Received: 8 May 2022 | Revised: 21 August 2022 | Accepted: 6 September 2022

DOI: 10.1111/bcp.15533

ORIGINAL ARTICLE

Psychotropic medication in pregnancy and lactation and early development of exposed children

Anna Linda Leutritz[1] | Lara van Braam[1] | Katharina Preis[2] | Andrea Gehrmann[1] | Maike Scherf-Clavel[1] | Katrin Fiedler[2] | Stefan Unterecker[1] | Sarah Kittel-Schneider[1,2]

[1]Department of Psychiatry, Psychotherapy and Psychosomatic Medicine, University Hospital Würzburg, University of Würzburg, Würzburg, Germany

[2]Department of Psychiatry, Psychotherapy and Psychosomatic Medicine, University Hospital Frankfurt, Goethe-University, Frankfurt, Germany

Correspondence
Sarah Kittel-Schneider, Department of Psychiatry, Psychosomatic Medicine and Psychotherapy, University Hospital Würzburg, Margarete-Höppel-Platz 1, D-97080 Würzburg, Germany.
Email: kittel_s@ukw.de

There is still limited knowledge about alterations of blood concentrations of psychotropic drugs during pregnancy, the transfer of psychotropic drugs into breastmilk and the effects on exposed children. We investigated changes in concentrations of psychopharmacological medication during pregnancy and lactation in serum and breastmilk at different time points in a naturalistic sample of 60 mothers and observed the development of the exposed children in the first 12 months. We found a decrease in serum concentrations from the first to the second trimester of amitriptyline, duloxetine, escitalopram, quetiapine and sertraline. Citalopram stayed rather stable during pregnancy, sertraline levels interestingly increased again from the second to the third trimester. High concentration-by-dose ratios in breastmilk were found for venlafaxine as well as lamotrigine, low for quetiapine and clomipramine. Similarly, clomipramine and quetiapine showed low milk/serum–penetration ratios. Regarding the birth outcome measures in children, we found no significant differences between in utero exposed compared to nonexposed newborns. There were no significant differences in the development in the first 12 months. Psychotropic medication in the peripartum needs a balancing of risks and benefits and a continuous therapeutic drug monitoring can be a guidance for clinicians to monitor drug alteration patterns, which are likely to occur due to physiological pregnancy-associated changes in pharmacokinetics. Accordingly, therapeutic drug monitoring can optimize a medication in pregnancy and lactation with the lowest effective dose.

KEYWORDS
antidepressants, child development, lactation, mental disorders, peripartum, pregnancy, psychotropic medication

Anna Linda Leutritz, Lara van Braam and Katharina Preis contributed equally to this work.

The authors confirm that the Principal Investigator for this paper is S.K.S. and that she had direct clinical responsibility for included patients.

1 | INTRODUCTION

Treatment with antidepressants in pregnancy and lactation is an increasing issue due to the rising numbers of antidepressant prescriptions to women of childbearing age.[1] Furthermore, women in industrial nations are significantly older when giving birth to their first child which increases the risk of a history of either a depressive, anxiety or obsessive compulsive disorder, and treatment with antidepressants and other psychotropic medication before children are born (for example, in Germany, retrieved on the 16 April 2022: https://www.bib.bund.de/DE/Fakten/Fertilitaet/Alter-Familienstand.html). Several studies and meta-analyses have already shown that most antidepressants are not associated with risks of teratogenicity; only **fluoxetine** and **paroxetine** have been repeatedly associated with small risk of birth defects.[2] However, there are few insights into the long-term effects of antidepressant exposure during pregnancy on the development of the children later in life. Additionally, there are few published data about the use of antidepressant medication in breast feeding and potential short- and long-term impacts on the exposed children. Breastmilk is the gold standard of nutrition for newborns and babies according to the World Health Organization (WHO) and the American Academy of Pediatrics (*Global strategy for infant and young child feeding*. Geneva. WHO; http://www.who.int/nutrition/publications/gs_infant_feeding_text_eng.pdf. Accessed 22.1.19). Breastmilk is recommended as the only nutritional source in the first 6 month of life because the evidence for several health outcomes is strong for the children: breastfed children are at lower risk of infections and have a decreased risk for obesity, diabetes mellitus type II, allergic asthma and other atopic diseases later in life.[3–5] Furthermore, mothers also have beneficial health effects from breastfeeding: faster involution of the uterus has been described as well as faster postnatal weight loss, and less postnatal bleeding complication. In the long term, there are hints of a decreased risk of metabolic syndrome as well as breast and ovarian cancers.[6] Additionally, a very recent meta-analysis described a reduced risk for cardiovascular and cerebrovascular disease for women who have breastfed.[7]

Regarding breastfeeding and antidepressant medication, a risk–benefit analysis is required, weighing the beneficial and health protective effects of breastfeeding against the potential negative influences of antidepressant concentrations in breastmilk.

The gold standard of studies——a prospective, randomized and double-blind controlled study——investigating long-term effects of antidepressant exposure in pregnancy and lactation is not feasible due to severe ethical issues. Still, there is evidence that insufficiently or untreated mental disorders in mothers (and fathers) have a negative impact on the development of the children and increase the risk of mental disorders of the children later in life.[8] Previous studies have hinted at several serotonin reuptake inhibitors (SSRIs) such as **sertraline**, **citalopram** and paroxetine as being relatively safe medications during lactation.[9,10] **Duloxetine** seems to be acceptable as a serotonin–noradrenalin-reuptake inhibitor for breastfeeding mothers.[11] Although a medication with **venlafaxine** leads to relatively high concentrations in breastmilk, there were no adverse effects shown in exposed babies and thus, venlafaxine is not completely contraindicated.[12] Most interestingly, a case series of medication with **mirtazapine** during pregnancy ($n = 54$) reports a shorter duration of neonatal adaptation symptoms in breastfed children in comparison with nonbreastfed children.[13] However, there is a lack of knowledge about long-term effects on the development of the children exposed to antidepressants in pregnancy and lactation. Additionally, it is not clear if there should be recommendation about prescribed dosages in lactation and the timing of the intake of the medication and the feeding of the children. Therefore, with our naturalistic study, we aimed to: (i) investigate serum concentration changes of psychopharmacological medication during pregnancy; (ii) explore correlations of dosage, steady state through levels in serum and steady state through

What is already known about this subject

- Pregnancy and peripartum are a vulnerable phase, especially for patients with mental illnesses. The medication should be based on a risk–benefit analysis for mother and (unborn) child.
- Little is known about changes in serum concentrations of psychotropic drugs during pregnancy, about the passage into breastmilk, and long-term effects on exposed children. There are no recommendations about prescribed dosages in lactation and the timing of the medication intake in relation to the timing of breastfeeding.
- We aimed at investigating serum concentration changes of antidepressants as well as quetiapine, aripirazole and lamotrigine during pregnancy, milk/–plasma penetration ratios at different time points during lactation and the development of exposed children (in utero and/or through lactation) in a naturalistic study.

What this study adds

- Most of the analysed medication showed a decrease of serum concentrations from the first to the second trimester. Concentration-by-dose ratios in breastmilk and milk/serum–penetration ratios were low for clomipramine and quetiapine, high concentration-by-dose ratios in breastmilk were found for venlafaxine and lamotrigine.
- Regarding the birth outcome measures and development of the children in the first 12 months, there were no clinically relevant differences between exposed and nonexposed children.
- Psychotropic medication in the peripartum needs a balancing of risks and benefits and /continuous therapeutic drug monitoring can optimize a medication in pregnancy and lactation with the lowest but effective dose.

levels in breastmilk in parallel; and (iii) at different time points in breastmilk. Furthermore, (iv) we compared the development of children exposed to antidepressant medication (as well as quetiapine, aripiprazole and lamotrigine) in utero and/or through lactation, retrospectively and prospectively from patients treated in 2 specialized psychiatric mother–child units.

2 | MATERIAL AND METHODS

2.1 | Participants

In this study, we investigated 2 naturalistic samples; the first sample consists of a retrospectively assessed group of $n = 40$ patients; here, medication serum levels in pregnancy and breastmilk levels were available from the clinical routine data. Furthermore, there were data of a prospective sample of $n = 20$ mothers, and their children from whom serum and breastmilk medication levels at different standardized time points were collected. All the patients were treated in the mother–child outpatient clinics of the University Hospitals of Würzburg and Frankfurt (between 2011 and 2019). For demographic and medical data of the whole sample, see Table 1. For some of the patients, data from the first and the second pregnancy were available or the medication were changed during pregnancy and lactation and measurements were repeated, which lead to $n = 77$ data sets from $n = 60$ patients.

The majority of the patients suffered from affective disorders (diagnosed using ICD-10) and were taking antidepressant medication in monotherapy. Additionally, 4 patients were taking **quetiapine**, 2 were taking **aripiprazole** and 1 patient was on **lamotrigine**. Maternal birth complications were assessed in $n = 19$ mother. Reported complications were rated as severe complications and occurred in $n = 4$ mothers and included: uterine atony ($n = 1$), uterine atony with following hysterectomy ($n = 1$); cervix insufficiency ($n = 1$); and oligohydramnion ($n = 1$).

As this was a naturalistic clinical sample, inclusion criteria were broad: age ≥18 years, a current or previous psychopharmacological or nonpsychopharmacological treatment for a peripartal mental illness and sufficient German language skills. Only patients who gave their written informed consent were included in the study. The study adhered to the Declaration of Helsinki, 17th revision, 2013. The study was approved by the ethic committees of the University Hospital of Frankfurt and Würzburg, Approval No. 136/17 and 18/20-sc.

2.2 | Sample collection

Serum samples for drug measurement were taken in steady state, defined as a stable dosage for at least 5 days. According to the AGNP consensus guideline,[14] we took trough levels, so the blood was drawn in the morning between 8 and 11 AM before the medication was taken. In case of medication usually taken in the morning, serum levels were 24-hour trough levels. For the medication taken in the evening, serum levels were 12-hour trough levels, as usual in clinical routine. Thirty-eight patients (63.3% of the whole sample) were already taking medication during pregnancy and we could get therapeutic drug level

TABLE 1 Demographic and phenotypic data of the whole sample

	n	Mean
Age (y)	58 (2 missing)	33.26 ± 2.45
BMI (k/m^2)	31 (29 missing)	26.55 ± 6.23
Diagnosis	***n***	**%**
Major depression	38	62.3
Anxiety disorders	8	13.1
Obsessive compulsive disorder	4	6.6
Bipolar affective disorder	5	8.2
Schizoaffective disorder	3	4.9
Adjustment disorder	1	1.6
Multiple substance abuse	1	1.6
Medication (data sets)	***n***	**%**
Amitriptyline	16	20.8
Aripiprazole	2	2.6
Bupropion	1	1.3
Citalopram	4	5.2
Clomipramine	4	5.2
Duloxetine	1	1.3
Escitalopram	8	10.4
Lamotrigine	2	2.6
Mirtazapine	11	14.3
Paroxetine	1	1.3
Quetiapine	8	10.4
Sertraline	11	14.3
Venlafaxine	8	10.4
Medication in pregnancy	***n***	**%**
Yes/no/missing	38/13/9	63.3/21.6/15.0
Marital status	***n***	**%**
Married	13	21.3
Relationship	5	8.2
Separated/divorced	3	4.9
Missing	39	63.9
Partner with mental illness	***n***	**%**
Yes/no/missing	4/12/44	6.6/20.0/73
Family history of mental illness	***n***	**%**
Yes/no/missing	15/4/41	25.0/6.6/68.3
Education	***n***	**%**
College	15	24.6
High school	5	8.2
Missing	40	65.6

Baseline data from the whole sample of $n = 60$ included patients are shown here. More detailed demographic data were only available from about 40% of the whole sample.

measurements from 9 patients in the first trimester, 24 patients in the second trimester and 22 patients in the third trimester. From 5 patients/datasets, data on the pregnancy trimesters, in which the drug levels were measured, were not available.

Regarding the lactation period, in the whole sample, we could analyse 15 samples of transitional milk (with serum levels measured in parallel until 2 weeks postpartum) and 36 in mature breastmilk >2 weeks postpartum (with serum levels measured in parallel).

In the prospective study, we aimed at investigating the concentration of the medication in the breastmilk at different time points. Those measurements all took place after 2 weeks postpartum. From 20 patients, we were able to collect breastmilk samples at several different time points. We aimed at collecting milk samples at the following time points: T1: trough level, 12 or 24 hours after intake of the last medication, collected in parallel to serum sample; T2: medication was taken directly before breastfeeding; T3: 1 hour after having taken the medication and after having breastfed; T4: directly before the next breastfeeding (approximately after 3–5 h intake of the medication and having breastfed); T5: 4 hours after intake of the medication; T6: 8 hours after intake of the medication.

2.3 | Quantification of drug levels in serum and breastmilk

Serum concentrations of the medications were determined by an isocratic reversed-phase high performance liquid chromatography in the therapeutic drug monitoring (TDM) laboratory of the University Hospital of Würzburg. The methodological approach is described in detail elsewhere.[15] The laboratory participates in an external quality control programme (INSTAND e.V. *Gesellschaft zur Förderung der Qualitätssicherung in medizinischen Laboratorien* e.V. Ubierstr. 20, D-40223 Düsseldorf, Germany) with external control samples analysed every 3 months. The quality control programme was operated without rejection.

2.4 | Outcome parameter children

Outcome parameters of the newborns were the following: gestational age at birth, APGAR values, birth weight, birth height, head circumference, base excess and pH of the umbilical artery as well as abnormalities directly postpartum. We rated those abnormalities in mild, moderate and severe to be able to statistically compare the groups. There was one child who was also not exposed to medication during pregnancy was later diagnosed with a genetic disease (Muenke's syndrome), this is termed as *other* in Table 6. Another child had a severe complication postpartum, with a necrotising enterocolitis; however, this infant was also not exposed to medication in pregnancy (Table 6). The other infants showed none, mild or moderate abnormalities. Abnormalities were rated as mild if those did not require medical treatment like haemangiomas, mild icterus and mild neonatal adaptation syndrome. Moderate abnormalities required treatment or closer monitoring such as hypoglycaemia, umbilical cord around neck without hypoxia, macrosomia, mild hip dysplasia and respiratory distress. Thirty-six (60.1%) infants were exposed to psychopharmacological medication in pregnancy.

2.5 | Statistical analysis

We tested the data for normal distribution using Kolmogorov–Smirnov test and applied parametric or nonparametric tests as required for our analysis. When the subgroups were very small, we also applied nonparametric tests. Spearman ρ correlation was used to investigate the correlation between drug concentrations in serum and breastmilk as well as daily dosage. Kruskal–Wallis test was used to analyse the effects of the 13 different medications on the development of the newborn. A Pearson χ^2 test was used to test for differences for abnormalities in newborns who were prenatally exposed to medication and those who were not. Furthermore, we calculated concentration-by-dose ratios for serum and breastmilk (daily dosage/serum or breastmilk concentration; C/D) as well as milk-to-serum ratio (M/P; milk concentration/serum concentration) as a measure for the penetration from mother's blood to breastmilk. When multiple psychotropic medication was used, we calculated the ratios for every medication separately. Statistical analyses were calculated using SPSS (V26, IBM, Armonk, NY, USA).

2.6 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20.[32]

3 | RESULTS

3.1 | Demographic data and sample description

The patients of the whole sample had a mean age of 33.26 years and the majority was suffering from affective disorders. They were taking 13 different medications. For demographic data of the whole combined sample please see Table 1.

3.2 | Serum concentration changes during pregnancy

Within the clinical routine, we measured medication levels during the pregnancy. We calculated the mean (if $n > 1$) concentration/dose ratio (C/D) in the first, second and third trimester measurements, and if possible, we calculated the fold change of the (mean) C/D from first to second, second to third and first to third trimester. Those are only preliminary and exploratory findings, but we could show an overall decrease in serum concentrations from the

first (T1) to the second trimester (T2) in **amitriptyline**, duloxetine, **escitalopram**, quetiapine and sertraline. Citalopram showed a stable C/D from first to second trimester. Taking the fold change of the (mean) C/D from the second trimester to the third trimester, a clinically relevant decrease could be found in aripiprazole, mirtazapine, quetiapine and venlafaxine. Most surprisingly, sertraline showed a slight increase in the mean C/D from second to third trimester (see Table 2).

3.3 | Correlation between dosage, serum and breastmilk concentration

In the whole sample, there was a significant correlation analysing all medication together between daily dosage and serum concentration (Spearman ρ, $R = 0.68$, $P < .0001$) as expected but no significant correlation between neither daily dosage nor serum concentration with breastmilk concentration (Spearman ρ, $R = 1.93$; $R = 2.63$, respectively, and $P = .18$; $P = .09$, respectively) taking all available trough levels.

3.4 | C/D and M/P ratios: Changes during the day

In 20 patients (22 data sets) of the prospective study, we measured drug levels in breastmilk at different time points during the day (T1–T6) and calculated C/Ds and M/Ps. Those measurement were all done 2 weeks postpartum in mature breastmilk. Foremilk and hindmilk were not specified. Table 3 shows the C/D serum, C/D mother's milk (= breastmilk) and M/P ratio at different available time points T1–T6 during the day. The most relevant value is the milk to serum/plasma penetration ratio; however, the concentration/dose ratio adds interesting information that could help clinically in the decision when dosage increase is discussed.

A relatively high C/D ratio in serum was found in lamotrigine; however, this was just in 1 patient. Regarding the C/D in breastmilk, venlafaxine and lamotrigine showed rather high values in T1; however, in T2 and T6, citalopram and sertraline were also relatively high. Rather low C/D breastmilk ratios could be found in **clomipramine**, which could not be detected in breastmilk at all and quetiapine. The milk-to-serum ratio could only be calculated in T1, relatively high values were found in mirtazapine, venlafaxine and sertraline. However, here we could also find very high standard deviations, speaking for interindividual wide differences in the measures. Low M/P ratios were found with clomipramine and quetiapine. We investigated, how the concentration of the medication in the breastmilk would change during the day and dependent from the breastfeeding intervals. We used the C/D ratios in breastmilk to make the different medication and the different daily dosages more comparable even if also then comparison is only possible to a limited extent. As seen in Figure 1, the C/Ds of most medication did not change remarkably 4, 8, 12 or 24 hours after intake of the medication, with the exception of sertraline and venlafaxine.

Figure 2 shows the C/D ratios in breastmilk directly before breastfeeding, 1 hour after and directly before the next breastfeeding interval (mostly 3–5 h later). Here again, there are no great changes in the C/D ratios, with an exception of sertraline and lamotrigine, which also had the highest C/D ratios of all the medication.

3.5 | C/D and M/P ratios: Transitional milk and mature breastmilk

With additional data sets from the retrospective, clinical data, we could measure C/D in serum, C/D in breastmilk and milk-to-serum penetration ratios of 12 patients in transitional milk (≤2 wk postpartum; see Table 4) and 36 datasets in mature breastmilk (≥2 wk postpartum; see Table 5). Here again, relatively high C/D in breastmilk was found in venlafaxine and lamotrigine. High milk to plasma/serum ratios were seen in mirtazapine, sertraline and venlafaxine. However, the standard deviations in mirtazapine and sertraline were again very high, speaking for a wide interindividual variability.

TABLE 2 Changes in concentration–dose ratios during pregnancy

Medication	*n*	C/D TR1 (mean)	*n*	C/D TR2 (mean)	FC1/2 (mean)	*n*	C/D TR3 (mean)	FC1/3 (mean)	FC2/3 (mean)
Amitriptyline	2	0.85	4	0.53	0.62	3	0.53	0.62	0.99
Aripiprazole	N/A	N/A	2	11.55	N/A	2	6.83	N/A	0.59
Citalopram	1	1.71	2	1.75	1.02	1	1.76	1.02	1
Clomipramine	1	N/A	1	2.29	N/A	1	2.16	N/A	0.94
Duloxetine	1	1.17	1	0.17	0.14	1	N/A	N/A	N/A
Escitalopram	1	1.93	1	1.47	0.76	1	0.6	N/A	N/A
Mirtazapine	1	0.73	2	0.77	N/A	3	0.48	N/A	0.63
Quetiapine	1	0.22	4	0.17	0.78	3	0.06	0.29	0.38
Sertraline	1	0.56	4	0.29	0.52	4	0.39	0.7	1.34
Venlafaxine	0	N/A	3	1.26	N/A	3	0.96	N/A	0.76

The mean of concentration/dose ratios (C/D) was calculated if $n > 1$ in the substance group. Fold changes (FC) were calculated from the (mean) C/D ratios between first and second, second and third and first and third trimesters. All values were in steady state and trough levels.

TABLE 3 Medication concentrations during 24 hours in breastmilk

Medication	*n*	C/D serum T1	C/D MM T1	M/P T1	C/D MM T2	C/D MM T3	C/D MM T4	C/D MM T5	C/D MM T6
		Mean ± SD							
Mirtazapine	3	0.93 ± −0.17	3.38 ± 3.61	3.92 ± 4.16	0.81 ± 0.44	1.09 ± 0.38	1.00 ± 0.24	1.00 ± 0.33	0.96 ± 0.30
Citalopram	2	1.99 ± 0.14	N/A	N/A	4.73	5.55	2.35	5.93	8.28
Escitalopram	4	2.25 ± 1.41	2.26 ± 0.08	1.47 ± 0.71	1.73 ± 1.08	2.05 ± 0.45	3.00 ± 0.0	2.51 ± 0.43	2.43 ± 0.03
Sertraline	2	1.37 ± 1.27	1.53 ± 1.09	13.18 ± 13.02	9.62 ± 2.83	12.78 ± 0.23	14.87 ± 11.27	10.00 ± 8.75	11.02 ± 4.36
Lamotrigine	1	18.5	10.00	0.54	10.00	14.00	11.00	N/A	12.00
Venlafaxine	3	2.71 ± 0.17	4.93 ± 2.22	2.4 ± 0.17	2.16 ± 2.77	4.31 ± 2.90	3.86 ± 3.67	9.89 ± 3.50	6.65 ± 6.47
Clomipramine	2	2.26 ± 0.11	0.00	0.00	N/A	N/A	N/A	N/A	N/A
Amitriptyline	2	2.22 ± 0.38	2.57 ± 0.41	1.22 ± 0.39	0.21 ± 0.05	0.32 ± −0.13	1.03 ± 0.61	0.23 ± 0.11	1.54 ± 1.12
Quetiapine	3	0.51 ± 0.28	0.01 ± 0.02	0.03 ± 0.03	0.11	0.04	0.02	0.02	0.02

T1: Trough levels of the medication were measured in serum and breastmilk in parallel, after 12 (mirtazapine, amitriptyline and quetiapine) or 24 hours (citalopram, escitalopram, sertraline, lamotrigine, venlafaxine and clomipramine) after last intake of the medication in steady state. T2: medication was taken directly before breastfeeding; T3: 1 hour after having taken the medication and after having breastfed; T4: directly before the next breastfeeding (approximately after 4–5 h intake of the medication and having breastfed); T5: 4 hours after intake of the medication; T6: 8 hours after intake of the medication. The mean of concentration/dose ratios (C/D) in serum and breastmilk were calculated if $n > 1$ in the substance group.
MM, mother's milk = breastmilk; M/P, milk–plasma (serum) ratio; SD, standard deviation.

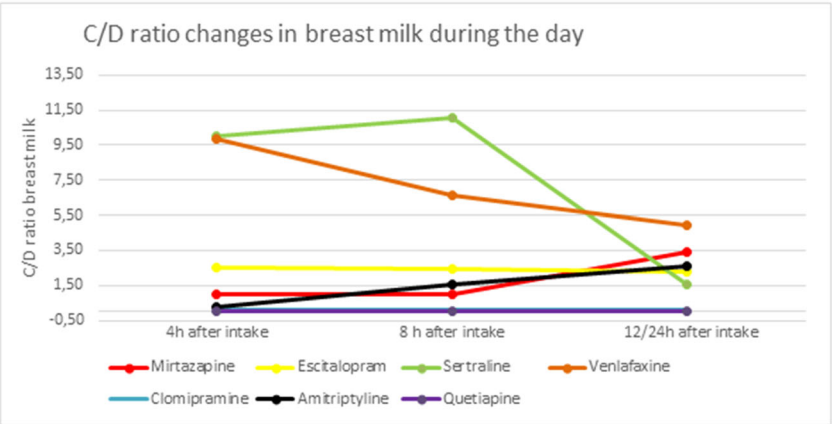

FIGURE 1 Concentration-by-dose (C/D) ratio changes in breastmilk during the day. Data sets of mirtazapine $n = 3$, escitalopram $n = 4$, sertraline $n = 2$, venlafaxine $n = 3$, clomipramine $n = 2$, amitriptyline $n = 2$, and quetiapine $n = 3$ were used. Mean concentration/dose in breastmilk were calculated for the substance separately. Breastmilk samples were taken at 4 and 8 hours and at trough levels (which mean after 12 h [regular intake in the evening]) or 24 hours after intake (regular intake in the morning).

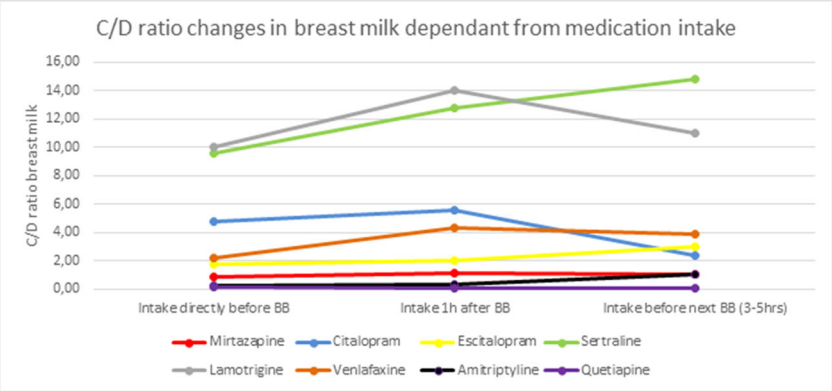

FIGURE 2 Concentration-by-dose (C/D) ratio changes in breastmilk dependent from medication intake. Data sets of mirtazapine $n = 3$, citalopram $n = 2$, escitalopram $n = 4$, sertraline $n = 2$, venlafaxine $n = 3$, lamotrigin $n = 1$, amitriptyline $n = 2$ and quetiapine $n = 3$ were used. Mean concentration/dose in breastmilk was calculated for the substance separately. Breastmilk samples were taken directly before breastfeeding, 1 hour after and directly before the next breastfeeding interval (mostly 3–5 h later).

TABLE 4 C/D serum, breastmilk and milk plasma ratio after ≤2 weeks postpartum

		C/D serum		C/D MM		M/P	
Medication	***n***	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Amitriptyline	4	0.87	0.23	0.78	1.27	0.83	1.35
Quetiapine	3	0.44	0.18	0.08	0.08	0.05	0.05
Sertraline	2	0.43	0.02	0.32	0.18	0.72	0.38
Venlafaxine	3	1.9	0.72	4.55	2.41	2.27	0.65

The mean of concentration/dose ratios (C/D) in serum and breastmilk were calculated if $n > 1$ in the substance group.
MM, mother's milk = breastmilk; M/P, milk–plasma (serum) ratio; SD, standard deviation.

3.6 | Outcome parameter children

From 39 children, we could assess basic parameters with regard to pregnancy and birth complications and the development in the first 12 months (see Table 6). Comparing APGAR values, birth weight, birth height, head circumference, base excess and pH of the umbilical artery, there were no significant differences between the newborns that had been exposed in pregnancy compared with those whose mother have not been taking psychopharmacological medication during pregnancy in the prospective group of our study (Student *t* test, all *P*-values ≥ .05). Also, there were no significant differences between the different medications, which the newborns were exposed to regarding birth weight, birth height, and head circumference (Kruskal–Wallis test, all *P*-values ≥.072). There was one relevant significant difference between the group that was already exposed in pregnancy and the group that was only exposed by breastfeeding: there was a higher number of moderate birth complications directly postpartum in the pregnancy exposed group whereas the number of mild complications in the nonexposed group was higher (χ^2; $P = .01$). There were no significant differences regarding pregnancy and birth complications and the development of the children between the different medications (all *P*-values ≥ .05; Table 6).

TABLE 5 C/D serum, breastmilk and milk plasma ratio after >2 weeks postpartum

		C/D serum		C/D MM		M/P	
Medication	***n***	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Amitriptyline	9	1.93	1.14	0.65	0.87	0.34	0.47
Citalopram	1	2.63		0.65		0.25	
Clomipramine	2	2.26	0.11	0.00	0.00	0.00	0.00
Escitalopram	5	1.91	1.35	2.52	0.45	1.75	0.60
Lamotrigine	1	18.50		10.00		0.54	
Mirtazapine	4	1.30	0.66	2.78	3.29	3.04	3.91
Paroxetine	1	5.55		1.15		0.21	
Quetiapine	3	0.60	0.22	0.01	0.02	0.03	0.05
Sertraline	8	0.80	0.79	1.15	1.60	3.99	8.59
Venlafaxine	2	2.71	0.08	6.50		2.41	0.17

The mean of concentration/dose ratios (C/D) in serum and breastmilk were calculated if $n > 1$ in the substance group.
MM, mother's milk = breastmilk; M/P, milk–plasma (serum) ratio; SD, standard deviation.

4 | DISCUSSION

The present study aimed at investigating changes in concentrations of psychopharmacological medication during pregnancy and lactation in serum and breastmilk at different time points in a naturalistic combined sample, consisting of a prospectively assessed sample of 20 patients and in addition retrospective data of 60 patients. In 39 children, pregnancy and birth complication as well as the development at age 12 months were assessed.

Regarding the serum concentration changes during pregnancy, we found a decrease in serum concentrations of the antidepressants/mood stabilizers from the first trimester to the second trimester and again to the third trimester. The only exception was sertraline with an increase of serum concentrations in the course of pregnancy; the reason here is unclear. A decrease in serum concentrations of psychotropic drug levels during pregnancy is in line with prior findings and explained by pregnancy-associated changes in pharmacokinetics.[16] Among others, these changes are based on an increased plasma volume, a change in protein binding, an increased glomerular filtration rate or an altered hepatic metabolism in pregnant women (reviewed, e.g., in Pariente *et al.*[17]). The alteration patterns of antidepressants during the course of pregnancy are understudied, and available data are based on small sample sizes. Nevertheless, Schoretsanitis and colleagues reported in a recent review article a decrease of dose-adjusted blood concentrations for citalopram and clomipramine, which is in line with our findings. In contrast, venlafaxine was considered to be relatively stable[18] while we found a decrease of around 50% from second trimester to third trimester with the critical limitation that for venlafaxine alteration patterns we could only include one pregnant woman. An increase of sertraline serum concentration in the third trimester around 60–70% compared with baseline was also shown in a Norwegian study investigating SSRI and venlafaxine serum concentrations in 281 pregnant women.[19] Westin and colleagues hypothesized that this increase during the course of pregnancy is mainly driven by the CYP2C19 inhibition. In contrast to our findings, Westin and colleagues found no significant change for venlafaxine.[19]

Investigating the correlation between dosage, serum and breastmilk concentration, we found a significant correlation of daily dosage and serum concentration taking all medication together. This correlation was expected, as the TDM of the psychopharmacological medication investigated in this study is well established with TDM recommendation levels 1 and 2.[20] Concerning the relationship between serum and breastmilk concentration we found no significant correlation, either taking all medication together or analysing the different drugs separately. Highest concentration-by-dose ratios in breastmilk were found for venlafaxine and lamotrigine in the different samples and timepoints, lowest for quetiapine and clomipramine, the latter could not be detected in breastmilk at all. Similarly, clomipramine and quetiapine showed lowest milk to serum/plasma penetration ratios, highest were found in mirtazapine, venlafaxine and surprisingly also sertraline. However, in sertraline, there were great interindividual differences seen; in most women, the M/P ratio was rather low but there were 2 individuals with high ratios. The reasons for those differences remain unclear; it might also concern differences in sampling hindmilk *vs.* foremilk. In principle, psychotropic medication can passively diffuse into breastmilk. The higher the amount of lipid soluble molecules, the faster diffuse these drugs into breastmilk. Higher concentrations can be found in hindmilk as it has a higher fat content than foremilk.[21] In a recent systematic review and combined analysis investigating the transfer of antidepressants into amniotic fluid, umbilical cord blood and breastmilk, Schoretsanitis and colleagues published combined penetration ratios (equivalent to M/Ps in breastmilk). The M/Ps in breastmilk in our study for venlafaxine and amitriptyline were in the range reported by Schoretsanitis *et al.* Clomipramine and escitalopram showed lower penetration ratios (only slightly lower for escitalopram) and, for mirtazapine, we found a higher M/P ratio mean value compared to the Schoretsanitis

TABLE 6 Birth outcomes and development after 12 months of the whole sample

Age of mother [y]	Diagnosis of mother	Medication	Medication during pregnancy	Pregnancy complication	Gestational week at birth	Birth mode	Birth complications	Position at birth	Sex of child
N/A	MDD	Escitalopram	Yes	N/A	40	N/A	N/A	N/A	N/A
N/A	MDD	Mirtazapine	No	N/A	40	N/A	N/A	N/A	N/A
34	MDD	Sertraline	No	N/A	41	N/A	N/A	N/A	N/A
29	MDD	Sertraline	Yes	N/A	39	N/A	N/A	N/A	N/A
35	MDD	Escitalopram	Yes	N/A	40	N/A	N/A	N/A	N/A
37	BD	Lamotrigine	No	N/A	40	N/A	N/A	N/A	N/A
34	MDD	Escitalopram	Yes	N/A	36	N/A	N/A	N/A	N/A
30	OCD	Clomipramine	No	N/A	39	N/A	N/A	N/A	N/A
34	AD	Mirtazapine	No	N/A	40	N/A	N/A	N/A	N/A
24	MDD	Amitriptyline	No	N/A	40	N/A	N/A	N/A	N/A
31	MDD	Venlafaxine	Yes	N/A	37	N/A	N/A	N/A	N/A
37	MDD	Escitalopram	Yes	Moderate	40	N/A	N/A	N/A	N/A
33	MDD	Amitriptyline	Yes	N/A	40	N/A	N/A	N/A	N/A
32	BD	Quetiapine	Yes	Severe	40	N/A	N/A	N/A	N/A
36	MDD	Citalopram	Yes	Mild	37	Vacuum extraction	None	Cephalic presentation	Male
34	AD	Venlafaxine	Yes	N/A	38	N/A	N/A	N/A	N/A
38	SCZ Aff	Quetiapine	Yes	N/A	39	N/A	N/A	N/A	Male
38	SCZ Aff	Quetiapine	Yes	N/A	39	N/A	N/A	N/A	Female
35	SCZ Aff	Quetiapine	Yes	No	42	Emergency CS	N/A	N/A	Female
31	MDD	Escitalopram	Yes	Moderate	38	PDA	None	Cephalic presentation	Male
30	MDD	Sertraline	Yes	Mild	39	PDA	None	Cephalic presentation	Female
38	OCD	Clomipramine	Yes	Mild	35	Secondary CS	Severe	Cephalic presentation	Female
38	OCD	Clomipramine	Yes	Mild	35	Secondary CS	Severe	Cephalic presentation	Female
36	MDD	Mirtazapine	Yes	Mild	N/A	Spontaneous vaginal	None	Cephalic presentation	Female
39	MDD	Venlafaxine	Yes	Severe	35	Emergency CS	Severe	Cephalic presentation	Male
39	MDD	Venlafaxine	Yes	Severe	35	Emergency CS	Severe	Transverse	Male

TABLE 6 (Continued)

Age of mother [y]	Diagnosis of mother	Medication	Medication during pregnancy	Pregnancy complication	Gestational week at birth	Birth mode	Birth complications	Position at birth	Sex of child
35	Adjustment disorder	Mirtazapine	No	Severe	26	Emergency CS	N/A	Cephalic presentation	Male
38	MDD	Sertraline	Yes	No	40	PDA	None	Cephalic presentation	Male
32	AD	Mirtazapine	Yes	Moderate	38	Spontaneous vaginal	None	Cephalic presentation	Female
41	MDD	Citalopram	Yes	No	41	Spontaneous vaginal	None	Cephalic presentation	Male
41	MDD	Bupropion	Yes	No	41	Spontaneous vaginal	None	Cephalic presentation	Male
35	MDD	Venlafaxine	Yes	Mild	38	PDA	None	Cephalic presentation	Male
40	BD	Quetiapine	Yes	Moderate	36	Secondary CS	None	Cephalic presentation	Male
40	MDD	Sertraline	Yes	Moderate	40	PDA	None	Cephalic presentation	Male
36	MDD	Amitriptyline	No	No	41	Secondary CS	None	Cephalic presentation	Female
35	MDD	Amitriptyline	No	No	37	Spontaneous vaginal	None	Cephalic presentation	Female
35	MDD	Citalopram	No	No	37	Spontaneous vaginal	None	Cephalic presentation	Female
29	MDD	Venlafaxine	Yes	Mild	38	Secondary CS	None	Cephalic presentation	Female
30	MDD	Amitriptyline	N/A	N/A	35	Spontaneous vaginal	N/A	Cephalic presentation	Male

MDD, Major depression; BD, Bipolar affective disorder; AD, anxiety disorder; SCZ aff, schizoaffective disorder; OCD, obsessive compulsive disorder; N/A, not available; CS, cesar section; PDA, peridural anesthesia.

TABLE 6 (Continued)

Age of mother [y]	Abnormalities postpartum	APGAR1	APGAR2	Birth weight (g)	Birth height (cm)	Head circumference (cm)	pH arterial cord blood	Base excess (mmol/L)	Breast feeding	Child development at 12 mo
N/A	Mild	9	10	3840	52	35	7.30	0.8	N/A	Normal
N/A	Mild	10	10	3670	55	34.5	7.19	−2.6	N/A	Normal
34	None	10	10	3550	53	36	7.13	N/A	N/A	Normal
29	None	10	10	3100	52	36	7.31	−5.7	N/A	N/A
35	Other	10	10	3520	51	34	7.16	−7.6	N/A	Normal
37	Mild	10	10	3590	52	35.5	7.25	N/A	N/A	Normal
34	Moderate	9	10	3550	50.5	32	7.19	−2.9	N/A	Normal
30	Mild	10	10	3500	50	35	7.25	N/A	N/A	N/A
34	Mild	10	10	3300	52	35	7.16	−4.6	N/A	N/A
24	Mild	9	10	3010	49	34	7.19	−5.6	N/A	Normal
31	None	9	10	2850	49	33	7.29	N/A	N/A	Normal
37	Mild	9	10	2590	46	33.5	7.10	−13.3	N/A	Normal
33	None	9	10	4500	56	36.5	7.19	−7.2	N/A	Normal
32	None	10	10	4020	54	36	7.26	−5.5	N/A	Normal
36	None	8	9	3550	53	35	7.18	−7.6	Yes	Normal
34	None	10	10	3210	50	34	7.30	−8.6	N/A	Normal
38	None	9	10	3230	53	36	7.25	−3.6	N/A	Normal
38	Mild	8	9	3440	55	36.5	7.22	−3.1	N/A	Normal
35	Mild	6	N/A	5360	53	35	7.09	−17.0	N/A	Normal
31	Mild	10	10	2776	47	N/A	7.17	−6.7	Yes	Normal
30	Mild	9	10	2890	49	33	7.20	−3.8	Yes	Mildly delayed
38	Moderate	8	9	2610	47	34	7.27	−3.1	No	Normal
38	Moderate	9	9	2045	46	32.5	7.27	−2.2	No	Mildly delayed
36	None	N/A	N/A	3040	52	N/A	N/A	N/A	No	Mildly delayed
39	Moderate	9	9	2700	47	33.5	7.33	−6.2	Yes	Normal
39	Moderate	8	9	1600	41	33	7.29	−8.1	Yes	Normal
35	Severe	8	8	680	30	N/A	7.40	N/A	N/A	Mildly delayed
38	None	10	10	3050	51	36	7.13	−11.8	Yes	Normal
32	Other	10	10	2730	54	34	7.15	−3.7	No	Normal
41	None	10	10	4050	57	37	7.15	−10.0	Yes	Normal

TABLE 6 (Continued)

Age of mother [y]	Abnormalities postpartum	APGAR1	APGAR2	Birth weight (g)	Birth height (cm)	Head circumference (cm)	pH arterial cord blood	Base excess (mmol/L)	Breast feeding	Child development at 12 mo
41	None	10	10	4050	57	37	7.15	−10.0	Yes	Normal
35	None	10	10	2950	49	32	7.24	N/A	Yes	Normal
40	N/A	8	10	3550	52	N/A	7.18	N/A	Yes	Normal
40	Mild	N/A	N/A	3300	50	N/A	N/A	N/A	No	Normal
36	Mild	10	10	3585	52	35	7.23	N/A	Yes	Normal
35	Mild	10	10	2830	49	N/A	7.35	N/A	Yes	Normal
35	Mild	10	10	2830	49	N/A	7.35	N/A	Yes	Normal
29	Moderate	10	10	4160	57	35.5	7.29	N/A	Yes	Normal
30	N/A	N/A	N/A	2445	49	33.5	7.28	−2.2	Yes	N/A

MDD, Major depression; BD, Bipolar affective disorder; AD, anxiety disorder; SCZ aff, schizoaffective disorder; OCD, obsessive compulsive disorder; N/A, not available; CS, cesar section; PDA, peridural anesthesia.

study.[22] The M/P ratio mean value for quetiapine in our study was lower than the combined penetration ratio in a similar review and combined analysis investigating the transfer of antipsychotics into breastmilk.[21] For lamotrigine, the M/P ratio value in our study was within the wide range of M/P ratio reported in a review article by Pacchiarotti *et al.*[23]

Regarding the outcome measures in children, we found no significant differences between newborns that had been exposed in pregnancy compared to those whose mother have not been taking psychopharmacological medication during pregnancy in the prospective group of our study. Analysing outcome measures between the different medications, which the newborns were exposed to, there were also no significant differences regarding birth weight, birth height and head circumference. Comparing children exposed to psychotropic drugs in utero and by breastfeeding, we found a significantly higher number of moderate abnormalities directly postpartum in the pregnancy exposed group whereas the number of mild abnormalities in the nonexposed group was higher. There were no significant differences regarding birth complications and the development of the children between the different medications.

Current reviews and meta-analyses summarize and critically discuss the existing data on exposure to psychopharmacology during pregnancy or by breastmilk. A placental exposure could be demonstrated by TDM measurements in amniotic fluid and umbilical cord blood (see Schoretsanitis *et al.*[22] for a review). A moderately increased risk of neonatal and childhood outcomes in children (e.g., preterm birth, low birth weight or autism) exposed to antidepressants in utero was reported, although some meta-analyses outlined that these increased risks of complication were no longer significant when compared to a group of untreated depressed mother–child pairs. Thus, the author of this review article including 21 meta-analyses concluded that it is difficult to disentangle whether underlying mechanisms are related to medication or maternal psychiatric disorders.[24] In contrast, Xing and colleagues concluded in their meta-analysis (including 48 cohort and 6 case–control studies) that children exposed to antidepressants during pregnancy had increased risks of preterm birth, low birth weight and admissions to neonatal intensive care units compared with newborns of depressed but unmedicated mothers. Risks of spontaneous abortions, low APGAR scores at 5 min or neonatal convulsions were higher when mothers were treated with antidepressant medication during pregnancy compared to newborns of healthy mothers.[25] For SSRIs, a higher risk of cardiovascular defects in infants exposed to SSRIs in utero[26] as well as adverse but self-limiting effects on neonatal adaption after placental exposure[27] are discussed, while exposure through breastfeeding results in much lower drug concentrations with an relative infant drug doses of <10% for SSRIs. Accordingly, drug concentrations in plasma are often undetectable in healthy infants.[28] Also, for tricyclic antidepressants the daily doses of drugs ingested through breastmilk were reported to be around 1% of the maternal dose/kg and only small amounts of the drugs were detected in infants' plasma and urine.[29]

4.1 | Limitations

Our findings need to be interpreted with caution as several limitations need to be considered. The most critical limitation of this study is the small size of the subsamples, which is a common limitation for naturalistic samples in clinical research, but still needs to be considered, for example, when interpreting the development of the children. To gain a better understanding of the amount of exposure in utero and through breastmilk as well as the impact on the development of the exposed children, future large-scale and longitudinal studies are needed.

While TDM for blood concentrations is well established and our laboratory fulfilled the quality control programme without rejection, studies with TDM for breastmilk concentrations are scarce, and thus a lack of clinical validation needs to be taken into account.

The milk-to-serum/plasma ratio is a well-established parameter to analyse the excretion of a drug in the breastmilk. However, it needs to be considered that higher M/P ratios can be misleading as the excretion of a drug into breastmilk is a function of the maternal plasma concentration: the higher the blood concentration, the higher the transfer into breastmilk.[23,30] Additionally, we did not control if hindmilk or foremilk was sampled and we did not analyse the composition of the breastmilk, which also could have influenced the concentration of the medication.

4.2 | Conclusion

With this study, we added original data to the seriously understudied topic of safety of psychotropic medication in the peripartum. It is a wide consent that the use of psychotropic medication needs a balancing of risks and benefits and that alternative treatments (e.g., psychotherapy) should be (additionally) considered (e.g., Trifu *et al.*[31]). During pregnancy, a continuous TDM can be a guidance for clinicians to monitor drug alteration patterns, which are likely to occur due to physiological pregnancy-associated changes in pharmacokinetics.[18] Accordingly, TDM can optimize a medication in pregnancy and lactation with the lowest but effective dose.

ACKNOWLEDGEMENTS

This work did not receive funding from any internal or external funding institution. We thank the team of the TDM lab in Würzburg for excellent technical support and patients for their participation in the study. Open Access funding enabled and organized by Projekt DEAL.

COMPETING INTERESTS

The authors have no conflict of interest to declare.

CONTRIBUTORS

A.G., K.F. and S.K.S. treated the patients; L.v.B., A.G., K.P. and S.K.S. recruited the patients and did the data acquisition; A.L.L., M.S.C., L.v.B, S.U. and S.K.S. did the data analysis. All authors drafted and finalized the manuscript.

PATIENT CONSENT

Patients gave written informed consent.

DATA AVAILABILITY STATEMENT

Anonymised raw data can be made available on request.

ORCID

Maike Scherf-Clavel https://orcid.org/0000-0002-4780-612X
Sarah Kittel-Schneider https://orcid.org/0000-0003-3057-6150

REFERENCES

1. Cao TXD, Fraga LFC, Fergusson E, et al. Prescribing trends of antidepressants and psychotropic coprescription for youths in UK primary care, 2000–2018. *J Affect Disord*. 2021;287:19-25. doi:10.1016/j.jad.2021.03.022
2. Huybrechts KF, Hernandez-Diaz S, Avorn J. Antidepressant use in pregnancy and the risk of cardiac defects. *N Engl J Med*. 2014;371(12):1168-1169. doi:10.1056/NEJMc1409203
3. Sankar MJ, Sinha B, Chowdhury R, et al. Optimal breastfeeding practices and infant and child mortality: a systematic review and meta-analysis. *Acta Paediatr*. 2015;104(467):3-13. doi:10.1111/apa.13147
4. Tham R, Bowatte G, Dharmage SC, et al. Breastfeeding and the risk of dental caries: a systematic review and meta-analysis. *Acta Paediatr*. 2015;104(467):62-84. doi:10.1111/apa.13118
5. Oddy WH, Sherriff JL, de Klerk NH, et al. The relation of breastfeeding and body mass index to asthma and atopy in children: a prospective cohort study to age 6 years. *Am J Public Health*. 2004;94(9):1531-1537. doi:10.2105/AJPH.94.9.1531
6. Shema L, Ore L, Ben-Shachar M, Haj M, Linn S. The association between breastfeeding and breast cancer occurrence among Israeli Jewish women: a case control study. *J Cancer Res Clin Oncol*. 2007;133(8):539-546. doi:10.1007/s00432-007-0199-8
7. Tschiderer L, Seekircher L, Kunutsor SK, Peters SAE, O'Keeffe LM, Willeit P. Breastfeeding is associated with a reduced maternal cardiovascular risk: systematic review and meta-analysis involving data from 8 studies and 1 192 700 parous women. *J Am Heart Assoc*. 2022;11(2):e022746. doi:10.1161/JAHA.121.022746
8. Gunlicks ML, Weissman MM. Change in child psychopathology with improvement in parental depression: a systematic review. *J Am Acad Child Adolesc Psychiatry*. 2008;47(4):379-389. doi:10.1097/CHI.0b013e3181640805
9. Orsolini L, Bellantuono C. Serotonin reuptake inhibitors and breastfeeding: a systematic review. *Hum Psychopharmacol*. 2015;30(1):4-20. doi:10.1002/hup.2451
10. Kronenfeld N, Berlin M, Shaniv D, Berkovitch M. Use of psychotropic medications in breastfeeding women. *Birth Defects Res*. 2017;109(12):957-997. doi:10.1002/bdr2.1077
11. Bellantuono C, Vargas M, Mandarelli G, Nardi B, Martini MG. The safety of serotonin-noradrenaline reuptake inhibitors (SNRIs) in pregnancy and breastfeeding: a comprehensive review. *Hum Psychopharmacol*. 2015;30(3):143-151. doi:10.1002/hup.2473
12. Schoretsanitis G, Augustin M, Saßmannshausen H, Franz C, Gründer G, Paulzen M. Antidepressants in breast milk; comparative analysis of excretion ratios. *Arch Womens Ment Health*. 2019;22(3):383-390. doi:10.1007/s00737-018-0905-3
13. Smit M, Wennink HJMB, Heres MMHB, Dolman KKM, Honig A. Mirtazapine in pregnancy and lactation: data from a case series. *J Clin Psychopharmacol*. 2015;35(2):163-167. doi:10.1097/JCP.0000000000000279
14. Hiemke C, Bergemann N, Clement HW, et al. Consensus guidelines for therapeutic drug monitoring in neuropsychopharmacology: update 2017. *Pharmacopsychiatry*. 2018;51(1-02):e1. doi:10.1055/s-0037-1600991

15. Pfuhlmann B, Gerlach M, Burger R, et al. Therapeutic drug monitoring of tricyclic antidepressants in everyday clinical practice. *J Neural Transm Suppl*. 2007;72:287-296. doi:10.1007/978-3-211-73574-9_35
16. Deligiannidis KM, Byatt N, Freeman MP. Pharmacotherapy for mood disorders in pregnancy: a review of pharmacokinetic changes and clinical recommendations for therapeutic drug monitoring. *J Clin Psychopharmacol*. 2014;34(2):244-255. doi:10.1097/JCP.0000000000000087
17. 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. doi:10.1371/journal.pmed.1002160
18. Schoretsanitis G, Spigset O, Stingl JC, Deligiannidis KM, Paulzen M, Westin AA. The impact of pregnancy on the pharmacokinetics of antidepressants: a systematic critical review and meta-analysis. *Expert Opin Drug Metab Toxicol*. 2020;16(5):431-440. doi:10.1080/17425255.2020.1750598
19. 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. doi:10.1371/journal.pone.0181082
20. Schoretsanitis G, Paulzen M, Unterecker S, et al. TDM in psychiatry and neurology: a comprehensive summary of the consensus guidelines for therapeutic drug monitoring in neuropsychopharmacology, update 2017; a tool for clinicians. *World J Biol Psychiatry*. 2018;19(3):162-174. doi:10.1080/15622975.2018.1439595
21. Yoshida K, Smith B, Kumar R. Psychotropic drugs in mothers' milk: a comprehensive review of assay methods, pharmacokinetics and of safety of breast-feeding. *J Psychopharmacol*. 1999;13(1):64-80. doi:10.1177/026988119901300108
22. Schoretsanitis G, Westin AA, Deligiannidis KM, Spigset O, Paulzen M. Excretion of antipsychotics into the amniotic fluid, umbilical cord blood, and breast milk: a systematic critical review and combined analysis. *Ther Drug Monit*. 2020;42(2):245-254. doi:10.1097/FTD.0000000000000692
23. Pacchiarotti I, León-Caballero J, Murru A, et al. Mood stabilizers and antipsychotics during breastfeeding: focus on bipolar disorder. *Eur Neuropsychopharmacol*. 2016;26(10):1562-1578. doi:10.1016/j.euroneuro.2016.08.008
24. Uguz F. Neonatal and childhood outcomes in offspring of pregnant women using antidepressant medications: a critical review of current meta-analyses. *J Clin Pharmacol*. 2021;61(2):146-158. doi:10.1002/jcph.1724
25. Xing D, Wu R, Chen L, Wang T. Maternal use of antidepressants during pregnancy and risks for adverse perinatal outcomes: a meta-analysis. *J Psychosom Res*. 2020;137:110231. doi:10.1016/j.jpsychores.2020.110231
26. Uguz F. Selective serotonin reuptake inhibitors and the risk of congenital anomalies: a systematic review of current meta-analyses. *Expert Opin Drug Saf*. 2020;19(12):1595-1604. doi:10.1080/14740338.2020.1832080
27. Gentile S. The safety of newer antidepressants in pregnancy and breastfeeding. *Drug Saf*. 2005;28(2):137-152. doi:10.2165/00002018-200528020-00005
28. Fischer Fumeaux CJ, Morisod Harari M, Weisskopf E, et al. Risk-benefit balance assessment of SSRI antidepressant use during pregnancy and lactation based on best available evidence—an update. *Expert Opin Drug Saf*. 2019;18(10):949-963. doi:10.1080/14740338.2019.1658740
29. Yoshida K, Smith B, Craggs M, Channi Kumar R. Investigation of pharmacokinetics and of possible adverse effects in infants exposed to tricyclic antidepressants in breast-milk. *J Affect Disord*. 1997;43(3):225-237. doi:10.1016/S0165-0327(97)01433-X
30. Rowe H, Baker T, Hale TW. Maternal medication, drug use, and breastfeeding. *Child Adolesc Psychiatr Clin N Am*. 2015;24(1):1-20. doi:10.1016/j.chc.2014.09.005
31. Trifu SC, Popescu A, Marian MA. Affective disorders: a question of continuing treatment during pregnancy (Review). *Exp Ther Med*. 2020;20(4):3474-3482. doi:10.3892/etm.2020.8989
32. Alexander SPH, Kelly E, Mathie A, et al. The concise guide to pharmacology 2021/22: introduction and other protein targets. *Br J Pharmacol*. 2021;178(S1): S1-S26. doi:10.1111/bph.15537

How to cite this article: 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. doi:10.1111/bcp.15533