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ORIGINAL REPORT

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Modeling exposures of medications used episodically during pregnancy: Triptans as a motivating example

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Abstract

Purpose: To assess the validity of dispensed prescription to classify exposure to medications used episodically during pregnancy, and to explore individual trajectories of episodic medication use across pregnancy, using triptans for migraine as the motivating example.

Methods: We compared self-reported triptan use during pregnancy in The Norwegian Mother, Father and Child Cohort Study (MoBa) to dispensed prescriptions in The Norwegian Prescription Database and calculated Cohen's kappa coefficient (κ), sensitivity, specificity and predictive values using MoBa as reference standard. We used group-based trajectory modeling to estimate exposure trajectories in MoBa according to probability of triptan use across pregnancy.

Results: We identified 6051 pregnancies where mothers filled at least one triptan prescription or reported migraine or triptan use in the 6 months before or during pregnancy. Sensitivity of prescribed triptans during pregnancy was low (39.1%), but specificity was quite high (95.4%). Agreement between the two data sources was fair (κ 0.36). We identified three trajectory groups in MoBa including constant-high, decreasing-medium and decreasing-low probability of triptan use across pregnancy.

Conclusions: Using dispensed prescriptions rather than self-report to classify exposure to triptans during pregnancy is likely to result in substantial under-estimation of exposure. In this study, traditional definitions of ever-exposed vs never-exposed failed to capture variations in drug utilization during pregnancy.

KEYWORDS

group-based trajectory modeling, MoBa, NorPD, pharmacoepidemiology, pregnancy exposure misclassification, sensitivity and specificity, triptans

1 | INTRODUCTION

Information about the accuracy of medication exposure is essential to avoid biased risk estimates in pharmacoepidemiological studies.[1] Correct exposure classification is of special importance in studies on medication safety during pregnancy, as windows of fetal vulnerability often are narrow and misclassification may lead to unpredictable biases that could give rise to either false-positive signals of teratogenicity or false-negative reassuring findings.[2,3] Exposure misclassification is of particular concern in studies using information on dispensed prescription instead of actual time of medication intake to determine safety of medications used on "as needed" basis.[4] Previous

This work has not been submitted or presented elsewhere.

Nordic studies have found low agreement between dispensed medications and self-reported use for episodically used medications during pregnancy, with predictive values ranging from 21.4% for antimigraine drugs and 21.5% for opioids to 24.7% for hypnotics,[5] and sensitivity ranging from 27.8% for hypnotics to 48.8% for opioids when using self-report as the reference standard.[6]

Exposure to medications in pregnancy has traditionally been defined as ever-exposed or never-exposed, which may fail to capture more complicated drug utilization patterns. Fetal teratogenicity depends on the timing, intensity and duration of medication use.[7] These aspects have been addressed in some studies by categorizing exposure by specific time periods or summarizing the number of days of exposure; however, these methods are not able to incorporate changes in medication use during pregnancy.[8] Modeling individual trajectories of medication exposure through clustering methods such as group-based trajectory modeling (GBTM)[9] is an approach that can summarize complex patterns of medication use across pregnancy.[10] GBTM has previously been applied to estimate medication adherence,[11] and has to a limited extent been used in studies of medication safety in pregnancy.[10] For example, one study used GBTM to cluster women according to their probability of use of thyroid replacement therapy before, during and after pregnancy, and identified four disjoint trajectories.[12] However, no studies to date have used GBTM to identify longitudinal clusters of intermittently used drugs during pregnancy.

This study focused on triptans used for migraine during pregnancy. Triptans are used intermittently, in response to a migraine attack, which means that dispensed medications are often not taken at the same time as the dispensing. This may influence both exposure data validity and the patterns of use, which may vary between women according to migraine frequency and severity. Based on this, we defined two main objectives: First, we aimed to assess the agreement of triptan exposure based on records from the Norwegian Prescription Database (NorPD) compared to self-reported use in the Norwegian Mother, Father and Child Cohort Study (MoBa). Secondly, we aimed to explore triptan utilization patterns across pregnancy using GBTM.

KEY POINTS

- Medications used episodically during pregnancy, like triptans, are particularly susceptible to exposure misclassification in studies of medication safety during pregnancy.
- Agreement between self-reported and dispensed triptans during pregnancy was fair. Sensitivity of dispensed triptans during pregnancy was low (39.1%) and specificity was high (95.4%), compared to self-reported use. Researchers using dispensed prescription to classify medication exposure should perform bias analysis taking into account exposure misclassification.
- Three utilization trajectories were identified using self-report, including constant-high, decreasing-medium, and decreasing-low probability of triptan use during pregnancy.
- Drug utilization patterns should be explored and guide researchers in studies of medication safety during pregnancy.

2 | METHODS

2.1 | Data sources

This study used data from The Norwegian Mother, Father and Child Cohort Study (MoBa), The Medical Birth Registry of Norway (MBRN), and The Norwegian Prescription Database (NorPD). MoBa is a population-based pregnancy cohort study conducted by the Norwegian Institute of Public Health.[13] All pregnant women who could speak Norwegian were invited to participate in the period 1999 to 2008, and 41% of those invited participated in the study.[14] The cohort now includes 114 500 children, 95 200 mothers and 75 200 fathers. The current study is based on data file version 9, released for research in November 2015. MBRN is a national health registry containing information about all births in Norway since 1967, including stillbirths and elective abortions after week 12.[15] NorPD contains information about all prescriptions dispensed to individual patients from pharmacies in Norway since 2004.[16]

2.2 | Study population

A total of 61 774 pregnancies that were enrolled in MoBa after 2005 and had a record in MBRN were linked to NorPD using each pregnancy's unique identification number. Women participating before 2005 were excluded in order to ensure complete capture of prescriptions before pregnancy, as NorPD includes prescriptions starting from 2004. We excluded pregnancies where the mother did not complete questionnaires in both the first and third trimesters (Q1 and Q3). Pregnancies with missing gestational age or missing date of childbirth were also excluded, as well as pregnancies where timing of triptan exposure was unknown (ie, pregnancies where the woman reported triptans but not whether it was used during pregnancy). The study sample comprised 51 386 pregnancies. From this sample we defined a migraine sample of 6051 pregnancies in which mothers reported migraine or triptan use 6 months before or during pregnancy, or filled a triptan prescription in the 6 months before or during pregnancy (as triptans are used exclusively for migraine). A flow chart of study sample selection is shown in Figure 1.

2.3 | Definition of triptan exposure

We defined binary exposure variables for the pregnancy period, trimesters, 4-week gestational intervals (weeks 0-4, 5-8, 9-12, 13-16, 17-20, 21-24, and 25-28), and the 6-month period before pregnancy, based on (a) self-reported triptan use in MoBa, and (b) dispensed triptan prescriptions in NorPD. Medications were coded based on the Anatomical Therapeutic Chemical (ATC) Classification System,[17] where N02CC indicates triptans. A timeline of the reporting periods available in MoBa and the correspondence with NorPD is presented in Figure S1.

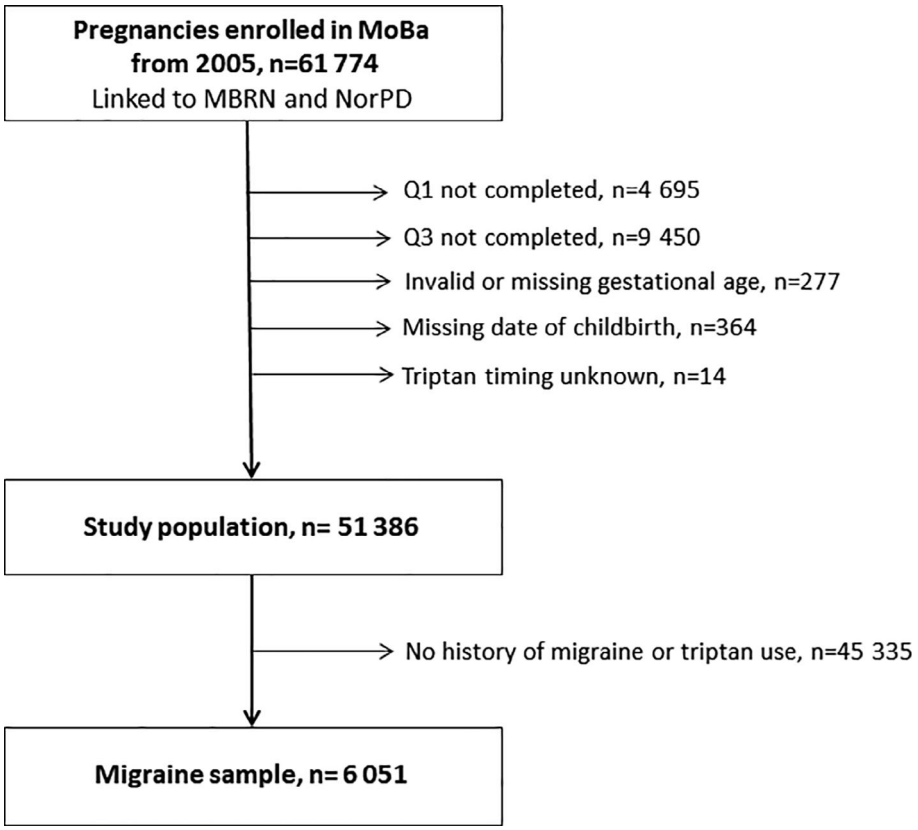

FIGURE 1 Flow chart of study sample selection. Conditions of exclusion can overlap. Triptan timing unknown reflects pregnancies where we cannot determine if exposure was before, during or after pregnancy. The migraine sample consists of mothers who reported migraine or use of triptans during pregnancy or during the 6 months before pregnancy, or filled at least one triptan prescription within the same period

MoBa includes three health-related questionnaires during pregnancy where women could report their medication use (Q1, Q3 and Q4).[18] Medication exposure was classified as occurring prior to pregnancy (Q1), during weeks 0-4, 5-8, 9-12, and 13+ (Q1), 13-16, 17-20, 21-24, 25-28 (Q3), and late pregnancy (Q4); additional information about the questionnaires can be found in Appendix S1. As the weeks 13+ from Q1 and 13-16 from Q3 overlapped, we combined them into one group (13–16) in the analysis.

In NorPD, we used the date of dispensing, the child birth date and the gestational length of pregnancy obtained from MBRN, to define the same time periods as in MoBa. The gestational length was estimated on a routine ultrasound scan offered free of charge to all pregnant women in Norway (if ultrasound information was not available, date of last menstrual period was used). A pregnancy was considered exposed in a given exposure period if the woman filled at least one triptan prescription during the particular period. We also considered two alternative definitions of pregnancy exposure: (a) the requirement of two prescriptions during pregnancy, which increases the likelihood of capturing true exposures in pregnancy; and (b) at least one prescription within 30 days prior to pregnancy whose supply overlapped with the pregnancy period, which increases the likelihood of capturing use of medications stockpiled before pregnancy. The supply was calculated based on the defined daily dose (DDD) on each prescription, assuming one DDD per day.

2.4 | Maternal characteristics

Maternal age at delivery, parity, and marital status were obtained from MBRN. Highest level of completed or on-going education, pre-pregnancy body mass index (BMI), folate supplementation before pregnancy or during first trimester, alcohol intake during pregnancy, and use of other medications during pregnancy were self-reported in MoBa. Other medications were classified as shown in Table 1. The 5-item version of The Hopkins Symptoms Checklist (SCL-5),[19] measuring symptoms of depression and anxiety, was included in Q1 and Q3. The SCL-5 was converted to a z-score with SD units; a positive score indicates depression/anxiety symptoms higher than the sample mean, and a negative score indicates lower depression/anxiety symptoms. For smoking during pregnancy, we combined information in MBRN (smoking status at time of delivery) and MoBa (smoking status and number of cigarettes in Q1, Q3, and Q4), in order to minimize the amount of missing information.

2.5 | Statistical analyses

We described and compared the characteristics of the study sample and the migraine sample, and calculated the prevalence of triptan use during pregnancy, in each trimester, in each 4-week period, and in the 6 months prior to pregnancy; according to both self-report in MoBa and dispensed prescriptions in NorPD. We then calculated the agreement between self-report and prescription records for each time period, using Cohen's kappa coefficient (κ)[20] with 95% confidence intervals (95% CIs). We used the following subdivision to describe the level of agreement: slight agreement 0 to 0.20, fair agreement 0.21 to 0.40, moderate agreement 0.41 to 0.60, considerable agreement 0.61 to 0.80, and perfect agreement 0.81 to 1.[21] Using MoBa as the

TABLE 1 Characteristics of women in the study sample and the migraine sample

	Study sample (n = 51 386), % or mean (SD)	Migraine sample (n = 6051), % or mean (SD)
Age at time of delivery, mean (SD)	30.4 (4.5)	30.4 (4.6)
Primiparous, %	48.2	49.3
Married/ cohabiting, %	95.8	94.9
College/university education[a], %	72.1	69.2
Pre-pregnancy BMI (kg/m^2), mean (SD)	23.9 (4.2)	24.3 (4.6)
Folate supplement[b], %	85.3	85.6
SCL-5 score during pregnancy[c], mean (SD)	−0.009 (0.99)	0.16 (1.1)
Smoking during pregnancy[d], %	20.9	23.1
Alcohol during pregnancy[e], %	10.3	9.7
Other medications during pregnancy[f], %		
NSAIDs	6.1	12.6
Paracetamol	47.7	68.3
Opioids	1.9	5.3
Preventive anti-migraine therapy	0.03	0.21
Psychotropic drugs	2.4	3.8

Abbreviations: BMI, body mass index; SCL-5, Hopkins Symptoms Checklist (5-item version).

Notes: Age, parity, marital status, and smoking status obtained from MBRN. Education, BMI, folate supplement, SCL-5, smoking, alcohol intake, and other medications reported in MoBa. Missing <5% for all variables except smoking (11.4%).

[a]Highest level of completed or ongoing education.

[b]Folate supplement before pregnancy or during first trimester.

[c]Standardized mean of SCL-5 scores in Q1 and/or Q3.

[d]Smoking at time of delivery in MBRN or indicated that she smoked at some point during pregnancy in Q1, Q3 or Q4.

[e]Reported use of alcohol at least once per month in Q1, Q3 or Q4.

[f]ATC groups M01A (NSAIDs), N02BE01 (paracetamol), N02A (opioids); psychotropic drugs in ATC groups N05A (antipsychotics), N05BA (benzodiazepines), N05CF (benzodiazepine-like), N06A (antidepressants), N06BA (stimulants); preventive anti-migraine therapy in groups N06AA (tricyclic antidepressants), N03A (antiepileptics), C07A (beta blockers), C09A (ACE-inhibitors), C09C (AII-blockers) and M03AX (botulinum toxin).

reference standard, we calculated sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV), along with 95% CIs, for prescriptions filled during each time period. These calculations were done according to definitions and equations described in Table S1. We also calculated the same measures using the two alternative definitions of triptan exposure during pregnancy in NorPD.

We used GBTM to estimate exposure trajectories among women who self-reported use of triptans before or during pregnancy, according to each woman's probability of use in each of the 4-week intervals. As recommended by previous researchers,[10] we excluded pregnancies with a gestational length shorter than 28 weeks (n = 3) to ensure equal follow-up time for all pregnancies in the analysis. GBTM uses maximum likelihood estimation to estimate clusters of individuals following similar trajectories of an outcome over time.[22,23] Unsupervised clustering methods like GBTM may be used to identify groups of women with similar patterns of medication exposure across pregnancy.[10] As it is known that many women with migraine discontinue triptans during pregnancy, we limited the model selection process to two- and three-group models (more groups resulted in small group numbers and problems with convergence) and systematically varied the polynomial order (up to third order) of each trajectory group, as recommended.[22] We used the Bayesian Information Criterion (BIC) to assess model fit, where the model with the highest (least negative) BIC was preferred,[24] and calculated Bayes factor to evaluate meaningful differences in BIC values.[25] Additional details regarding model selection and adequacy of the selected model can be found in Appendix S1. Finally, we compared the trajectory groups by maternal characteristics, and for women who filled at least one triptan prescription during pregnancy, we calculated additional drug utilization measures, including number of prescriptions, the number of DDDs, and the proportion of days covered (number of DDDs divided by gestational length).

As women could participate with several pregnancies, we performed sensitivity analyses testing sensitivity, specificity, agreement and GBTM model fit in the subsample of women that only participated once. We used Stata MP 15.1[26] in all analyses, with the plugin "traj" to estimate group-based trajectory models.[27]

3 | RESULTS

The study sample comprised 51 386 pregnancies, of which 6051 (11.8%) were pregnancies where the mother reported migraine or triptan use, or filled a triptan prescription, 6 months before or during pregnancy. Characteristics of the total study sample and the migraine sample are shown in Table 1. Women with migraine were more likely to use other medications during pregnancy; otherwise the differences between the samples were small (Table 1). A total of 8.5% of the women in the migraine sample reported use of triptans during pregnancy, whereas 7.6% filled at least one triptan prescription during pregnancy. Triptan use decreased during pregnancy, from 6.3% in MoBa and 6.4% in NorPD during first trimester, to 3.1% and 1.7% in second trimester, and 0.81% and 0.71% in third trimester. Before pregnancy, 19.0% of women with migraine used triptans according to MoBa, and 19.6% filled triptan prescriptions according to NorPD.

3.1 | Agreement between self-reported and dispensed triptans

Cohen's kappa coefficient (κ) for the entire pregnancy period was 0.36 (95% CI 0.32-0.40), and it was similar for the three trimesters (Table 2), which corresponds to fair agreement.[21] For the 4-week intervals, agreement ranged from 0.17 to 0.34 (Table S2). Sensitivity, specificity, and predictive values varied across pregnancy (Table 3 and S3). Sensitivity for the pregnancy period was 39.1% (95% CI 34.8-43.4) and specificity was 95.4% (95% CI 94.8-95.9). When we included prescriptions 30 days before pregnancy where supply overlapped with the pregnancy period to define an exposed pregnancy, we identified 90 more exposed pregnancies, and increased sensitivity (39.1%-45.5%), but decreased specificity (95.4%-94.3%) and PPV (44.1%-42.9%) (Table S4). Requiring at least two prescriptions during pregnancy to be classified as exposed resulted in 334 fewer exposed pregnancies, with marked increase in specificity and PPV, but a substantial decrease in sensitivity to only 16.4% (Table S4). Agreement and sensitivity were highest, and specificity was lowest in the 6-month period before pregnancy (Table 3).

3.2 | Trajectories

Among 1308 pregnancies where mothers self-reported use of triptans before or during pregnancy, we identified a model with three trajectory groups as the best fitting model (Table S5 and S6). Each woman was assigned to the group for which her probability of membership was highest: 77.1% followed a decreasing trajectory of low probability of triptan use (decreasing-low group), 19.6% followed a quadratic trajectory of increasing then decreasing probability of use (decreasing-medium group), and 3.3% followed a constant trajectory of high probability of use the entire period (constant-high group) (Figure 2).

Women in the constant-high group were more likely to drink alcohol during pregnancy and report use of other medications (Table 4). Drug utilization measures also varied by trajectory group: women in the constant-high group filled on average more than three prescriptions during pregnancy, with DDDs covering 21.7% of the pregnancy period, whereas women in the decreasing-low group filled on average 1 prescription during pregnancy with DDDs covering 5.5% of the pregnancy period (Table 5).

Sensitivity analyses among women who participated only once (n = 5646) yielded similar results for sensitivity, specificity, and agreement. GBTM analysis resulted in selecting the same three-group model; however, the relative proportions of the groups changed slightly (87.8% (decreasing-low group), 8.2% (decreasing-medium group) and 4.0% (constant-high group)).

4 | DISCUSSION

This study showed that agreement between dispensed and self-reported triptan use during pregnancy was fair, and that when using

TABLE 2 Agreement between self-reported use of triptans in MoBa and dispensed triptan prescription in NorPD during pregnancy, by trimester, and 6 months before pregnancy

	MoBa total n	NorPD total n	MoBa only n	NorPD only n	Both n	Neither n	Agreement κ (95% CI)	Level[a]
During pregnancy	517	458	315	256	202	5278	0.36 (0.32-0.40)	Fair
First trimester	382	387	229	234	153	5435	0.36 (0.31-0.40)	Fair
Second trimester	185	100	131	46	54	5820	0.37 (0.29-0.44)	Fair
Third trimester	49	43	33	27	16	5975	0.34 (0.22-0.47)	Fair
Before pregnancy	1152	1185	422	455	730	4444	0.54 (0.51-0.56)	Moderate

Abbreviations: κ, Cohen's kappa coefficient; CI, confidence interval; NorPD, Norwegian Prescription Database.
Notes: Calculations were performed in the migraine sample, n = 6051.
[a]Level of agreement: 0 to 0.20 slight agreement, 0.21 to 0.40 fair agreement, 0.41 to 0.60 moderate agreement, 0.61 to 0.80 considerable agreement, 0.81 to 1 perfect agreement.

TABLE 3 Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of dispensed triptan prescription during pregnancy, by trimester, and 6 months before pregnancy, using self-reported triptan use in MoBa as the reference standard

	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV, % (95% CI)	NPV, % (95% CI)
During pregnancy	39.1 (34.8-43.4)	95.4 (94.8-95.9)	44.1 (39.5-48.8)	94.4 (93.7-95.0)
First trimester	40.1 (35.1-45.2)	95.9 (95.3-96.4)	39.5 (34.6-44.6)	96.0 (95.4-96.5)
Second trimester	29.2 (22.8-36.3)	99.2 (99.0-99.4)	54.0 (43.7-64.0)	97.8 (97.4-98.2)
Third trimester	32.7 (19.9-47.5)	99.6 (99.3-99.7)	37.2 (23.0-53.3)	99.5 (99.2-99.6)
Before pregnancy	63.4 (60.5-66.2)	90.7 (89.9-91.5)	61.6 (58.8-64.4)	91.3 (90.5-92.1)

Abbreviations: CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value.
Notes: Calculations were performed in the migraine sample, n = 6051.

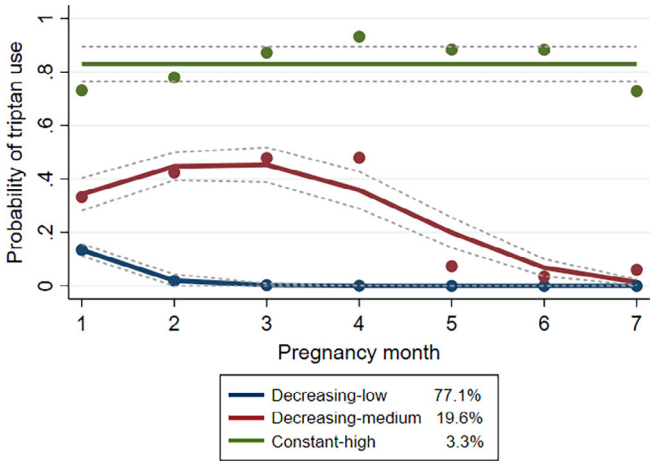

FIGURE 2 Estimated trajectories according to probability of triptan use during pregnancy (solid lines), including decreasing-low (77.1%), decreasing-medium (19.6%) and constant-high (3.3%) trajectory groups, with 95% confidence intervals (dashed lines). Pregnancy month 1 corresponds to gestational weeks 0 to 4, etc [Colour figure can be viewed at wileyonlinelibrary.com]

self-report as the reference standard, sensitivity was generally low, whereas specificity was quite high. Moreover, this study provides insight into triptan utilization patterns during pregnancy. To the best of our knowledge, this is the first time longitudinal trajectory models have been applied to triptan use during pregnancy.

Our findings suggest that some women used triptans during pregnancy from prescriptions filled before pregnancy, which implies that studies based entirely on dispensed prescriptions may be misclassifying some women as unexposed when they were actually exposed according to self-report. When we included prescriptions filled in the 30 days prior to pregnancy, sensitivity increased but specificity decreased. When we required two prescriptions during pregnancy to be classified as exposed, specificity increased, but sensitivity dropped markedly. Low specificity has a stronger impact on effect estimates than low sensitivity when prevalence of exposure is low,[6] as is the case with triptans and many other medications used episodically. Specificity was generally quite high, and the potential for serious misclassification of truly unexposed women seems to be low. The results were fairly consistent across timing of use, although agreement and sensitivity were lower when we examined exposure by 4-week intervals during pregnancy. As narrow windows are more susceptible to inaccuracies, researchers should consider using trimesters rather than shorter exposure periods.

Our study is in line with the previous studies, many of which have found low agreement between dispensed and self-reported episodically used medications during pregnancy. Stephansson et al compared prescription records and birth registry records in Sweden and calculated predictive values for the period from 90 days before until time of first antenatal visit, which occurred around gestational week 12.[5] They found 21.4% agreement for antimigraine drugs, 21.5% for opioids, and 24.7% for hypnotics, which is lower than the predictive values for triptans in our study (PPV was 39.5% in the first trimester). Skurtveit et al compared prescription records in NorPD with self-report in MoBa and found sensitivity of 27.8% for benzodiazepine hypnotics, 44.8% for benzodiazepine anxiolytics and 48.8% for opioids, and high specificity for all medication groups.[6] When prescriptions dispensed 30 days before pregnancy and 60 days before pregnancy were included, sensitivity increased, but not to a very high level, and specificity decreased slightly,[6] which is similar to what we observed. Olesen et al reported 77% agreement for prescribed analgesics in Denmark compared to self-reported use according to telephone interview during early pregnancy in the Danish National Birth Cohort (DNBC),[28] which is higher than our estimates and those of other studies. The authors discuss that the inclusion of medications available over-the-counter in DNBC, but not in the prescription registry, may have led to an overestimation of agreement for medication groups such as analgesics.[28] Together with these studies, our findings suggest a need for caution when relying on prescription fills to define exposure to episodically used medications. Quantitative bias analysis, a method for correcting observed associations to account for systematic biases such as exposure misclassification should be considered.[29] The results of this study, especially measures of agreement between self-report and dispensed prescriptions, may serve as a useful reference for researchers, as quantitative bias analysis requires an estimate of exposure quality to parameterize the model.

GBTM identified three trajectories of triptan utilization during pregnancy. The largest group "decreasing-low" is likely to consist of women who discontinued triptans in early pregnancy. The second group "decreasing-medium" tended to discontinue triptans toward the end of the period whereas the third and smallest group "constant high" probably indicates the most severe chronic migraineurs. Previous studies have reported improvement of migraine during pregnancy for a majority of women[30] and decreased drug utilization across pregnancy.[31,32] The trajectories described in this study illustrate that there seems to be different drug utilization patterns during pregnancy among women using triptans, and that a definition of ever-exposed vs never-exposed may not fully capture exposure to such medications during pregnancy. Future studies of safety of triptans during pregnancy could consider defining exposure groups that reflect heterogeneous discontinuation patterns during pregnancy.

The use of self-report as the reference standard in the validity analysis and to estimate exposure trajectories has some limitations. Correct exposure classification depends on accurate recall of medication use. Migraine was specifically queried in Q1 and Q3 to promote reporting, but not in Q4, which only asked about headaches. This could lead to some under-reporting of triptan use in the third trimester. Moreover, Q4 was filled out 6 months after delivery, and may be subject to poorer recall. An under-estimation of self-reported triptan use in MoBa will potentially reduce agreement between MoBa and NorPD. This would not affect the estimated trajectories, as they were based on information from Q1 and Q3 only. However, exposure misclassification more generally could have had an impact on clustering into trajectories. Our results suggest that low sensitivity was a particular problem for triptan exposure data extracted from prescription fill records. Although not specifically addressed in our analysis, which used self-report as the reference standard, self-reported exposure of

TABLE 4 Characteristics of women in the trajectory groups

	Decreasing-low group (n = 1022), % or mean (SD)	Decreasing-medium group (n = 246), % or mean (SD)	Constant-high group (n = 40), % or mean (SD)
Age at time of delivery, mean (SD)	30.8 (4.3)	31.0 (4.4)	32.4 (4.0)
Primiparous, %	56.0	50.0	45.0
Married/cohabiting, %	95.5	91.9	95.0
College/university education[a], %	75.7	71.1	77.5
Pre-pregnancy BMI (kg/m^2), mean (SD)	24.7 (4.8)	24.6 (4.4)	26.0 (5.6)
Folate supplement[b], %	88.1	85.8	80.0
SCL-5 score during pregnancy[c], mean (SD)	0.09 (1.1)	0.20 (1.1)	0.27 (1.2)
Smoking during pregnancy[d], %	17.7	20.7	15.0
Alcohol during pregnancy[e], %	9.5	14.6	17.5
Other medications during pregnancy[f], %			
NSAIDs	14.4	20.3	22.5
Paracetamol	76.1	85.8	85.0
Opioids	7.0	15.9	20.0
Preventive anti-migraine therapy	0.6	0.0	2.5
Psychotropic drugs	3.8	8.5	17.5

Abbreviations: BMI, body mass index; SCL-5, Hopkins Symptoms Checklist (5-item version).
Notes: Trajectory groups were estimated for women who reported migraine or triptan use in MoBa, n = 1308. Age, parity, marital status, and smoking status obtained from MBRN. Education, BMI, folate supplement, SCL-5, smoking, alcohol intake, and other medications reported in MoBa. Missing <5% for all variables except smoking (11.0%-22.5%) and alcohol (5.3% for descreasing-medium group).
[a]Highest level of completed or ongoing education.
[b]Folate supplement before pregnancy or during first trimester.
[c]Standardized mean of SCL-5 scores in Q1 and/or Q3.
[d]Smoking at time of delivery in MBRN or indicated that she smoked at some point during pregnancy in Q1, Q3 or Q4.
[e]Reported use of alcohol at least once per month in Q1, Q3 or Q4.
[f]ATC groups M01A (NSAIDs), N02BE01 (paracetamol), N02A (opioids); psychotropic drugs in ATC groups N05A (antipsychotics), N05BA (benzodiazepines), N05CF (benzodiazepine-like), N06A (antidepressants), N06BA (stimulants); preventive anti-migraine therapy in groups N06AA (tricyclic antidepressants), N03A (antiepileptics), C07A (beta blockers), C09A (ACE-inhibitors), C09C (AII-blockers) and M03AX (botulinum toxin).

intermittently used medications is also vulnerable to exposure misclassification, especially if women forget using the medication. If women who rarely use triptans are more likely to forget their use than frequent users, we would expect this to result in assigning women to the decreasing-low trajectory who might better belong to the decreasing-medium group. It is also possible that different trajectories would have been selected in a dataset with less-exposure misclassification. Research on the effect of exposure misclassification on GBTM performance is regrettably lacking. Another limitation is the low participation rate in MoBa (41%) which may limit the

TABLE 5 Drug utilization measures during pregnancy for women in the trajectory groups with at least one triptan prescription

	Decreasing-low group (n = 191)	Decreasing-medium group (n = 101)	Constant-high group (n = 34)
Number of prescriptions			
Mean (SD)	1.2 (0.62)	1.9 (1.8)	3.3 (2.7)
Median (range)	1 (1-5)	1 (1-13)	3 (1-14)
Number of DDDs			
Mean (SD)	15.4 (13.4)	25.0 (28.9)	60.5 (49.0)
Median (range)	12 (3-72)	18 (3-216)	54 (6-204)
Proportion of days covered[a], %			
Mean (SD)	5.5 (4.7)	9.0 (10.3)	21.7 (18.0)
Median (range)	4.3 (1.0-27.6)	6.4 (1.1-76.3)	19.3 (2.0-80.3)

Abbreviations: DDD, defined daily dose.
Notes: The numbers in each trajectory group differ from those in Table 4, because drug utilization measures were only calculated for women with at least one triptan prescription during pregnancy.
[a]Proportion of days covered, number of DDD's during pregnancy divided by gestational length in days.

generalizability of our findings. Women in MoBa were older and more often married, smoked less, and used folic acid and other supplements more frequently than the general birthing population in Norway.[33] The extent to which these results are generalizable to other countries is also not known.

In conclusion, in studies of triptans, and possibly other medications used episodically during pregnancy, classifying exposure based on filled prescriptions rather than self-report likely results in substantial under-estimation of exposure. If self-reported exposure information is unavailable, researchers using prescriptions records should consider methods for mitigating possible biases arising from misclassification, such as quantitative bias analysis. Moreover, the identification of three trajectories with different profiles of probability of triptan use during pregnancy illustrates that commonly used exposure definitions such as ever-exposed vs never-exposed do not capture variations in utilization patterns of these medications, and researchers should carefully choose exposure groups that reflects a more realistic pattern of use.

ETHICS STATEMENT

The establishment of MoBa and initial data collection was based on a license from the Norwegian Data protection agency and approval from The Regional Committees for Medical and Health Research Ethics (REK). The MoBa cohort is based on regulations based on the Norwegian Health Registry Act. The current study was approved by REK, region South-East (2015/442).

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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REFERENCES

1. West SL, Ritchey ME, Poole C. Validity of pharmacoepidemiologic drug and diagnosis data. In: Strom B, Kimmel S, Hennessy S, eds. *Pharmacoepidemiology*. 2nd ed. Chichester, UK: John Wiley & Sons Ltd; 2013:205-227.
2. Skurtveit S, Selmer R, Tverdal A, Furu K, Nystad W, Handal M. Drug exposure: inclusion of dispensed drugs before pregnancy may lead to underestimation of risk associations. *J Clin Epidemiol*. 2013;66(9):964-972.
3. Copeland KT, Checkoway H, McMichael AJ, Holbrook RH. Bias due to misclassification in the estimation of relative risk. *Am J Epidemiol*. 1977;105(5):488-495.
4. Grzeskowiak LE, Gilbert AL, Morrison JL. Exposed or not exposed? Exploring exposure classification in studies using administrative data to investigate outcomes following medication use during pregnancy. *Eur J Clin Pharmacol*. 2012;68(5):459-467.
5. Stephansson O, Granath F, Svensson T, Haglund B, Ekbom A, Kieler H. Drug use during pregnancy in Sweden - assessed by the prescribed drug register and the medical birth register. *Clin Epidemiol*. 2011;3:43-50.
6. Skurtveit S, Selmer R, Odsbu I, Handal M. Self-reported data on medicine use in the Norwegian mother and child cohort study compared to data from the Norwegian prescription database. *Norsk Epidemiol*. 2014;24(1–2):209–216.
7. Grzeskowiak LE, Gilbert AL, Morrison JL. Investigating outcomes associated with medication use during pregnancy: a review of methodological challenges and observational study designs. *Reprod Toxicol*. 2012;33(3):280-289.
8. Hurault-Delarue C, Chouquet C, Savy N, et al. How to take into account exposure to drugs over time in pharmacoepidemiology studies of pregnant women? *Pharmacoepidemiol Drug Saf*. 2016;25(7):770-777.
9. Nagin DS. Analyzing developmental trajectories: a semiparametric, group-based approach. *Psychol Methods*. 1999;4(2):139-157.
10. Wood ME, Lupattelli A, Palmsten K, et al. Longitudinal methods for modeling exposures in pharmacoepidemiologic studies in pregnancy. *Epidemiol Rev*. In preparation.
11. Franklin JM, Shrank WH, Pakes J, et al. Group-based trajectory models: a new approach to classifying and predicting long-term medication adherence. *Med Care*. 2013;51(9):789-796.
12. Frank AS, Lupattelli A, Matteson DS, Nordeng H. Maternal use of thyroid hormone replacement therapy before, during, and after pregnancy: agreement between self-report and prescription records and group-based trajectory modeling of prescription patterns. *Clin Epidemiol*. 2018;10:1801-1816.
13. Magnus P, Irgens LM, Haug K, Nystad W, Skjaerven R, Stoltenberg C. Cohort profile: the Norwegian mother and child cohort study (MoBa). *Int J Epidemiol*. 2006;35(5):1146-1150.
14. Magnus P, Birke C, Vejrup K, et al. Cohort profile update: the Norwegian mother and child cohort study (MoBa). *Int J Epidemiol*. 2016;45(2):382-388.
15. Irgens LM. The medical birth registry of Norway; a source for epidemiological and clinical research. *Scand J Rheumatol Suppl*. 1998;107:105-108.
16. Furu K. Establishment of the nationwide Norwegian prescription database (NorPD) – new opportunities for research in pharmacoepidemiology in Norway. *Norsk Epidemiol*. 2009;18(2):129–136.
17. WHO Collaborating Centre for Drugs Statistics Methodology. ATC DDD index 2019. Oslo, Norway; 2018. https://www.whocc.no/atc_ddd_index/. Accessed November 14, 2019.
18. FHI. *Norwegian Mother, Father and Child Cohort Study (MoBa): Questionnaires from MoBa*. Oslo, Norway: The Norwegian Institute of Public Health; 2005 (updated 2016; cited November 14, 2019). Available from: https://www.fhi.no/en/studies/moba/for-forskere-artikler/questionnaires-from-moba/.
19. Strand BH, Dalgard OS, Tambs K, Rognerud M. Measuring the mental health status of the Norwegian population: a comparison of the instruments SCL-25, SCL-10, SCL-5 and MHI-5 (SF-36). *Nord J Psychiatry*. 2003;57(2):113-118.
20. Cohen J. A coefficient of agreement for nominal scales. *Educ Psychol Meas*. 1960;20:37-46.

21. Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics*. 1977;33(1):159-174.
22. Nagin D. *Group-Based Modeling of Development*. Vol 201. Cambridge, MA: Harvard University Press; 2005.
23. Nagin DS. Group-based trajectory modeling: an overview. *Ann Nutr Metab*. 2014;65(2–3):205-210.
24. Schwarz G. Estimating the dimension of a model. *Ann Statist*. 1978;6 (2):461-464.
25. Wasserman L. Bayesian model selection and model averaging. *J Math Psychol*. 2000;44(1):92-107.
26. StataCorp. *Stata Statistical Software*. College Station, TX: StataCorp LLC; 2017.
27. Jones BL, Nagin DS. A note on a Stata plugin for estimating group-based trajectory models. *Sociol Methods Res*. 2013;42(4):608-613.
28. Olesen C, Sondergaard C, Thrane N, Nielsen GL, de Jong-van den Berg L, Olsen J. Do pregnant women report use of dispensed medications? *Epidemiology*. 2001;12(5):497-501.
29. Lash TL, Fox MP, MacLehose RF, Maldonado G, McCandless LC, Greenland S. Good practices for quantitative bias analysis. *Int J Epidemiol*. 2014;43(6):1969-1985.
30. MacGregor EA. Headache in pregnancy. *Neurol Clin*. 2012;30(3): 835-866.
31. Amundsen S, Ovrebo TG, Amble NM, Poole AC, Nordeng H. Use of antimigraine medications and information needs during pregnancy and breastfeeding: a cross-sectional study among 401 Norwegian women. *Eur J Clin Pharmacol*. 2016;72(12):1525-1535.
32. Harris G-ME, Wood M, Eberhard-Gran M, Lundqvist C, Nordeng H. Patterns and predictors of analgesic use in pregnancy: a longitudinal drug utilization study with special focus on women with migraine. *BMC Pregnancy Childbirth*. 2017;17(1):224.
33. Nilsen RM, Vollset SE, Gjessing HK, et al. Self-selection and bias in a large prospective pregnancy cohort in Norway. *Paediatr Perinat Epidemiol*. 2009;23(6):597-608.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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