in the third trimester appeared to be lower than those postpartum or before pregnancy.[26,60] The desmethylclomipramine/clomipramine ratio decreased during pregnancy, which may be attributed to decreased CYP2C19 and CYP1A2 activity.[60]

Nortriptyline. Sit et al.[38] and Loughhead et al.[32] both measured maternal serum and cord blood concentrations of nortriptyline at delivery (Table 9). The 10-hydroxynortriptyline concentrations were also measured, but most of them were BLQ. The C/M ratio range was 0.25–26.3 for nortriptyline and 0−7.3 for the metabolite.

Six women taking nortriptyline were included in the study by Wisner et al.[26] Prior to pregnancy, the median daily dose was 75 mg (35–150 mg), and the average serum concentrations were 91.2 ± 17.2 ng/mL. In the third trimester, the median daily dose was 100 mg (50–200 mg), and the average serum nortriptyline concentrations were 67.8 ± 22.9 ng/mL. On average, patients required 1.58-fold higher doses during pregnancy to maintain the therapeutic effect.

Two additional case reports described nortriptyline concentrations across gestation and postpartum. In one case, a woman was treated with nortriptyline (125 mg/day) and sertraline (100 mg/day).[27] The woman's nortriptyline concentration was 139−150 ng/mL before pregnancy but was only 50 ng/mL in the sixth month of pregnancy. The daily dose was increased to 150 mg due to recurrence of depressive symptoms. The dose was subsequently decreased to 125 mg/day during the first month postpartum. The nortriptyline C/D ratios were 0.4, 0.54, and 0.51 (ng/mL)/mg at the end of Months 6, 7, and 8 of pregnancy, respectively. The C/D ratios increased to 0.80 (ng/mL)/mg at 2 weeks postpartum and 1.02 (ng/mL)/mg at 4 weeks postpartum. Another case reported the C/D ratios in a 31-year-old woman treated with nortriptyline as 1.1 (μg/L)/mg at 11 weeks' gestation, 1.21 (μg/L)/mg at 30 weeks' gestation, 1.01 (μg/L)/mg at 36 weeks' gestation, 2.45 (μg/L)/mg at 11 weeks postpartum, and 3.0 (μg/L)/mg at 33 weeks postpartum.[61]

Although data are limited, nortriptyline concentrations during pregnancy appear to be lower than those before pregnancy or in the postpartum period. Six of the eight cases required a dose increase during pregnancy due to increased symptoms.

Imipramine. Plasma concentrations of imipramine in pregnancy were reported in two cases. Wisner and colleagues'[26] study included a woman who was taking 150 mg/day of imipramine prior to conception. This dose was maintained through 20 weeks' gestation, when the woman's symptoms began to recur. The dose was gradually increased to 300 mg from

Table 9. Maternal Plasma/Serum and Cord Blood Concentrations of Nortriptyline.

				Nortriptyline			10-hydroxynortriptyline		
Study	*N*	Dose (mg/day)	Study location	Maternal concentration at delivery (ng/mL)	Cord concentration at delivery (ng/mL)	Cord/Maternal ratio	Maternal concentration at delivery (ng/mL)	Cord concentration at delivery (ng/mL)	Cord/Maternal ratio
Sit et al. (2011)[38,c]	1	0[a]	USA	22.6	10.6	0.47	30.8	20.1	0.65
Loughhead et al. (2006)[32,b,d]	10	75 (30–150)	USA	27.8 (1.88–102)	25.5 (2.8–124)	0.84 (0.25–26.3)	18.4 (0–132)	26.1 (0–119)	0.39 (0–7.3)

[a] 75 mg/day at 36 weeks, tapered to 0 mg at delivery.
[b] Median (range).
[c] E-10-hydroxynortriptyline.
[d] Cis-10-hydroxynortriptyline.

20 to 32 weeks. The maternal serum concentration of imipramine prior to pregnancy was 204 ng/mL on 150 mg/day and 276 ng/mL when taking 300 mg/day during the third trimester. In a second case, the patient was stable on 175 mg/day of imipramine with a total blood imipramine and desipramine concentration of 185 ng/mL 6 months before pregnancy.[27] She discontinued imipramine 4 months before pregnancy but restarted on 175 mg of imipramine at 11 weeks' gestation because of the recurrence of significant depressive symptoms. The daily dose was increased to 200 mg at the end of the fifth month of pregnancy and then 275 mg to achieve the pregravid blood concentration. The imipramine C/D ratios were 0.83, 0.61, 0.67, 0.95, and 1.29 (ng/mL)/mg at the end of Months 5, 6, and 7 of pregnancy and 2 and 4 weeks postpartum, respectively. Both cases showed a decreased imipramine level during pregnancy and required dose increase due to recurrence of symptoms.

Amitriptyline. Amitriptyline PK data in pregnancy were identified in only one study, which indicates decreased exposure during pregnancy.[42] The mean C/D ratio was 0.85, 0.53, and 0.53 at the first ($n = 2$), second ($n = 4$), and third ($n = 3$) trimesters. The mean ± SD C/D ratio was 0.87 ± 0.23 and 1.93 ± 1.14 within ($n = 4$) and after 2 weeks postpartum ($n = 9$).

Mirtazapine. Only the Leutritz et al.[42] study reports mirtazapine PK in pregnancy. The mean C/D ratio was 0.73, 0.77, and 0.48 in the first ($n = 1$), second ($n = 2$), and third trimesters ($n = 3$). After 2 weeks postpartum, the mean ± SD C/D ratio was 1.3 ± 0.66 among 4 women. While the sample size is extremely limited, it appears that mirtazapine concentrations are decreased during pregnancy, likely due to increased CYP2D6 and CYP3A4 activity.

Other Antidepressants

Bupropion. Fokina et al.[62,63] conducted two studies on the same cohort of patients. One reports PK in 28 pregnant women, comparing PK parameters between subjects receiving the same dose and formulation of bupropion. The CL/F was 359 ± 389 L/h in the midpregnancy group (22–26 weeks' gestation, $n = 8$) and 321 ± 152 L/h in the late-pregnancy group (34–38 weeks' gestation, $n = 8$). The metabolite/parent ratios of hydroxybupropion (OHBUP), threohydroxybupropion (TB), and erythrohydroxybupropion (EB) in the midpregnancy group trended higher than in the late-pregnancy group, but only the EB/bupropion metabolic ratio was significantly different. A comparison of 12 women during late pregnancy and 12 women postpartum showed higher CL/F in late pregnancy (259 ± 117 L/h) versus postpartum (208 ± 93 L/h).

There was no significant difference between the metabolic ratios of the three metabolites between the two groups. However, the percentage of dose recovered as OHBUP–glucuronide and TB–glucuronide in the late-pregnancy group was higher than in the postpartum group. Genotype of CYP2B6 and CYP2C19 were reported, but no comparison was made between different periods of pregnancy. A second paper by this group reports maternal plasma and umbilical cord blood concentrations from 22 mother–infant dyads in the same cohort.[63] Amniotic fluid samples were available from nine mothers at delivery. The median daily dose of bupropion was 225 mg (75–300 mg). The C/M ratio of bupropion, OHBUP, and TB were 0.53, 0.21, and 0.61, respectively. For the nine women with amniotic fluid samples, the amniotic fluid/maternal plasma concentration ratios of bupropion, OHBUP, and TB were 0.51, 0.14, and 1.34, respectively.

A longitudinal PK study included eight pregnant subjects, seven taking once-daily sustained-release bupropion.[64] One subject took the twice-daily immediate-release dosage form during pregnancy and switched to once-daily dosing postpartum. The median (range) daily dose was 225 mg (150–450 mg). The steady-state maternal C/D ratios; metabolic ratios; formation clearance of TB, EB, and OHBUP; and renal clearance for bupropion, OHBUP, S,S-OHBUP, R,R-OHBUP, TB, and EB were compared in the same subjects in the second trimester versus postpartum and in the third trimester versus postpartum. Considerable interindividual variability was observed. The only significant difference identified between the second or third trimester and postpartum for any PK parameter was a higher EB-OH formation clearance in the second trimester (10.8 L/h vs. 5.1 L/h; $P = .025$). For the three infant–mother pairs with data at delivery, the respective mean C/M ratio for BUP, S,S-OHBUP, R,R-OHBUP, TB, and EB were 0.5 ± 0.1, 0.6 ± 0.2, 0.4 ± 0.1, 0.7 ± 0.1, and 0.6 ± 0.1. Among all the subjects, there was one CYP2B6 rapid metabolizer (*1/*22) and two IMs (*1/*6) with one of them also a CYP2C19 UM (*1/*17). However, the impact of genotype was not studied.

Bupropion can be metabolized by 11β-hydroxysteroid dehydrogenase 1 and carbonyl reductases to EB and TB.[62] CYP2B6 and CYP2C19 catalyze the hydroxylation of bupropion, EB, and TB. OHBUP, EB, and TB also go through glucuronidation.[62] Increased hepatic blood flow, renal clearance, CYP2B6, and uridine diphosphoglucuronosyltransferase activity and decreased CYP2C19 activity all contribute to the change of bupropion metabolism during pregnancy. The decreased EB/bupropion ratio and increased formation clearance of EB-OH during pregnancy may result from increased CYP2B6 activity.[62,64] The insignificant change of OHBUP/bupropion and TB/bupropion ratios may be attributed to the countereffect of increased glucuronidation and increased CYP2B6 activity.[62,64]

Discussion

In general, there are relatively few PK studies of antidepressants in pregnancy, and many of these are of poor quality. Our search identified only a total of 40 articles on 15 drugs, with no PK data available on 17 antidepressants in pregnancy. Most antidepressants appeared in fewer than 10 studies and were studied in fewer than 100 patients. Though selective serotonin reuptake inhibitors and venlafaxine had data from relatively more subjects, about a third of them were from a single retrospective study.[39] Four drugs had data from fewer than 10 patients. Most studies (30/40) were case series or small cohort studies, reporting no more than 10 subjects for each drug. Without sufficient sample size, the study may be underpowered for statistical inference and any reported *P* value may not be reliable. Several studies provided information on metabolite concentrations, parent/metabolite ratios, and genotype. However, due to small sample sizes, studies did not have sufficient power to evaluate changes based on genotype.

The majority of data in pregnancy are obtained at delivery. Ten of the 40 studies reported only drug concentrations at delivery, typically reporting maternal plasma and cord blood drug concentrations and C/M ratios.[29,31,32,36,38,43,54,58,63,65] However, cord and maternal concentrations may not have been captured simultaneously. Data at delivery may not reflect the normal pregnant state because of physiological changes during labor and delivery. Cardiac output increases up to 50% during labor due to uterine contraction[66] and returns to prelabor levels at about 1 h postpartum.[66] The change of cardiac output, as well as fluid intake and other hemodynamic changes due to cesarean section and maternal anesthesia, could impact plasma volume, making concentrations measured at delivery different from a typical third-trimester concentration.

Although 24 studies included longitudinal data with maternal plasma trough concentrations during pregnancy (most in the third trimester), at delivery, and/or postpartum, there was often a large amount of missing data.[26–28,30,34,35,37,39,40,42,45–49,51–53,55,56,59–61,64] For example, a study of paroxetine reported data from 74 subjects total, but data were missing from 20 subjects in the first trimester, 8 in the second trimester, and 4 in the third trimester.[52] Another study of 55 subjects had 27 missing in the third trimester and 11 missing at delivery.[40] This is common for many studies, making

the samples available for longitudinal within-subject comparison even smaller.

Several studies do not sufficiently report information required to evaluate PK data, including times and adequate dose information. While many studies reported PK for patients taking different doses of medication, in one third of such studies, data were not dose corrected or provided at an individual level with dosing information. As the daily dose could be different for each subject or at different time points during pregnancy, this introduces considerable variability of drug and metabolite concentrations, and the direct comparison of concentrations would not be informative. For antidepressants that exhibit nonlinear PK (i.e., fluoxetine, paroxetine, fluvoxamine, duloxetine, and clomipramine), variability in concentration and metabolic ratio introduced by different doses cannot be eliminated by dose correction and may require more sophisticated analysis like population or physiologically based PK (PBPK) modeling. Sample collection time was not well documented in many studies, including longitudinal studies. Only five of the 10 delivery-only studies and four of the 24 longitudinal studies provided the exact time of sample collection after last-dose administration, and four of them were case reports.[28,34,56,58] There were another six longitudinal studies that reported range or mean and SD of sample collection time.[26,39,40,42,46,59] For other studies, it was unclear if the reported concentrations were true trough concentrations. Even if the steady state was reached at the time of sampling, the drug concentration still could vary considerably, particularly for drugs with short half-lives like venlafaxine. Difference in sampling time could also introduce variability to metabolic ratios and C/M or amniotic fluid/maternal plasma ratios, due to delay in the formation of metabolites or the distribution to cord blood or amniotic fluid. Only four studies collected rich samples (5–18 samples) after a single dose or at steady state and reported PK parameters such as C_{max}, half-life, AUC, CL/F, and apparent volume of distribution V/F.[41,44,50,62] The Campbell study only reported PK data at 36 weeks' gestation.[41] The Carvalho study reported PK data of fluoxetine in the third trimester (32–34 weeks' gestation) with single concentration at delivery.[50] The other two studies reported longitudinal PK data in the second trimester, third trimester, and postpartum.[44,62] In another case report, AUC and half-life were reported, but it was unclear how many plasma samples were collected for monitoring.[34] In a recent bupropion study, a single steady-state plasma sample and dosing interval urine sample were collected, and renal clearances and steady-state concentrations of bupropion and its metabolites were reported.[64]

Highly polymorphic enzymes such as CYP2C19, CYP2D6, and CYP2B6 play important role in the metabolism of many antidepressants, and changes in metabolism by these enzymes during pregnancy is likely to be dependent on genotype. Among the seven studies reporting genotypes of metabolizing enzymes for each subject, one showed impact of CYP2C19 genotypes on sertraline concentrations throughout pregnancy,[46] and one showed opposite effects on paroxetine concentrations during pregnancy based on CYP2D6 genotype.[52] The other five studies either had limited sample size or missing data[40,61] or did not analyze the impact of genetic polymorphisms on longitudinal change of PK during pregnancy.[60,62,64] While other studies did not evaluate genotype, it is possible that pharmacogenomics may play a role in variability between patients and studies for other antidepressants.

About half of the studies reported cord blood drug concentrations at delivery, which covered most of the drugs except amitriptyline and mirtazapine. All the drugs were detected in cord blood, while the concentrations were usually lower than the maternal plasma concentrations. Amniotic fluid concentrations were reported for 65 subjects in seven articles.[28,33,43,50,54,63,65] Amniotic fluid samples were collected at delivery in five studies.[43,50,54,63,65] Two studies reported concentrations obtained during amniocentesis, usually during the second trimester.[28,33] In general, amniotic fluid concentrations were lower than maternal plasma concentration, with the exceptions of venlafaxine,[33,54] citalopram,[65] and threohydroxybupropion.[63] In four of the five studies with both amniotic fluid and umbilical cord blood collected at delivery, the penetration ratios of amniotic fluid were higher than that of cord blood.

One study used the ratio of drug/metabolite concentration in hair to demonstrate the change of antidepressant metabolism during pregnancy.[37] Hair analysis is useful for retrospective investigation of long-term drug exposure and is widely used in forensic toxicology[67] to describe changes in nicotine metabolism,[68] and as a biomarker of adherence for antiretroviral drugs.[69,70] Hair analysis is advantageous, as it is a noninvasive approach and provides a long-term assessment of drug and metabolite exposure. However, high variability of drug concentration could be observed due to differences in the physicochemical property of the drug, hair color, hair growth rate, environmental contamination, or cosmetic treatment.[67,71,72] Wang et al.[73] demonstrated the correlation of hair concentration with history of drug administration and accumulated dose for citalopram but not for sertraline, which may be attributed to the higher lipophilicity of sertraline. Caution should be taken

with the analysis and interpretation of hair drug concentration.

The majority of the drugs covered in this review showed decreased exposure and required increased dosing during pregnancy compared to the postpartum period. Some antidepressants also had decreased parent/metabolite ratio, indicating increased metabolism during pregnancy, which may be attributed to the increased activity of CYP3A4, CYP2D6, CYP2C9, and CYP2B6.[13] On the other hand, this can be countered by the decrease in CYP2C19 and CYP1A2 activity, which can make the PK changes of antidepressants in pregnancy difficult to predict. For drugs with high plasma protein binding, pregnancy-induced decrease of albumin could also impact their distribution and metabolism.

One limitation of our study is that the literature search may not be exhaustive. There could be missing articles, particularly those that were not designed for PK purposes but reported drug concentrations in pregnancy. As we included only articles from PubMed, additional PK data may be available in abstracts and other presentations. This review focused only on exposure data. Studies on drug efficacy and toxicity, including teratogenic risks, were outside of the scope of the review.

PK data in pregnancy are critical to help inform optimal dosing and understanding of fetal exposure, improving efficacy and safety of antidepressants in both the mothers and the fetuses. Literature data can be integrated to inform pharmacometric approaches, such as PBPK modeling, to model and predict changes in PK across pregnancy. However, as identified in our analysis, deficits in reporting critical details such as dose and dosing or sampling times limits the reusability of these data. Our analysis highlights the limited PK data available for many antidepressants in pregnancy. Studies reported that data should be made available in a public repository, such as the Data and Specimen Hub.[74]

Whereas additional longitudinal PK studies throughout pregnancy with larger sample sizes would be beneficial in understanding the effect of pregnancy on maternal PK, even small data sets or case reports can be valuable to pharmacometric modeling efforts if sufficient detail is provided. Future efforts from our group will build on a mechanistic understanding of the pharmacological (i.e., absorption, distribution, metabolism, excretion, and toxicity) properties of drugs and physiologic changes in pregnancy, to develop PBPK models of antidepressants in pregnancy.[75] Through integration of reported data with these mechanistic models, future studies can be designed to support more personalized and efficacious dosing of antidepressants in pregnancy.

Conflicts of Interest

The authors declare no conflicts of interest.

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Data Availability Statement

To help expand the knowledge base for maternal-pediatric medicine, the MPRINT Hub is pleased to share data from its completed and published studies with interested investigators. For requests, please contact Sara K. Quinney at squinney@iu.edu. In addition, data from this review will be made available through the MPRINT Hub Knowledge Portal, available at mprint.org.

References

1. Weissman MM, Olfson M. Depression in women: implications for health care research. *Science*. 1995;269(5225):799-801.
2. Witt WP, DeLeire T, Hagen EW, et al. The prevalence and determinants of antepartum mental health problems among women in the USA: a nationally representative population-based study. *Arch Womens Ment Health*. 2010;13(5):425-437.
3. Dietz PM, Williams SB, Callaghan WM, Bachman DJ, Whitlock EP, Hornbrook MC. Clinically identified maternal depression before, during, and after pregnancies ending in live births. *Am J Psychiatry*. 2007;164(10):1515-1520.
4. Farr SL, Bitsko RH, Hayes DK, Dietz PM. Mental health and access to services among US women of reproductive age. *Am J Obstet Gynecol*. 2010;203(6):542.e1-9.
5. Le Strat Y, Dubertret C, Le Foll B. Prevalence and correlates of major depressive episode in pregnant and postpartum women in the United States. *J Affect Disord*. 2011;135(1-3):128-138.
6. Byatt N, Xiao RS, Dinh KH, Waring ME. Mental health care use in relation to depressive symptoms among pregnant women in the USA. *Arch Womens Ment Health*. 2016;19(1):187-191.
7. Guo N, Robakis T, Miller C, Butwick A. Prevalence of depression among women of reproductive age in the United States. *Obstet Gynecol*. 2018;131(4):671-679.
8. Liu D, Younger E, Baker S, Touch S, Willmoth T, Hartos JL. Does current general mental health status relate to current smoking status in pregnant women? *J Pregnancy*. 2019;2019:7801465.
9. Vesga-López O, Blanco C, Keyes K, Olfson M, Grant BF, Hasin DS. Psychiatric disorders in pregnant and postpartum women in the United States. *Arch Gen Psychiatry*. 2008;65(7):805-815.
10. Ko JY, Farr SL, Dietz PM, Robbins CL. Depression and treatment among U.S. pregnant and nonpregnant women of reproductive age, 2005–2009. *J Womens Health (Larchmt)*. 2012;21(8):830-836.
11. Angelotta C, Wisner KL. Treating depression during pregnancy: are we asking the right questions? *Birth Defects Res*. 2017;109(12):879-887.

12. Marks C, Silvola R, Teal E, Quinney SK, Haas DM. Comparing newborn outcomes after prenatal exposure to individual antidepressants: a retrospective cohort study. *Pharmacotherapy*. 2021; Nov;41(11):907-914.
13. Pariente G, Leibson T, Carls A, Adams-Webber T, Ito S, Koren G. Pregnancy-associated changes in pharmacokinetics: a systematic review. *PLoS Med*. 2016;13(11):e1002160.
14. Matsui DM. Therapeutic drug monitoring in pregnancy. *Ther Drug Monit*. 2012;34(5):507-511.
15. Grigoriadis S, VonderPorten EH, Mamisashvili L, et al. Antidepressant exposure during pregnancy and congenital malformations: is there an association? A systematic review and meta-analysis of the best evidence. *J Clin Psychiatry*. 2013;74(4):e293-308.
16. Grigoriadis S, VonderPorten EH, Mamisashvili L, et al. The effect of prenatal antidepressant exposure on neonatal adaptation: a systematic review and meta-analysis. *J Clin Psychiatry*. 2013;74(4):e309-20.
17. Ewing G, Tatarchuk Y, Appleby D, Schwartz N, Kim D. Placental transfer of antidepressant medications: implications for postnatal adaptation syndrome. *Clin Pharmacokinet*. 2015;54(4):359-370.
18. Womersley K, Ripullone K, Agius M. What are the risks associated with different Selective Serotonin Re-uptake Inhibitors (SSRIs) to treat depression and anxiety in pregnancy? An evaluation of current evidence. *Psychiatr Danub*. 2017;29(3):629-644.
19. Suarez EA, Bateman BT, Hernandez-Diaz S, et al. Association of antidepressant use during pregnancy with risk of neurodevelopmental disorders in children. *JAMA Intern Med*. 2022;182(11):1149-1160.
20. Huybrechts KF, Palmsten K, Avorn J, et al. Antidepressant use in pregnancy and the risk of cardiac defects. *N Engl J Med*. 2014;370(25):2397-407.
21. Cohen LS, Altshuler LL, Harlow BL, et al. Relapse of major depression during pregnancy in women who maintain or discontinue antidepressant treatment. *Jama*. 2006;295(5):499-507.
22. Vlenterie R, van Gelder M, Anderson HR, et al. Associations between maternal depression, antidepressant use during pregnancy, and adverse pregnancy outcomes: an individual participant data meta-analysis. *Obstet Gynecol*. 2021;138(4):633-646.
23. Lebin LG, Novick AM. Selective Serotonin Reuptake Inhibitors (SSRIs) in pregnancy: an updated review on risks to mother, fetus, and child. *Curr Psychiatry Rep*. 2022;24(11):687-695.
24. Alwan S, Friedman JM, Chambers C. Safety of selective serotonin reuptake inhibitors in pregnancy: a review of current evidence. *CNS Drugs*. 2016;30(6):499-515.
25. Ornoy A, Weinstein-Fudim L, Ergaz Z. Antidepressants, antipsychotics, and mood stabilizers in pregnancy: what do we know and how should we treat pregnant women with depression. *Birth Defects Res*. 2017;109(12):933-956.
26. Wisner KL, Perel JM, Wheeler SB. Tricyclic dose requirements across pregnancy. *Am J Psychiatry*. 1993;150(10):1541-1542.
27. Altshuler LL, Hendrick VC. Pregnancy and psychotropic medication: changes in blood levels. *J Clin Psychopharmacol*. 1996;16(1):78-80.
28. Hostetter A, Ritchie JC, Stowe ZN. Amniotic fluid and umbilical cord blood concentrations of antidepressants in three women. *Biol Psychiatry*. 2000;48(10):1032-1034.
29. Hendrick V, Stowe ZN, Altshuler LL, Hwang S, Lee E, Haynes D. Placental passage of antidepressant medications. *Am J Psychiatry*. 2003;160(5):993-996.
30. Laine K, Heikkinen T, Ekblad U, Kero P. Effects of exposure to selective serotonin reuptake inhibitors during pregnancy on serotonergic symptoms in newborns and cord blood monoamine and prolactin concentrations. *Arch Gen Psychiatry*. 2003;60(7):720-726.
31. Rampono J, Proud S, Hackett LP, Kristensen JH, Ilett KF. A pilot study of newer antidepressant concentrations in cord and maternal serum and possible effects in the neonate. *Int J Neuropsychopharmacol*. 2004;7(3):329-334.
32. Loughhead AM, Stowe ZN, Newport DJ, Ritchie JC, DeVane CL, Owens MJ. Placental passage of tricyclic antidepressants. *Biol Psychiatry*. 2006;59(3):287-290.
33. Loughhead AM, Fisher AD, Newport DJ, et al. Antidepressants in amniotic fluid: another route of fetal exposure. *Am J Psychiatry*. 2006;163(1):145-147.
34. Klier CM, Mossaheb N, Saria A, Schloegelhofer M, Zernig G. Pharmacokinetics and elimination of quetiapine, venlafaxine, and trazodone during pregnancy and postpartum. *J Clin Psychopharmacol*. 2007;27(6):720-722.
35. Sit DK, Perel JM, Helsel JC, Wisner KL. Changes in antidepressant metabolism and dosing across pregnancy and early postpartum. *J Clin Psychiatry*. 2008;69(4):652-658.
36. Rampono J, Simmer K, Ilett KF, et al. Placental transfer of SSRI and SNRI antidepressants and effects on the neonate. *Pharmacopsychiatry*. 2009;42(3):95-100.
37. O'Brien L, Baumer C, Thieme D, Sachs H, Koren G. Changes in antidepressant metabolism in pregnancy evidenced by metabolic ratios in hair: a novel approach. *Forensic Sci Int*. 2010;196(1-3):93-96.
38. Sit D, Perel JM, Wisniewski SR, Helsel JC, Luther JF, Wisner KL. Mother-infant antidepressant concentrations, maternal depression, and perinatal events. *J Clin Psychiatry*. 2011;72(7):994-1001.
39. Westin AA, Brekke M, Molden E, Skogvoll E, Spigset O. Selective serotonin reuptake inhibitors and venlafaxine in pregnancy: changes in drug disposition. *PLoS One*. 2017;12(7):e0181082.
40. Colombo A, Giordano F, Giorgetti F, et al. Correlation between pharmacokinetics and pharmacogenetics of selective serotonin reuptake inhibitors and selective serotonin and noradrenaline reuptake inhibitors and maternal and neonatal outcomes: results from a naturalistic study in patients with affective disorders. *Hum Psychopharmacol*. 2020:e2772.
41. Campbell KSJ, Collier AC, Irvine MA, et al. Maternal serotonin reuptake inhibitor antidepressants have acute effects on fetal heart rate variability in late gestation. *Front Psychiatry*. 2021;12:680177.
42. Leutritz AL, van Braam L, Preis K, et al. Psychotropic medication in pregnancy and lactation and early development of exposed children. *Br J Clin Pharmacol*. 2023;89(2):737-750.
43. Paulzen M, Goecke TW, Stickeler E, Grunder G, Schoretsanitis G. Sertraline in pregnancy - therapeutic drug monitoring in maternal blood, amniotic fluid and cord blood. *J Affect Disord*. 2017;212:1-6.
44. Freeman MP, Nolan PE, Jr., Davis MF, et al. Pharmacokinetics of sertraline across pregnancy and postpartum. *J Clin Psychopharmacol*. 2008;28(6):646-653.
45. Heinonen E, Blennow M, Blomdahl-Wetterholm M, et al. Sertraline concentrations in pregnant women are steady and the drug transfer to their infants is low. *Eur J Clin Pharmacol*. 2021; Sep;77(9):1323-1331.
46. Stika CS, Wisner KL, George AL, Jr., et al. Changes in sertraline plasma concentrations across pregnancy and postpartum. *Clin Pharmacol Ther*. 2022;112(6):1280-1290.
47. Heikkinen T, Ekblad U, Palo P, Laine K. Pharmacokinetics of fluoxetine and norfluoxetine in pregnancy and lactation. *Clin Pharmacol Ther*. 2003;73(4):330-337.

48. Kim J, Riggs KW, Misri S, et al. Stereoselective disposition of fluoxetine and norfluoxetine during pregnancy and breastfeeding. *Br J Clin Pharmacol*. 2006;61(2):155-163.
49. Sit D, Perel JM, Luther JF, Wisniewski SR, Helsel JC, Wisner KL. Disposition of chiral and racemic fluoxetine and norfluoxetine across childbearing. *J Clin Psychopharmacol*. 2010;30(4):381-386.
50. Carvalho DM, Lanchote VL, Filgueira GCO, et al. Pharmacokinetics and transplacental transfer of fluoxetine enantiomers and their metabolites in pregnant women. *Clin Pharmacol Ther*. 2019;105(4):1003-1008.
51. Oberlander TF, Misri S, Fitzgerald CE, Kostaras X, Rurak D, Riggs W. Pharmacologic factors associated with transient neonatal symptoms following prenatal psychotropic medication exposure. *J Clin Psychiatry*. 2004;65(2):230-237.
52. Ververs FF, Voorbij HA, Zwarts P, et al. Effect of cytochrome P450 2D6 genotype on maternal paroxetine plasma concentrations during pregnancy. *Clin Pharmacokinet*. 2009;48(10):677-683.
53. Heikkinen T, Ekblad U, Kero P, Ekblad S, Laine K. Citalopram in pregnancy and lactation. *Clin Pharmacol Ther*. 2002;72(2):184-191.
54. Paulzen M, Schoretsanitis G, Gründer G, Franz C, Stingl JC, Augustin M. Pregnancy exposure to venlafaxine-Therapeutic drug monitoring in maternal blood, amniotic fluid and umbilical cord blood and obstetrical outcomes. *J Affect Disord*. 2020;266:578-584.
55. ter Horst PG, Larmené-Beld KH, Bosman J, van der Veen EL, Wieringa A, Smit JP. Concentrations of venlafaxine and its main metabolite O-desmethylvenlafaxine during pregnancy. *J Clin Pharm Ther*. 2014;39(5):541-544.
56. Boyce PM, Hackett LP, Ilett KF. Duloxetine transfer across the placenta during pregnancy and into milk during lactation. *Arch Womens Ment Health*. 2011;14(2):169-172.
57. Briggs GG, Ambrose PJ, Ilett KF, Hackett LP, Nageotte MP, Padilla G. Use of duloxetine in pregnancy and lactation. *Ann Pharmacother*. 2009;43(11):1898-1902.
58. Saito J, Ishii M, Mito A, et al. Trazodone levels in maternal serum, cord blood, breast milk, and neonatal serum. *Breastfeed Med*. 2021;16(11):922-925.
59. Schimmell MS, Katz EZ, Shaag Y, Pastuszak A, Koren G. Toxic neonatal effects following maternal clomipramine therapy. *J Toxicol Clin Toxicol*. 1991;29(4):479-484.
60. Ter Horst PG, Proost JH, Smit JP, Vries MT, de Jong-van de Berg LT, Wilffert B. Pharmacokinetics of clomipramine during pregnancy. *Eur J Clin Pharmacol*. 2015;71(12):1493-1500.
61. Osborne LM, Birndorf CA, Szkodny LE, Wisner KL. Returning to tricyclic antidepressants for depression during childbearing: clinical and dosing challenges. *Arch Womens Ment Health*. 2014;17(3):239-46.
62. Fokina VM, Xu M, Rytting E, et al. Pharmacokinetics of bupropion and its pharmacologically active metabolites in pregnancy. *Drug Metab Dispos*. 2016;44(11):1832-1838.
63. Fokina VM, West H, Oncken C, et al. Bupropion therapy during pregnancy: the drug and its major metabolites in umbilical cord plasma and amniotic fluid. *Am J Obstet Gynecol*. 2016;215(4):497.e1-7.
64. Fay EE, Czuba LC, Sager JE, Shum S, Stephenson-Famy A, Isoherranen N. Pregnancy has no clinically significant effect on the pharmacokinetics of bupropion or its metabolites. *Ther Drug Monit*. 2021;43(6):780-788.
65. Paulzen M, Goecke TW, Stingl JC, et al. Pregnancy exposure to citalopram - therapeutic drug monitoring in maternal blood, amniotic fluid and cord blood. *Prog Neuropsychopharmacol Biol Psychiatry*. 2017;79(Pt B):213-219.
66. Ouzounian JG, Elkayam U. Physiologic changes during normal pregnancy and delivery. *Cardiol Clin*. 2012;30(3):317-329.
67. Methling M, Krumbiegel F, Hartwig S. Hair analysis of antidepressants and antipsychotics-overview of quantitative data. *Drug Test Anal*. 2020;12(6):659-676.
68. Koren G, Blanchette P, Lubetzky A, Kramer M. Hair nicotine:cotinine metabolic ratio in pregnant women: a new method to study metabolism in late pregnancy. *Ther Drug Monit*. 2008;30(2):246-248.
69. Bartelink IH, Savic RM, Mwesigwa J, et al. Pharmacokinetics of lopinavir/ritonavir and efavirenz in food insecure HIV-infected pregnant and breastfeeding women in Tororo, Uganda. *J Clin Pharmacol*. 2014;54(2):121-132.
70. Zhang Q, Li X, Qiao S, Yang X. Factors related to hair antiretroviral concentration: a systematic review of global literature. *AIDS Rev*. 2020;22(1):25-33.
71. Pragst F, Balikova MA. State of the art in hair analysis for detection of drug and alcohol abuse. *Clin Chim Acta*. 2006;370(1-2):17-49.
72. Wong D, Cazabon S, Ali H, et al. Can the sequential use of conventional silicone oil and heavy oil be a strategy for the management of proliferative vitreoretinopathy? *Ann Acad Med Singap*. 2006;35(3):181-184.
73. Wang X, Johansen SS, Nielsen MKK, Linnet K. Segmental hair analysis-interpretation of the time of drug intake in two patients undergoing drug treatment. *J Forensic Sci*. 2019;64(3):950-955.
74. Data and Specimen Hub (DASH). Eunice Kennedy Shriver National Institute of Child Health and Human Development. https://dash.nichd.nih.gov/
75. Quinney SK, Bies RR, Grannis SJ, et al. The MPRINT hub data, model, knowledge and research coordination center: bridging the gap in maternal-pediatric therapeutics research through data integration and pharmacometrics. *Pharmacotherapy*. 2023;43(5):391-402.
76. DeVane CL, Liston HL, Markowitz JS. Clinical pharmacokinetics of sertraline. *Clin Pharmacokinet*. 2002;41(15):1247-1266.
77. Zoloft (sertraline hydrochloired) [package insert]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/019839S74S86S87_20990S35S44S45lbl.pdf
78. Altamura AC, Moro AR, Percudani M. Clinical pharmacokinetics of fluoxetine. *Clin Pharmacokinet*. 1994;26(3):201-214.
79. Prozac (fluoxetine hydrochloride) [package insert]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/018936s111lbl.pdf
80. Paxil (paroxetine hydrochloride) [package insert]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/020031s012,020710s047lbl.pdf
81. Sangkuhl K, Klein TE, Altman RB. PharmGKB summary: citalopram pharmacokinetics pathway. *Pharmacogenet Genomics*. 2011;21(11):769-772.
82. Celexa®(citalopram hydrobromide) [package insert]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/020822s042,021046s019lbl.pdf
83. Rao N. The clinical pharmacokinetics of escitalopram. *Clin Pharmacokinet*. 2007;46(4):281-290.
84. Lexapro® (escitalopram oxalate) [package insert]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/021323s047lbl.pdf
85. Perucca E, Gatti G, Spina E. Clinical pharmacokinetics of fluvoxamine. *Clin Pharmacokinet*. Sep 1994;27(3):175-190.
86. Magalhães P, Alves G, Llerena A, Falcão A. Venlafaxine pharmacokinetics focused on drug metabolism and potential biomarkers. *Drug Metabol Drug Interact*. 2014;29(3):129-141.

87. Effexor® (venlafaxine hydrochloride) [package insert]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2008/020151s051lbl.pdf
88. Cymbalta (duloxetine hydrochloride) [package insert]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2004/21427lbl.pdf
89. Trazodone medical review. Center for drug evaluation and research. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022411s000MedR.pdf
90. Nielsen KK, Flinois JP, Beaune P, Brosen K. The biotransformation of clomipramine in vitro, identification of the cytochrome P450s responsible for the separate metabolic pathways. *J Pharmacol Exp Ther*. 1996;277(3):1659-1664.
91. Anafranil (clomipramine hydrochloride) [package insert]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/019906s043lbl.pdf
92. Amitriptyline [package insert]. https://s3-us-west-2.amazonaws.com/drugbank/fda_labels/DB00321.pdf?1519147983
93. Alexanderson B. Pharmacokinetics of nortriptyline in man after single and multiple oral doses: the predictability of steady-state plasma concentrations from single-dose plasma-level data. *Eur J Clin Pharmacol*. 1972;4(2):82-91.
94. Jerling M, Merlé Y, Mentré F, Mallet A. Population pharmacokinetics of nortriptyline during monotherapy and during concomitant treatment with drugs that inhibit CYP2D6–an evaluation with the nonparametric maximum likelihood method. *Br J Clin Pharmacol*. 1994;38(5):453-462.
95. Sallee FR, Pollock BG. Clinical pharmacokinetics of imipramine and desipramine. *Clin Pharmacokinet*. 1990;18(5):346-364.
96. Remeron (mirtazapine) [package insert]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/020415s023s024.pdf
97. Davis R, Wilde MI. Mirtazapine : a review of its pharmacology and therapeutic potential in the management of major depression. *CNS Drugs*. 1996;5(5):389-402.
98. Wellbutrin (bupropion hydrochloride) [package insert]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/018644s054lbl.pdf
99. Costa R, Oliveira NG, Dinis-Oliveira RJ. Pharmacokinetic and pharmacodynamic of bupropion: integrative overview of relevant clinical and forensic aspects. *Drug Metab Rev*. 2019;51(3):293-313.

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