Treatment With Antipsychotics in Pregnancy: Changes in Drug Disposition

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Although pregnancy is known to cause changes in drug pharmacokinetics, little is known about its impact on serum levels of antipsychotics. In this study we retrospectively assessed 201 routine serum antipsychotic therapeutic drug monitoring concentration measurements obtained from a total of 110 pregnancies in 103 women, and 512 measurements from the same women before and after pregnancy. Serum concentrations in the third trimester were significantly lower than baseline for quetiapine (−76%; confidence interval (CI), −83%, −66%; $P < 0.001$) and aripiprazole (−52%; CI, −62%, −39%; $P < 0.001$), but not for olanzapine (−9%; CI, −28%, +14%; $P = 0.40$). For the remaining antipsychotics (perphenazine, haloperidol, ziprasidone, risperidone, and clozapine), our dataset was limited, but it indicates that concentrations may decline at least for perphenazine and possibly also for haloperidol. Even though the clinical consequence of the serum concentrations decline remains to be elucidated, our results warrant close clinical monitoring throughout pregnancy, preferentially supported by therapeutic drug monitoring.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ Drug pharmacokinetics may undergo pronounced alterations in pregnancy, and dose requirements may change. For antipsychotics, only case reports are available to provide guidelines for dose adjustments.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ We used routine therapeutic monitoring data to explore the impact of pregnancy on serum levels of antipsychotics.

WHAT THIS STUDY ADDS TO OUR KNOWLEDGE

☑ With data from 110 pregnancies, this study is by far the largest to date. There was a pronounced decline in the serum concentrations of quetiapine and aripiprazole, whereas concentrations of olanzapine did not change. The study also provides limited data for other antipsychotics.

HOW THIS MIGHT CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE

☑ Our results warrant reconsideration of the general advice of using the prepregnancy "minimum effective dose" of antipsychotics during pregnancy. Increased drug clearance in pregnancy may cause subtherapeutic concentrations. Although the clinical implications of the lowered drug levels require further research, our results call for close clinical monitoring of all patients using antipsychotics in pregnancy.

Whether or not to prescribe antipsychotic drugs during pregnancy is a challenging dilemma. One the one hand, treating the mother necessarily implies exposing the fetus to the drug, thereby potentially causing harmful effects to the unborn child. On the other hand, abstaining from treatment puts the mother at risk of a worsened psychiatric condition, with the dangers this involves for the mother and child. Weighing these options against each other, the recommendation has often been to discontinue treatment, especially during the first trimester.[1] However, during the past decade more safety data have accumulated suggesting that antipsychotics are relatively safe to use in pregnancy.[1–3] It has also been demonstrated that discontinuing ongoing maintenance treatment for severe mood and psychotic disorders during pregnancy carries a high risk of disease recurrence.[2] Thus, for women with substantial psychiatric morbidity and good treatment response, maintained use of an antipsychotic during pregnancy might often represent the best risk–benefit option.

When a decision has been made to commence or continue pharmacological treatment during pregnancy, there is a paucity of data to ensure appropriate dosing. Numerous physiological changes occur during pregnancy, some of which may cause changes in drug disposition, e.g., due to alterations in body weight, plasma volume, hepatic metabolic capacity, and renal function.[4–7] Thus, the right drug dose for a woman prior to conception or for the patient group in general is not necessarily the right dose during pregnancy. For antipsychotics, evidence on changes in drug disposition in pregnancy is extremely

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Table 1 The study population

	Mode of administration	Number of serum drug concentration measurements: During pregnancy	First 12 weeks following delivery	At baseline	Number of pregnancies	Number of women
Quetiapine	PO	66	11	144	35	33
Olanzapine	PO	47	11	84	29	28
Aripiprazole	PO	31	5	44	14	12
Perphenazine	IM	13	1	40	8	8
Perphenazine	PO	7	1	17	7	5
Clozapine	PO	10	2	114	4	4
Ziprasidone	PO	7	4	14	3	3
Risperidone	PO	5	1	9	4	4
Haloperidol	PO	5	0	2	2	2
Other antipsychotics[a]	PO/IM	10	0	8	10	10
Total		201	36	476	110[b]	103[b,c]

PO, oral; IM, intramuscular depot injections.
[a]Other antipsychotics included chlorprothixene ($n = 5$), risperidone intramuscular depot injections ($n = 2$), flupentixol ($n = 1$), zuclopenthixol ($n = 1$), and levomepromazine ($n = 1$). [b]In six pregnancies serum drug concentrations were measured for two different antipsychotics in the same pregnancy. [c]Four women contributed with two pregnancies each, and one woman contributed with four pregnancies.

scarce and confined to one case report on quetiapine[8] and a small cases series on aripiprazole.[9] The aim of this study was to elucidate to what extent pregnancy affects serum concentrations of antipsychotic drugs in a large target population in a naturalistic setting.

RESULTS

Table 1 and **Figure 1** provide an overview of all serum drug concentration measurements and pregnancies included in the study. Overall, the mean duration of pregnancy was 274 ± 19 days, and the mean maternal age at delivery was 29.8 ± 6.6 years.

The model estimates for the $\log_e$-transformed serum concentrations across pregnancy for nine antipsychotics are given in **Supplementary Table S1**. **Table 2** shows the estimated serum concentrations at baseline and by trimester during pregnancy, as well as the relative changes from baseline in percent. For the three drugs with the most observations (>10 pregnancies) there were statistically significant decreases in serum concentrations in mid-third trimester compared to baseline for quetiapine (−76%) and aripiprazole (−52%), but not olanzapine. For the remaining drugs our dataset was more limited (**Table 2**).

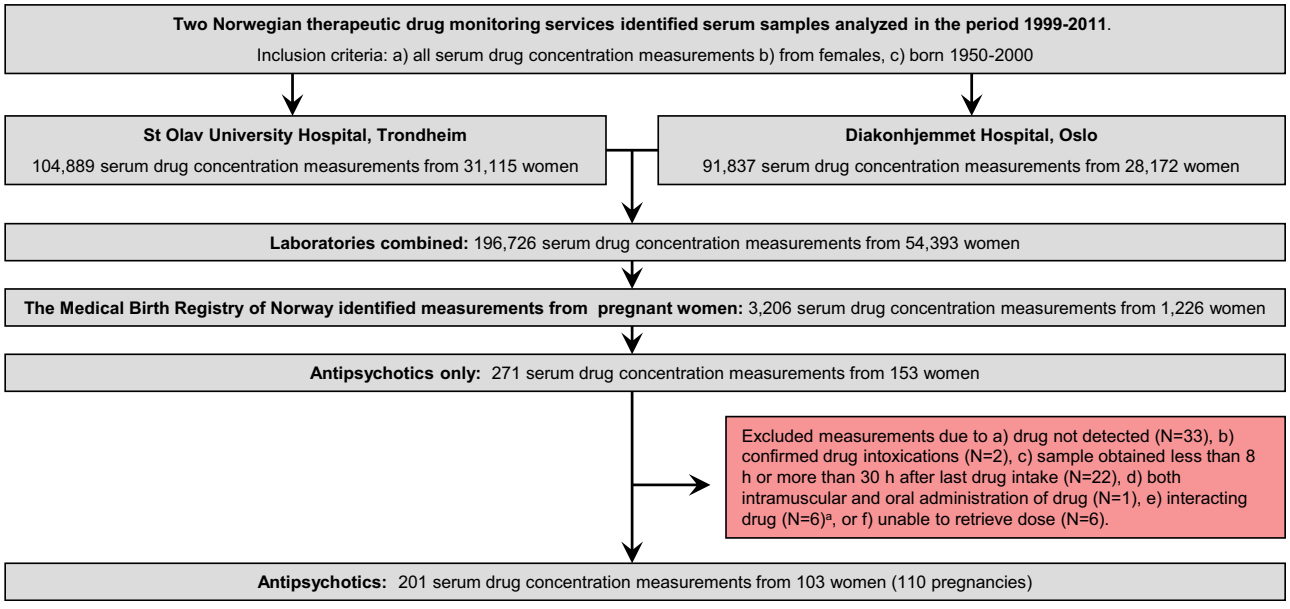

Figure 1 Flow of sample identification and inclusion of therapeutic drug monitoring samples of antipsychotic drugs obtained during pregnancy. [a]Six measurements were excluded due to the following drug interactions: clozapine + fluvoxamine ($n = 1$), olanzapine + carbamazepine ($n = 1$), perphenazine + paroxetine ($n = 2$), perphenazine + fluoxetine ($n = 1$), and risperidone + fluoxetine ($n = 1$). [Color figure can be viewed at cpt-journal.com]

Table 2 Serum antipsychotic concentrations across pregnancy

			Estimated serum concentrations												
			Baseline	1st trimester		2nd trimester		3rd trimester							
	Number of pregnancies	Dose[a]	Conc	Conc	Change	Conc	Change	Conc	CI low	CI high	Change	CI low	CI high		
Measure	*N*	mg/day	ng/mL	ng/mL	%	ng/mL	%	ng/mL	ng/mL	ng/mL	%	%	%	*P*[c]	CF[b]
Quetiapine	35	400	75.6	58.7	−22	32.5	−57	18.0	12.6	25.7	−76	−83	−66	<0.001	2.61
Olanzapine	29	10	21.3	20.9	−2	20.1	−6	19.3	15.3	24.3	−9	−28	+14	0.40	3.20
Aripiprazole[d]	14	15	232.4	204.2	−12	151.1	−35	111.7	87.6	142.6	−52	−62	−39	<0.001	2.23
Perphenazine IM	8	7[e]	2.1	1.8	−15	1.2	−41	0.9	0.6	1.2	−59	−71	−42	—	2.48
Perphenazine PO	7	30	2.5	2.1	−18	1.3	−48	0.8	0.4	1.9	−67	−85	−25	—	2.48
Clozapine	4	300	418.6	399.7	−5	358.8	−14	322.1	227.3	456.6	−23	−46	+9	—	3.06
Ziprasidone	3	80	56.7	50.1	−12	37.5	−34	28.0	13.1	59.9	−51	−77	+6	—	2.42
Risperidone[d]	4	5	24.4	23.2	−5	20.7	−15	18.4	8.9	37.7	−25	−63	+54	—	2.35
Haloperidol	2	8	5.0	4.4	−12	3.2	−35	2.4	1.3	4.5	−52	−74	−10	—	2.66

The column "baseline" provides the model estimates for the dose-adjusted serum antipsychotic concentrations at day 0 (nonpregnant). The first, second, and third trimester columns provide the model estimates for the concentrations in gestational weeks 6, 20, and 34, respectively. The columns "change" provide the change from baseline concentration, in percent.

IM, intramuscular depot injections; PO, oral; Conc, concentration; CI, 95% confidence interval limits.

[a]Dose = defined daily dose. [b]Serum concentrations in mass units can be converted to molar units by multiplication with the conversion factor (CF). Nanomol/L = ng/mL x CF. [c]*P*-value for the regression line in the statistical model. *P*-values are not given for drugs with observations from less than 10 pregnancies. [d]For drugs with clinically significant pharmacologically active metabolites the total active moiety concentrations were used for calculations (i.e., aripiprazole plus dehydroaripiprazole and risperidone plus 9-hydroxyrisperidone). [e]For perphenazine intramuscular depot injections the 7 mg dose corresponds to ~100 mg perphenazine decanoate given every 14 days.

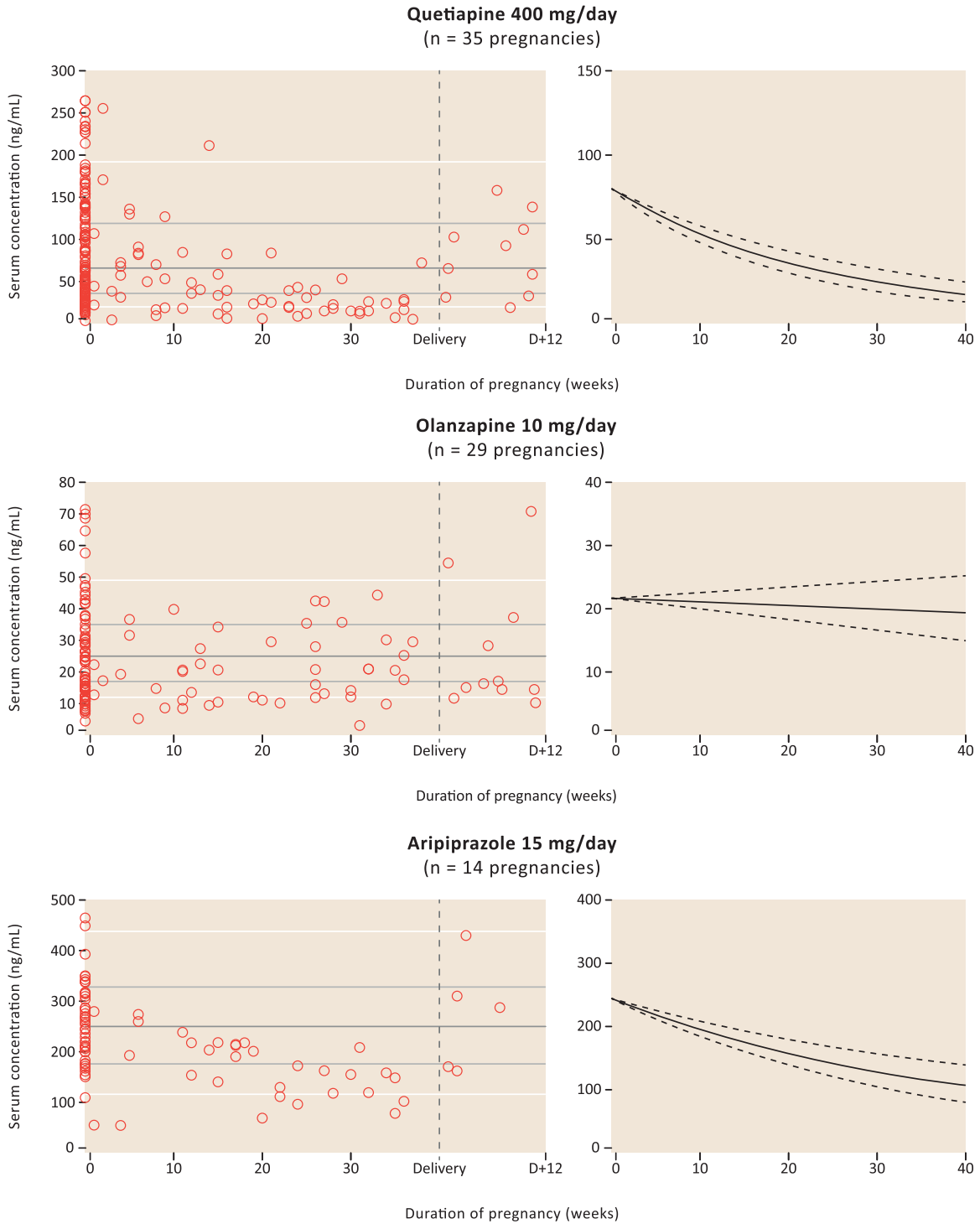

Figure 2 Quetiapine, olanzapine, and aripiprazole serum concentrations in pregnancy. The figures to the left show each of the observed serum concentrations of the study, adjusted to the doses presented in the figure headings. Measurements from the same women in a nonpregnant state (baseline values) are shown as pregnancy week 0. Delivery is set to pregnancy week 40. Thus, for a woman who gave birth in week 38, a sample drawn *t* weeks after delivery would be shown *t* weeks to the right of the vertical dashed line. For aripiprazole the concentrations shown represent the active moiety (parent drug + metabolite). Six outliers for quetiapine are not shown in the figure. These were four measurements at week 0 (concentrations of 554, 536, 470, 440 ng/mL), one measurement at week 7 (302 ng/mL), and one measurement at week D+3 (315 ng/mL). The horizontal lines represent the median (dark gray), 25- and 75-percentiles (light gray), and 10- and 90-percentiles (white) for concentration measurements (adjusted to the doses presented in the figure headings) for all women aged 18–45 years from the St Olav University Hospital TDM database. The figures to the right show the expected serum concentrations across pregnancy for women using the antipsychotic doses presented in the figure headings. The regression lines are shown with solid lines, and the 95% confidence limits with dashed lines. For aripiprazole the concentrations shown represent the active moiety (parent drug + metabolite). D+12 = Delivery + 12 weeks. [Color figure can be viewed at cpt-journal.com]

Table 3 Parent compound / metabolite ratios across pregnancy

Ratio	Number of pregnancies N	Estimated ratios							
		Baseline	1st trimester		2nd trimester		3rd trimester		
		ratio	ratio	%	ratio	%	ratio	%	P^a
Quetiapine / norquetiapine	12	0.44	0.42	−5	0.38	−15	0.34	−24	0.16
Olanzapine / N-demethylolanzapine	8	6.87	8.06	+17	11.70	+70	16.98	+147	—
Aripiprazole / dehydroaripiprazole	14	3.20	2.99	−6	2.57	−20	2.20	−31	<0.001
Clozapine / norclozapine	2	1.31	1.34	+2	1.41	+8	1.49	+14	—
Risperidone / 9-hydroxyrisperidone	4	0.09	0.08	−8	0.07	−24	0.05	−37	—

Only analyses with available metabolite data (see Table S2) are included. The column "baseline" provides the model estimates for the parent compound / metabolite ratio at day 0 (nonpregnant). The first, second, and third trimester columns provide the model estimates for the parent compound / metabolite ratios in gestational weeks 6, 20, and 34, respectively.

[a]*P*-value for the regression line in the statistical model. *P*-values are not given for drugs with observations from fewer than 10 pregnancies.

Individual concentrations related to gestational week, as well as when the women were not pregnant, are shown in **Figure 2** for quetiapine, olanzapine, and aripiprazole, and in **Figure S1** for the remaining drugs. The figures also show the percentile values derived from the concentrations in the general female reference population. The regression lines with 95% confidence limits showing the expected serum concentrations for each antipsychotic drug during pregnancy are shown in **Figure 2** for quetiapine, olanzapine, and aripiprazole, and in **Figure S2** for the remaining drugs.

For quetiapine, olanzapine, aripiprazole, clozapine, and risperidone, metabolites had been measured in all or some samples, allowing us to study parent compound / metabolite ratios. The original $\log_e$-transformed values (**Table S2**) are converted to actual ratios in **Table 3**. For aripiprazole, there was a statistically significant decline in parent compound / metabolite ratio throughout pregnancy (**Table 3**).

DISCUSSION

The present study, including antipsychotic serum concentration data from 110 pregnancies, is by far the largest study to date regarding the disposition of antipsychotics in pregnancy. The principal finding is that the serum concentrations of quetiapine and aripiprazole decrease by more than 50% during pregnancy, a change that is likely to be of clinical relevance. In contrast, olanzapine concentrations did not change during pregnancy. For the remaining antipsychotics (perphenazine, haloperidol, ziprasidone, risperidone, and clozapine) our dataset was limited, although some information may be drawn from **Figures S1** and **S2**.

A myriad of physiological changes may occur during pregnancy and alter drug disposition.[4–7] Changes in volume of distribution may alter the concentration after the first dose and the loading dose requirements, and alter peak concentrations and elimination half-life,[6] but generally have little influence on the trough concentration at steady state. Concentrations of binding protein for drugs in plasma (albumin and α-1-acid glycoprotein) may be reduced by 20–30% in the third trimester.[10] This effect might be relevant for antipsychotics, which are all highly protein bound,[11] but it is still not sufficient to fully explain the extent of changes in the observed total drug levels, nor the differences between them. Renal filtration in pregnancy is also considered to be of minor relevance for our results, as all drugs in our study have a negligible degree of unmetabolized urinary excretion (<10%).[11]

In contrast, we consider changes in hepatic clearance to be of high relevance for our results. Since all drugs in our study are predominantly eliminated by hepatic cytochrome P450 (CYP) enzymes,[11–13] we believe these enzymes to be the crucial explanatory factor for changes (or lack thereof) in the observed drug concentrations in our study. Our findings are also largely in line with what could be expected from data on the activity of drug-metabolizing enzymes in pregnancy.

Quetiapine is metabolized mainly by CYP3A4,[13] an enzyme known to be induced during pregnancy.[4–7] Similar drug concentration declines in pregnancy have also been reported for other CYP3A4 substrates,[14,15] and also in a previous case report for quetiapine.[8] In that publication, trough serum levels of quetiapine in the first, second, and third trimester were 42%, 55%, and 53% lower than the nonpregnant levels, respectively. Our study confirms and extends the observed decline in that case report, and suggests that the quetiapine serum concentration decline in the third trimester may in fact be even greater than previously described.[8] We also found that the observed decline in our study was not caused by use of different formulations of quetiapine (extended release vs. immediate release), as a separate analysis for each of these groups provided similar results (data not shown).

Aripiprazole is metabolized by CYP2D6 to the active metabolite dehydroaripiprazole, which is in turn further metabolized by CYP3A4.[13] CYP2D6 expression and activity also increase during pregnancy,[4–6,16] and for other CYP2D6 substrates a 2–13-fold increase in clearance has been described.[17] A previously published case series described aripiprazole plasma concentrations in three pregnancies in two women.[9] Aripiprazole concentrations declined by more than two-thirds during pregnancy, and returned to baseline within 2–3 weeks after delivery.[9] In the present study, we found a 52% reduction of the active moiety (aripiprazole + dehydroapiprazole) concentration in the third trimester compared to baseline, and a similar reduction also for the parent compound as such (data not shown).

None of the remaining drugs of our study have previously been investigated with respect to changes in serum levels in pregnancy. From a theoretic perspective, the major CYP enzymes involved in

the metabolism of perphenazine (CYP2D6), ziprasidone (CYP3A4), and haloperidol and risperidone (CYP2D6 and CYP3A4)[13] suggest that their serum levels could decline in pregnancy, as they do for aripiprazole and quetiapine. We did find a trend towards declining perphenazine concentrations in pregnancy. For instance, in **Figure S2** almost all serum perphenazine intramuscular concentrations in pregnant women were below the median (gray line) of the nonpregnant population. This is particularly interesting, as nonadherence is not an issue for intramuscular administration. Also for oral perphenazine and haloperidol, a corresponding trend was found. However, it should be emphasized that the number of observations was low, thus being vulnerable to variations caused by confounding factors in single subjects, such as outlier observations due to nonadherence or erroneous dose information. For ziprasidone and risperidone the numbers were even smaller and the trends even less clear.

For olanzapine and clozapine the estimates for alterations in the serum concentrations during pregnancy were closer to zero, indicating no or little change. Although the confidence intervals for these estimates are narrower for olanzapine (with observations from 29 pregnancies) than for clozapine (with observations from four pregnancies only) it is interesting to note that both these drugs have a metabolism largely dependent on CYP1A2,[13] an enzyme that has been shown to have a *decreased* activity during the second and third trimesters.[6,18] This could explain why our results for these drugs may differ from the others. Another explanation that cannot be excluded is reduced cigarette smoking during pregnancy, which would also result in decreased CYP1A2 activity.[19] Unfortunately, information on smoking habits was not available in our dataset.

It is also of importance to explore when and how maternal serum concentrations return to normal following delivery. Some researchers have provided evidence of a postpartum drop in metabolic capacity that could result in briefly elevated drug concentrations (i.e., higher than baseline) for some antidepressants during the first 6–8 weeks following delivery.[20–24] Due to few postpartum observations our study can neither confirm nor rule out that such a refractory period occurs for antipsychotic agents. However, our data do indicate that serum concentrations return back to baseline values within the first weeks after delivery (**Figure 2** and **Figure S1),** as also shown previously for aripiprazole.[9]

Our study has some limitations that need to be addressed. First, as we did not have access to any clinical data we do not know whether the reduced serum antipsychotic concentrations actually caused clinical deterioration. Although it is reasonable to assume that this could occur, and similar studies on antidepressants[8,20,23,25] have indicated such an effect, this subject should be explored in future studies on antipsychotics.

Second, it is unknown to which degree patients were adherent to the prescribed medication; a challenge that not least could be of relevance during pregnancy.[26–28] In particular, for the drugs with low number of observations in our study, the results could be vulnerable to variations caused by variable adherence in single subjects. However, all measurements with a serum concentration of zero ($n = 33$, **Figure 1**) were excluded from the study. Also, even though an increased degree of nonadherence during pregnancy would cause lower concentrations, we consider it unlikely that such a situation should be confined to, e.g., quetiapine and aripiprazole and not to olanzapine.

Third, our study relies on correct information from the requesting clinicians regarding drug doses. Although all measurements lacking information on drug dose ($n = 6$, **Figure 1**) were excluded from the study, we cannot exclude that erroneous dose information exists among the remaining measurements, and again, the results for drugs with the lowest number of observations would be most vulnerable to variations caused by this factor.

Fourth, there is a variability of the time interval from last dose to sampling. Ideally, this interval should have been standardized to 12 h, and all values calculated to such using drug-specific elimination half-lives, as in a previous publication from our group.[29] However, information for calculating the time interval was often missing on the requisition form, and excluding all such measurements would result in loss of precious data. We believe that some of the variability in our results (**Figure 2** and **Figure S1**) derives from variations in these time intervals, an inevitable factor given the retrospective nature of our study, but we found no systematic difference in the postdose time interval between measurements in pregnancy and measurements at baseline (**Table S3**).

Fifth, the statistical model used in our study assumes a linear change in the logarithm of serum concentrations for each week of pregnancy. It is possible that the changes in pregnancy may be better described by a more sophisticated function. However, we did not investigate this possibility further.

On the other hand, this study also has some strengths, the most obvious being the very large sample size. Due to the ethical issues involved in clinical drug trials during pregnancy,[30,31] retrospective studies of samples taken in a naturalistic setting are often the only available tool to obtain information on drug disposition in pregnancy. Due to the variability often seen in observational studies a large sample size is crucial, such as in our use of data from two large routine therapeutic drug monitoring (TDM) services over a time span of 11 years. It is also a strength that we could link the TDM data a national birth registry, thereby allowing precise identification of pregnant women in the dataset, and making misclassification of gestational week unlikely.

In conclusion, our results show that for quetiapine and aripiprazole, there is a pronounced decline in serum concentrations throughout pregnancy. These changes may warrant reconsideration of using the prepregnancy "minimum effective dose" during pregnancy. As drug clearance increases subtherapeutic drug levels may ensue, potentially exposing the mother and unborn child to both the medication and the illness. Based on our data, doubling the daily dose may be needed in order to compensate for the increased drug clearance in the third trimester for these drugs. For olanzapine, serum concentrations seem to remain largely unchanged during pregnancy, and dose adjustments might not be necessary. For the remaining antipsychotics our dataset was more limited, but indicates that concentrations may decline at least for perphenazine and possibly also for haloperidol. Even though the clinical consequence of the serum concentration declines remains to be elucidated, our results call for close clinical monitoring of all patients using antipsychotics in pregnancy. If available, therapeutic drug monitoring could be undertaken, preferentially beginning when the woman is well prior to or in an early stage of

pregnancy. The measured drug level could be used as that woman's target concentration across pregnancy, in a similar approach to what is already used for lamotrigine and other anticonvulsants.[32]

METHODS

A model relating dose-adjusted serum concentrations of antipsychotics to gestational week was developed in order to elucidate to what extent pregnancy affects drug disposition. To study infant outcomes was beyond the scope of the present study.

Therapeutic drug monitoring data

The Norwegian healthcare system has a tradition for routine TDM of psychotropic drugs.[33] After obtaining approval from the Regional Committee for Medical and Health Research Ethics, the Norwegian Centre for Research Data (Data Protection Official), the Norwegian Directorate of Health, and the Medical Birth Registry of Norway (MBRN) publication council, serum concentration data for antipsychotic drugs were collected from the two largest TDM services for psychotropic drugs in Norway (i.e., Department of Clinical Pharmacology at St. Olav University Hospital in Trondheim, and Center for Psychopharmacology at Diakonhjemmet Hospital in Oslo). The antipsychotics TDM data contain serum concentrations measured in a naturalistic setting from psychiatry inpatients and outpatients. In addition to measured serum concentrations, the TDM databases contain information obtained from the requisition forms, such as the prescribed antipsychotic drug dose, its mode of administration, time of last drug intake, time of blood sampling, and types and doses of concomitant drugs. Although a complete set of information is not always provided by the requisitioner, it is a general recommendation from the laboratory that TDM samples are collected as trough levels at steady state.

The Medical Birth Registry of Norway (MBRN)

The MBRN is a population-based registry containing information on all births in Norway since 1967.[34] The registry is based on compulsory notification of every birth or late abortion from 12 completed weeks of gestation onwards. The report form includes date of delivery and length of pregnancy as well as other information regarding the mother and infant.

Data linkage and available data

First, a combined laboratory TDM file was created, containing all serum concentration measurements (for any drug) in the period October 1999 to December 2011 for all women of reproductive age (i.e., born 1950–2000). The file consisted of a total of 196,726 measurements from 54,393 women (**Figure 1**). Using the unique 11-digit identification number assigned to all individuals living in Norway, the MBRN could identify all pregnant women in the dataset. By applying this procedure, 3,206 measurements from 1,226 pregnant women were identified (**Figure 1**). For the current study we retrieved the following information: the personal identification number, the measured drug serum concentration, time of last dose, time of sampling, drug dose, concomitant drug use, other clinical information, name of the responsible physician, gestational week at the time of sampling, and date of delivery.

Inclusion criteria

The basis of the present study is all samples analyzed for an antipsychotic agent, defined as a drug classified in the World Health Organization Anatomical Therapeutic Chemical group N05A,[35] except lithium. Then 271 measurements from 153 pregnant women were available (**Figure 1**). Measurements were excluded if 1) no drug was detected, 2) the sample was obtained as a result of drug intoxication, 3) the sample was obtained less than 8 hours or more than 30 hours after last oral drug intake, 4) both intramuscular and oral formulation of the drug was used at the same time, or 5) there was concomitant use of a known interacting drug (i.e., an interaction that, based upon information from an interaction database,[36] was described as having a major or moderate pharmacokinetic effect on the antipsychotic agent). If the requisition form lacked information on drug dose the authors contacted the responsible physician, who attempted to obtain this information from the medical record. If we were unable to retrieve this information, the measurement was excluded. The final dataset consisted of 201 serum drug concentrations from 103 women (**Figure 1**). The individual drugs available are listed in **Table 1**.

Control samples

Having identified the pregnant women and their individual pregnancy periods in the extracted data file, we used the original TDM databases to retrieve serum concentration measurements before and after pregnancy from the same women, to serve as baseline observations. Identical inclusion and exclusion criteria as presented above were used, and 512 measurements were identified (**Table 1**). Thirty-six of these were from the first 12 weeks following delivery (i.e., in the "returning to baseline" phase). These measurements were not used in the statistical model, but are included in **Figure 2** and **Figure S1**. The remaining 476 measurements were used for the statistical comparisons. Drugs with less than five observations in total during pregnancy or with no baseline observations for any of the subjects were excluded from further analysis. These drugs are categorized as "other antipsychotics" in **Table 1**.

In order to provide an estimate of expected antipsychotic drug concentrations in a female reference population, we extracted antipsychotic serum concentration data from all women aged 18–45 from the St. Olav University Hospital TDM database, using identical inclusion and exclusion criteria as presented above. These data were not included in the statistical analyses, but the 10, 25, 50, 75, and 90 percentile values derived from these data are shown in **Figure 2** and **Figure S1** for comparison purposes. The numbers of measurements upon which these calculations were based were 1,563 for quetiapine, 4,317 for olanzapine, 569 for aripiprazole, 521 for oral perphenazine, 600 for perphenazine intramuscular depot injections, 3,810 for clozapine, 804 for ziprasidone, 1,071 for risperidone, and 241 for haloperidol.

Determination of antipsychotic concentrations in serum

Quantification of the antipsychotic and metabolite concentrations was performed with liquid chromatography-mass spectrometry/tandem mass spectrometry. The analytical methods have been described in more detail previously.[37,38] During the timespan of the study, some assays had been improved and adjusted, but all modifications were cross-validated.

Data analysis

Serum concentrations in ng/mL were divided by the daily dose used by the woman at the time of sampling, providing a serum concentration/dose ratio, and then multiplied by the defined daily dose (DDD), which is the assumed average maintenance dose per day for that drug used for its main indication in adults.[35] This procedure assumes that pharmacokinetics of the drugs are dose-proportional over the typical dosing ranges, and provides an intra- and interindividually comparable concentration for each drug. All concentrations presented and discussed in this article, including tables and figures, are dose-adjusted to the DDD of the drug. The DDDs for the various drugs are given in **Table 2**.

As the concentration distributions were found to be heavily right-skewed, the logarithm of the concentrations was employed as the outcome variable in the statistical model, to achieve near normality. Since multiple measurements were available from the same patient, a linear mixed model was used. The model assumes that each individual patient possesses a random intercept (i.e., an individual "offset") in addition to being affected by the gestational week at the time of sampling. Baseline measurements were set to gestational week 0 in the model, as shown in **Figure 2** and **Figure S1**. This way, the effect of gestational week on concentration compared to baseline is estimated for each drug. The model assumes that changes in drug concentrations on the logarithmic scale are linear throughout pregnancy.

For drugs where both the parent drug and the metabolite were measured, parent drug/metabolite concentration ratios during pregnancy were compared to baseline values as described above; ratios were log transformed and fitted into a linear mixed model, estimating the baseline ratios and effect of each gestational week.

All model parameters, including variance components, were estimated by the method of maximum likelihood using STATA 13 (Statsoft, Tulsa, OK) command "mixed." Data are presented as means with 95% confidence intervals. $P < 0.05$ was considered statistically significant, if derived from observations from more than 10 pregnancies.

Additional Supporting Information may be found in the online version of this article.

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CONFLICTS OF INTEREST

The authors declared no conflicts of interest.

AUTHOR CONTRIBUTIONS

A.A.W., E.M., and O.S. designed the research; A.A.W., M.B., and I.C. performed the research; A.A.W., E.S., and O.S. analyzed the data, A.A.W. wrote the first manuscript draft, and all authors revised it critically, and approved the final manuscript.

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