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

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1. 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 breast milk, 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 during pregnancy, milk-plasma penetration rations at different time points during lactation and the development of exposed children (in utero and/or through lactation) in a naturalistic study.

2. What this study adds:

- Most of the analysed antidepressants showed a decrease of serum concentrations from the first to the second trimester. Concentration-by-dose ratios in breast milks and milk/serum-penetration-ratios were lowest for clomipramine and quetiapine, highest concentration-by-dose-ratios in breast milk 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 non-exposed children.

- Psychotropic medication in the peripartum needs a balancing of risks and benefits and a continuous TDM can optimize a medication in pregnancy and lactation with the lowest but effective dose.

Abstract

## Aim

There is still only little knowledge about alterations of blood concentrations of psychotropic drugs during pregnancy, the transfer of psychotropic drugs into breast-milk and the effects on exposed children.

## Methods

We investigated changes in concentrations of psychopharmacological medication during pregnancy and lactation in serum and breast milk at different time points in a naturalistic sample of 60 mothers and observed the development of the exposed children in the first 12 months.

## Results

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. Highest concentration-by-dose-ratios in breast milk were found for venlafaxine as well as lamotrigine, lowest for quetiapine and clomipramine. Similarly, clomipramine and quetiapine showed lowest milk/serum-penetration-ratios. Regarding the birth outcome measures in children we found no significant differences between in utero exposed compared to non-exposed new-borns. There were no significant differences in the development in the first 12 months.

## Conclusion

Psychotropic medication in the peripartum needs a balancing of risks and benefits and a continuous therapeutic drug monitoring (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. Accordingly, TDM can optimize a medication in pregnancy and lactation with the lowest but effective dose.

Introduction

Treatment with antidepressants in pregnancy and lactation is an increasing issue due to raising prescription numbers of antidepressants to women in child bearing age [1]. Furthermore, at least women in industry nations are significantly older when giving birth to their first child which increases the risk of a history of either a depressive disorder, an anxiety or obsessive compulsive disorder and a treatment with antidepressants 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-analysis have already shown that most antidepressant medication is not teratogenic, only fluoxetine and paroxetine have been repeatedly associated with small risk of birth defects [2]. However, there are only few insights about the long term effects of antidepressant exposure during pregnancy on the development of the children later in life. Additionally, there is sparse published data about the use of antidepressant medication in breast feeding and potential short and long term impacts on the exposed children. Breast milk is the gold standard of nutrition for new-borns and babies according to the World Health Organization (WHO) and the American Academy of Pediatrics (AAP) (*Global strategy for infant and young child feeding*. Geneva. WHO; [www.who.int/nutrition/publications/gs\_infant\_feeding\_text\_eng.pdf](http://www.who.int/nutrition/publications/gs_infant_feeding_text_eng.pdf). accessed 22.1.19). Breast milk is recommended as 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 less risk for infections and have a decreased risk for obesity, diabetes mellitus type II, allergic asthma, and other atopic diseased later in life [3-5]. Furthermore, also mothers have beneficial health effects from breastfeeding: a 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 for a decreased risk of metabolic syndrome as well as breast and ovarian cancer [6]. And 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 needs to be done weighing the beneficial and health protective effects of breastfeeding against the potential negative influences of antidepressant concentrations in the breast milk.

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 (SSRI) like sertraline, citalopram and paroxetine as being a relatively safe medication during lactation [9, 10]. Duloxetine seems to be acceptable as a serotonin-noradrenalin-reuptake inhibitor (SNRI) for breastfeeding mothers [11]. Although a medication with venlafaxine leads to relatively high concentrations in breast milk, there were no adverse effects shown in exposed babies and thus, venlafaxine is not contraindicated [12]. Most interestingly, a case series of medication with mirtazapine during pregnancy (n=54) reports a faster disappearance of neonatal adaptation symptoms in breastfed children in comparison with non-breastfed 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 at 1) investigating serum concentration changes of psychopharmacological medication during pregnancy, 2) exploring correlations of dosage, steady state through levels in serum and steady state through levels in breast milk in parallel and 3) at different time points in breast milk. Furthermore, 4) we compared the development of children exposed to antidepressant medication in utero and/or through lactation, retrospectively and prospectively from patients treated in two specialized psychiatric mother-child units.

Material and Methods

## Participants

In this study, we investigated two naturalistic samples, the first samples consists of a retrospectively assessed group of n= 40 patients, here, medication serum levels in pregnancy and breast milk levels were available from the clinical routine data. Furthermore, there was 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 Hospital 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 was 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, four patients were taking quetiapine, two were taking aripiprazole one patient was on lamotrigine.

As this was a naturalistic clinical sample, inclusion criteria were broad: age ≥ 18 years, a current or previous psychopharmacological or non-psychopharmacological treatment for a perinatal 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.

Table 1: Demographic and phenotypic data of the whole sample

|  |  |  |
| --- | --- | --- |
|  | **N** | **Mean** |
| **Age** | 58 (2 missing) | 33.26 +/- 2.45 |
| **BMI** | 31 (29 missing) | 26.55 +/- 6.23 |
| **Diagnosis** | **N** | **Percentage** |
| 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** | **Percentage** |
| Amitriptyline | 16 | 20.8 |
| Aripiprazole | 2 | 2.6 |
| Bupropione | 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** | **Percentage** |
| Yes/No/Missing | 38/13/9 | 63.3/21.6/15.0 |
| **Marital status** | **N** | **Percentage** |
| Married | 13 | 21.3 |
| Relationship | 5 | 8.2 |
| Separated/Divorced | 3 | 4.9 |
| Missing | 39 | 63.9 |
| **Partner with mental illness** | **N** | **Percentage** |
| Yes/No/Missing | 4/12/44 | 6.6/20.0/73 |
| **Family History of Mental Illness** | **N** | **Percentage** |
| Yes/No/Missing | 15/4/41 | 25.0/6.6/68.3 |
| **Education** | **N** | **Percentage** |
| 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.

## Sample collection

Serum samples for drug measurement were taken in steady state, defined as a stable dosage for at least five 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 hours trough levels. For the medication taken in the evening, serum levels were 12 hours trough levels, as usual in clinical routine. 63.3% patients of the whole sample were already taking medication during pregnancy and we could get therapeutic drug level measurements from nine patients in the first trimester, 24 patients in the second trimester and 22 patients in the third trimester. From 5 patients/datasets, data were not available, in which trimester of pregnancy the drug levels were measured.

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 the 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 breast milk at different time points. Those measurements all took place after 2 weeks postpartum. From 20 patients we were are able to collect breast milk samples at several different time points. We aimed at collecting milk samples at the following time points: T1: trough level, 12 hours 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 hours intake of the medication and having breastfed); T5: 4 hours after intake of the medication; T6: 8 hours after intake of the medication.

## Quantification of drug levels in serum and breast milk

Serum concentrations of the medications were determined by an isocratic reversed-phase high performance liquid chromatography (HPLC) 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 program (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 program was operated without rejection.

## Outcome parameter children

As outcome measures of the new-borns following parameters were compared: gestational age at birth,APGAR values, birth weight, birth height, head circumference, base excess and pH of the umbilical artery as well as abnormalities. 60.1% of the infants were exposed to psychopharmacological medication in pregnancy.

## Statistical analysis

We tested the data for normal distribution using Kolmogorov-Smirnov-test and applied parametric or non-parametric tests as required for our analysis. Spearman-Rho correlation was used to investigate the correlation between drug concentrations in serum and breast milk as well as daily dosage. ANOVA test was used to analyse the effects of the 13 different medications on the development of the new-born. A Pearson-Chi²-test was used to test for differences for abnormalities in new-borns, who were prenatally exposed to medication and those who were not. Furthermore, we calculated concentration-by-dose-ratios for serum and breast milk (daily dosage/serum or breast milk 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 breast milk. Statistical analyses were calculated using SPSS (V26, IBM, Armonk, NY, USA).

Results

## Demographic data and sample description

The patients of the whole sample had a mean age of 32.87 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.

## 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 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).

**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 |
| Aripiprazol | 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 trimester. All values were in steady state and trough levels. N=Number

## Correlation between dosage, serum and breast milk concentration

## In the whole sample, there was a significant correlation analysing all medication together between daily dosage and serum concentration (Spearman Rho, r=0.68, p<0.0001) as expected but no significant correlation between neither daily dosage nor serum concentration with breast milk concentration (Spearman rho, r= 1.93; r=2.63 respectively and p=0.18; p=0.09 respectively) taking all available trough levels.

## Concentration-by-dose-ratios (C/D) and milk to serum (plasma) penetration ratios (M/P): 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. Fore- und hindmilk was not specified. Table 3 is showing the C/D serum, C/D mothermilk (=breastmilk) and M/P ratio at different available time points T1-T6 during the day.

**Table 3: Medication concentrations during 24hrs 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 |
| Sertralin | 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 |
| Lamotrigin | 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 breast milk in parallel, after 12 (mirtazapine, amitriptyline, quetiapine) or 24 hrs (citalopram, escitalopram, sertraline, lamotrigine, venlafaxine, 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 hours 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. SD= standard deviation. M/P=milk-plasma (serum) ratio. MM=mother milk=breastmilk.

The highest C/D ratio in serum was found in lamotrigine, however this was just in one patient. Regarding the C/D in breast milk, venlafaxine and lamotrigine showed the highest values in T1, however in T2-T6, citalopram and sertraline were also relatively high. The lowest C/D breast milk ratios could be found in clomipramine, which could not be detected in breast milk at all and quetiapine. The milk-to-serum ratio could only be calculated in T1, here the highest 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. The lowest 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. As seen in Figure 1, the C/Ds of most medication did not change remarkably 4 hours, 8 hours and 12 or 24 hours after intake of the medication, with the exception of sertraline and venlafaxine.

**Figure 1:** C/D ratio changes in breast milk during the day

Data sets of Mirtazapine n=3, Escitalopram n=4, Sertraline n=2, Venlafaxine n=3, Clomipramine n=2, Amitriptyline n=2, Quetiapine n=3 were used. Mean concentration/dose in breastmilk were calculated for the substance separately. Breastmilk samples were taken 4 hours, 8 hours and trough levels (which mean after 12 hours (regular intake in the evening) or 24 hours after intake (regular intake in the morning).

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

Figure 2: C/D ratio changes in breast milk 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, Quetiapine n=3 were used. Mean concentration/dose in breastmilk were calculated for the substance separately. Breastmilk samples were taken directly before breastfeeding, 1 h after and directly before the next breastfeeding interval (mostly 3-5 hours later).

*Concentration-by-dose-ratios (C/D) and milk to serum (plasma) penetration ratios (M/P): Transitional milk and mature breast milk*

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 weeks postpartum) (see Table 4) and 36 datasets in mature breastmilk (≥ 2 weeks postpartum) (see Table 5). Here again, the highest C/D in breastmilk was found in venlafaxine and lamotrigine. The highest 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 inter-individual variability.

**Table 4: C/D serum, breastmilk and milk plasma ratio after <= 2 weeks postpartum**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Medication** | N | **C/D serum** | | **C/D MM** | | **M/P** | |
| 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. SD= standard deviation. M/P=milk-plasma (serum) ratio. MM=mother milk=breastmilk.

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

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Medication** | **N** | **C/D serum** | | **C/D MM** | | **M/P** | |
| 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. SD= standard deviation. M/P=milk-plasma (serum) ratio. MM=mother milk=breastmilk.

## Outcome parameter children

From 39 children, we could assess basic parameters with regards to pregnancy and birth complications and the development in the first 12 months (see Table 5). Comparing APGAR values, birth weight, birth height, head circumference, base excess and pH of the umbilical artery, there were no significant differences between the new-borns 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 (student`s t test, all p≥0.05). Also, there were no significant differences between the different medications, which the new-borns were exposed to regarding birth weight, birth height, and head circumference (Kruskal-Wallis test, all p≥0.072). 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 abnormalities directly postpartum in the pregnancy exposed group whereas the number of mild abnormalities in the non-exposed group was higher (χ²; p=0.01). There were no significant differences regarding pregnancy and birth complications and the development of the children between the different medications (all p≥0.05) (Table 6).

**Table 6:** Birth outcomes and development after 12 months of the whole sample [insert here]

**Discussion**

The present study aimed at investigating changes in concentrations of psychopharmacological medication during pregnancy and lactation in serum and breast milk 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 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 [17]). The alteration patterns of antidepressants during the course of pregnancy are understudied and available data is 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 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 to 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 breast milk concentration we found a significant correlation of daily dosage and serum concentration taking all medication together. This correlation was expected as the therapeutic drug monitoring of the psychopharmacological medication investigated in this study is well established with TDM recommendation levels 1 and 2 [20]. Concerning the relation between serum and breast milk concentration we found no significant correlation neither taking all medication together nor analysing the different drugs separately. Highest concentration-by-dose-ratios in breast milk were found for venlafaxine and lamotrigine in the different samples and timepoints, lowest for quetiapine and clomipramine, the latter could not be detected in breast milk 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 inter-individual differences seen, in most women the M/P ratio was rather low but there were two individuals with high ratios. The reasons for those differences remain unclear, it might have also to do with differences in sampling hind- vs. foremilk. In principle, psychotropic medication can passively diffuse into breast milk. The higher the amount of lipid soluble molecules, the faster diffuse these drugs into breast milk. Higher concentrations can be found in hind-milk as it has a higher fat content than fore-milk [21]. In a recent systematic review and combined analysis investigating the transfer of antidepressants into amniotic fluid, umbilical cord blood and breast milk, Schoretsanitis and colleagues published combined penetration ratios (equivalent to M/Ps in breast milk). The M/Ps in breast milk 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 Schoretsanitis 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 breast milk [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 new-borns 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 new-borns 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 non-exposed 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 breast-milk. A placental exposure could be demonstrated by TDM measurements in amniotic fluid and umbilical cord blood (see [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 to new-borns of depressed but unmedicated mothers. Risks of spontaneous abortions, low APGAR scores at five minutes or neonatal convulsions were higher when mothers were treated with antidepressant medication during pregnancy compared to new-borns 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 less than 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 breast-milk 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].

## 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. To gain a better understanding of the amount of exposure in utero and through breast-milk as well as the impact on the development of the exposed children, future large-scale and longitudinal studies are needed.

While therapeutic drug monitoring for blood concentrations is well established and our laboratory fulfilled the quality control program without rejection, studies with TDM for breast-milk 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 breast-milk. Still, it needs to be considered that higher M/P-ratios can be misleading as the excretion of a drug into breast-milk is a function of the maternal plasma concentration: the higher the blood concentration, the higher the transfer into breast-milk [23, 30]. Additionally, we did not control if hind- or fore-milk was sampled and we did not analyse the composition of the breast milk which also could have influenced the concentration of the medication.

## 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.[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.

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Ethical approval

The study was approved by the ethic committees of the University Hospital of Frankfurt and Würzburg, Approval No. 136/17 and 18/20-sc.

Conflict of interest

The authors have no conflict of interest to declare.

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