Using administrative healthcare database records to study trends in prescribed medication dispensed during pregnancy in Belgium from 2003 to 2017

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Abstract

Purpose: The aim of this study was to describe trends in medication prescriptions dispensed during pregnancy in Belgium using administrative healthcare database records from a representative sample of the Belgian population.

Methods: Pregnant women were identified with reimbursement codes associated with the delivery of a baby. Data were extracted for three study periods, each over 3 years: 2003–2005, 2009–2011, and 2015–2017. The age-standardized prevalence of dispensed medications during pregnancy were computed and logistic regression models were used to evaluate the trends in prevalence across the study periods. The most frequently dispensed medications were listed for each study period.

Results: The study included 23 912 pregnancies. The age-standardized prevalence of pregnant women with at least one dispensed medication increased across the three study periods from 81.8.% to 89.3%. The median number and interquartile range of the different medications dispensed during

pregnancy rose from 2 (1–6) to 3 (1–7) between the first and last study periods. In the 2015–2017 period, the most frequently dispensed medications during pregnancy included progesterone (25.5%), paracetamol (17.8%), and amoxicillin (17.1%). The data also showed an increasing trend for the dispensation of ibuprofen and ketorolac during pregnancy across the three study periods.

Conclusions: The prevalence of prescribed medications dispensed during pregnancy increased in Belgium from 2003 to 2017 with high proportion for Progesterone and Antibiotics. Utilization of certain nonsteroidal anti-inflammatory drugs (NSAIDs) increased between 2003 and 2017, despite recommendations to avoid them.

K E Y W O R D S
administrative healthcare database, medication, pharmacoepidemiology, pregnancy

Key Points

- The proportion of women for whom at least one prescribed medication was dispensed increased across the three study periods.
- The prescription of progesterone dispensed to the women included in our study was very high, and potential overuse should be evaluated.
- The use of recommended vaccines during pregnancy increased drastically between 2003 and 2017.
- The use of ibuprofen and ketorolac during pregnancy increased between 2003 and 2017.
- The permanent sample database can be used to follow up medication prescriptions to pregnant women in Belgium.

INTRODUCTION

The use of medications during pregnancy has reduced the risks associated with diseases, thereby improving the health of mothers and fetuses during pregnancy. However, due to the lack of available safety data, it is equally important to consider the possible risks associated with the use of medications during pregnancy. The relatively high prevalence of medications dispensed during pregnancy, varying from 60% to 97%, has been highlighted in several studies (1–5). Utilization should be prudent, and any uptrend at the population level should be monitored.

Many factors can influence prescription practices at the local level, such as the health system and reimbursement policies, the local prevalence of chronic diseases, and the average age of pregnant women in the population concerned. The collection of data related to local prescribing practices is

important for the development of recommendations for health professionals, and there is a need for more indepth research adapted to local needs.

In the Belgian context, little is known about medication prescribing practices during pregnancy. A cross-sectional study conducted by Ceulemans et al. revealed that the prevalence of medication use during the week prior to survey completion was 52% (6). A recent study conducted by an independent Health Insurance Fund (Mutualités Libres/Onafhankelijke ziekenfondsen) indicated that between 2013 and 2016, 8 out of 10 pregnant women had a medication prescription dispensed during pregnancy (7). Most of the available data do not describe the use of medication during pregnancy at the population level, and to date, no study, has looked specifically at trends in the use of medications during pregnancy. One of the recurrent areas of concern is the potential overuse of nonsteroidal anti-inflammatory drugs (NSAIDs) during pregnancy. Several warnings were given by Medicines Agencies in Europe about the risks associated with the use of NSAIDs during pregnancy. More recently, in March 2020 the Belgian agency for medicines and health products warned that pregnant women should avoid taking NSAIDs during pregnancy (8).

Indeed, many studies have shown that NSAID intake during pregnancy is an important risk factor for multiple adverse effects. During the last trimester, the risk of premature closure of the ductus arteriosus has been well documented, (9,10) and this might lead to cardiac and pulmonary complications for the fetus. Other adverse effects associated with NSAID use include the risk of miscarriage and the potential risk of congenital defects when taken during the first trimester of pregnancy (11,12). This study provides more information about the trends in the prevalence of medication dispensing during pregnancy across three periods of 3 years between 2003 and 2017.

In particular, we focus on the 20 most frequently dispensed medications and pay special attention to the most frequently dispensed NSAIDs during pregnancy.

METHODS

Data sources: The permanent sample (EPS)

The permanent sample (EPS) is a 1/40 representative data sample of the Belgian population covered by compulsory health insurance. It contains approximately 300 000 individuals and is representative in terms of sex and age for the national population. The EPS contains anonymized information on all reimbursed medications, only reimbursed medications are recorded from public pharmacies but all prescribed and dispensed medications are recorded from hospital pharmacies. Medications are captured in the database through a pharmaceutical product code containing a unique national code number for every product (CNK-code), from public or hospital pharmacies. Each medication was

classified according to the Anatomical Therapeutic Chemical (ATC) classification at the fifth level for extraction. Other information included in the database were the dispensing date, the region of residence and some sociodemographic data (13). The EPS data can be used by health administrative services or researchers based on strict authorization.

Participants

Participants were selected from the EPS. Participants were women who delivered within the three 3-year periods (2003–2005, 2009– 2011, and 2015–2017) as per the data available in the EPS. Pregnancies were identified by the INAMI-RIVIZ code nomenclature (14) related to all reimbursement acts associated with obstetric deliveries. The code list is displayed in Table S1.

We restricted our study to pregnancies associated with mothers residing in Belgium who were included in the EPS for the whole pregnancy period. Because self-employed persons in Belgium did not benefit from medication reimbursement in the first period of study (2003–2005), we excluded them for all three periods.

Periods of exposure and medication exposures

Because data on gestational age were not available, we used an algorithm that was previously used by Andrade et al (15,16) to define the first day of exposure. The algorithm assumes a pregnancy duration of 270 days. This period is then divided into three trimesters of 90 days, with the first trimester starting 270 days before the delivery date. The ATC classification was used at the fifth level to select and classify all medications. To list the 20 most dispensed medications during pregnancy all reimbursed medications covered by the social security system and all medications prescribed and dispensed at hopsital level were considered. To define NSAID exposure we use a list of NSAID excluding the Antithrombotic agents (ATC code B01). The NSAIDs list is displayed in Table S2. For each delivery, we determined whether the different pregnancy periods involved exposure to medication or not by determining if at least one prescribed medication was dispensed during the period under consideration.

Statistical analysis

Statistical analyzes were carried out using SAS Enterprise Guide 7 and Stata 15. The level of significance was fixed at 5%. The estimates prevalence of prescribed medications dispensed during pregnancy across study periods were standardized by the direct method to the year 2017 of women

population distribution as reference from Belgian national statistic using age groups 15–19, 20– 29, 30–39 and 40–50 years. Age-standardized estimates were calculated overall and by region of residence. Trends over time for the prevalence of prescribed medications dispensed during pregnancy were assessed using logistic regression models, with the study periods entered as a continuous variable. For each of the three study periods, we determined the 20 most dispensed medications by calculating the crude prevalence of each chemical substance dispensed during pregnancy. The crude prevalence of prescribed medications dispensed during pregnancy was obtained by dividing the number of pregnancies involving exposure to at least one drug identified at the fifth ATC level by the total number of pregnancies in the considered periods. Crude prevalence was calculated for the entire pregnancy and for each pregnancy trimester.

The most frequently dispensed NSAIDs were determined by calculating the prevalence of each NSAID reported in the preestablished NSAIDs list. We also present the prevalence with omission of the seven-day exposure period before delivery, because NSAIDs are known to be prescribed and dispensed for postpartum pain at the end of pregnancy. Trend tests in the crude prevalence of NSAIDs exposure during pregnancy across the study periods were performed using $\chi 2$.

RESULTS

Data on medications dispensed during pregnancy were available for 26 346 pregnancies for the three periods between 2003 and 2017. Women residing outside Belgium (n = 114), those not included in the EPS for the whole pregnancy period (n = 289), and self-employed women (n = 2031) were excluded, leaving 23 912 pregnancies in the study. The mean age of mothers at childbirth increased by 0.9 years across the three study periods, from 29.4 years in 2003–2005 to 30.3 years in 2015 2017. Table 1 shows the proportion of pregnancies in each age and region category for each three-year period. Table 2 reports the prevalence of at least one prescription dispensed during pregnancy overall and by maternal characteristics for the three periods of study.

For the 2003–2005 period, the age-standardized prevalence of at least one medication dispensed during pregnancy was 81.8%. The age-standardized prevalence increased to 84.8% for the 2009–2011 period and to 89.3.% for the 2015–2017 period. During the three consecutive periods, the prevalence of medication dispensing increased significantly across all categories of maternal age except ages ≥41 years. Similarly, all regions of residence had significant increase in prevalence of medication dispensed. An increase in the mean and standard deviation (SD) prescription of different medicines during pregnancy was also observed across the study periods, from 4.3 (5.4) for the 2003–

2005 period to 5 (5.2) for the 2015–2017 period. When we examined the median and interquartile range (IQR), the number of different medications prescribed during pregnancy was found to increase from 2 (1–6) for the 2003– 2005 period to 3 (1–6) for the 2009–2011 period and to 3 (1–7) for the most recent period (2015–2017). Table 3 presents the prevalence by pregnancy periods of the most dispensed medications during pregnancy for the three study periods. There were 22 different drugs among the top 20 for each period. Between 2003–2005 and 2015–2017, the three most significant increases in prevalence were observed for influenza purified antigen (from 0.2% to 12.2%), pertussis purified antigen (from 0% to 11%), and paracetamol (from 10.1% to 17.8%). Other increases of note were progesterone (from 20% to 25.5%), and fosfomycin (from 6.1% to 13.2%). The three most important declines in prevalence between 2003– 2005 and 2015–2017 occurred for amoxicillin (from 20.2% to 17.1%), amoxicillin and beta-lactamase inhibitor (from 12.5% to 8.8%), and miconazole (from 15.1% to 12.4%). Not considering the blood substitutes and perfusion solution ATC (B05), nontherapeutic product ATC (V07), and antiseptic and disinfectant ATC (D08) subgroups, the most frequently dispensed medications during pregnancy for the last study period (2015–2017) were progesterone (25.5%), paracetamol (17.8%), and amoxicillin (17.1%).

Table 4 presents for each of the 22 most dispensed medications the distribution of dispensations between the hospital and the community pharmacies. In the last study period (2015–2017), considering the list of 22 most frequently dispensed medications during pregnancy, not including the day of delivery, 60.4% of dispensed medications were inpatient medications and 39.6% were outpatient medications.

Table 5 presents the prevalence by pregnancy periods of the six most dispensed NSAIDS during pregnancy for the three study periods. In the last study period (2015–2017) not considering the 7 days before delivery, the six most prevalent NSAIDs dispensed during pregnancy were ibuprofen (4.42%), diclofenac (2.54%), ketorolac (0.78%), naproxen (0.63%), indomethacin (0.41%), and piroxicam (0.4%). Between 2003–2005 and 2015–2017, the dispensation of certain NSAIDs increased sharply. The proportion of pregnancies exposed to NSAIDs more than doubled: From 2.44% to 4.42% for ibuprofen and from 0.17% to 0.78% for ketorolac.

DISCUSSION

The use of medication during pregnancy is on the rise in Belgium

Between 2003 and 2017, the use of prescribed medications dispensed during pregnancy increased in Belgium. It is difficult to compare our results with those of other studies, for example our study only included reimbursed medications from public pharmacies while other studies might include over-the-counter medications. Additionaly, in our study, all inpatient medications prescribed and dispensed were also accounted for while they are often not captured in other studies. The increasing trend found in our study has been also observed in other contexts (1,17,18). Changes in the list of reimbursed medications during the three study periods have possibly influenced our results. Some medications could have been available in one period but not in the other. We have assessed the ATC codes present in one period but not in another that appear in the list of medications removed from reimbursement between 2002 and 2017. Two medications with a prevalence above 0.5% in the period 2003–2005: the mepartricin (2.8%) and the propacetamol (2.1%), were both removed from reimbursement in 2006. Other ATC codes had very low frequencies. In the two other periods, there were 24 ATC codes removed from the reimbursement list and all had a prevalence below 0.06%.

Most frequently dispensed medications during pregnancy: Points of attention

Progesterone

Progesterone was found to be in the top three medications for each of the three study periods. Compared to the Netherlands (8.3%) (19) and Italy (20.1%), (2) the use of progesterone during pregnancy in Belgium appears to be rather high (25.5%) in 2015–2017 period and deserves to be highlighted. The use of progesterone is common during pregnancy due to its expected reduction of the risk of preterm delivery in women with a single gestation, a history of spontaneous preterm delivery, or a short cervical length (20,21). On the contrary, potential side effects associated with the use of progesterone during pregnancy may exist. Increases in psychiatric disorders have been shown among children exposed to progesterone in utero (22). Other studies have associated vaginal progesterone treatment with a risk of gravidic cholestasis (23,24). Therefore, we should be mindful not to overprescribe progesterone.

Antibacterial for systemic use

Among the top 20 most frequently dispensed medications during pregnancy, the most represented therapeutic subgroup was systemic antibacterial medications. This result is consistent with those from other European and North American studies (25–27). In the context of a growing threat of antibiotic resistance, we should be conscious of this high rate of antibiotic use during pregnancy and be reasonable in the prescription of antibiotics, particularly fosfomycin, which showed a strong

increasing trend. Additionally, the level of safety in terms of risk associated with fosfomycin is less documented, and in general the long-term risks associated with the use of antibiotics remain poorly documented.

Increased use of recommended vaccinations

Vaccination rates during pregnancy increased sharply in Belgium between 2003 and 2017. This is because the influenza vaccine has been recommended by the Advisory Committee on Immunization Practices since 2004.28 The pertussis vaccine has been recommended by the Superior Health Council of Belgium during pregnancy since 2013, due to an increasing incidence of pertussis (29). In Belgium, the pertussis vaccine is also available free-of-charge directly through specific health programs subsidized by communities and is then not registered in our database of reimbursed medications. Therefore, the rate in our study likely underestimates the actual rate of coverage in Belgium.

NSAIDs dispensing

We looked at the six most frequently dispensed NSAIDs during pregnancy for analgesic and anti-inflammatory indications: Ibuprofen, diclofenac, ketorolac, naproxen, indomethacin, and piroxicam. We found that the majority of these NSAIDs were dispensed during hospital stays. In the 2015–2017 period and for pregnancy as a whole, the percentage of dispensation at the hospital level was 45.5% for ibuprofen, 72.1% for diclofenac, 100% for ketorolac, 40.3% for piroxicam, 22.2% for indomethacin, and 41.2% for naproxen. When we looked specifically at exposure during the third trimester, an interesting finding was that approximately 75% of the cases of the six most frequently dispensed during the third trimester occurred in the seven-day period before delivery. This high prevalence could be explained by prescriptions being dispensed just before delivery but being used afterward to treat pain in the postpartum period. The NSAIDs prescribed and dispensed during the seven-day predelivery period were mainly ibuprofen and diclofenac, which are frequently used to treat postpartum pain. Throughout the entire pregnancy, not considering the 7 days before delivery, increasing trends were observed for the dispensation of ibuprofen and ketorolac across the three study periods (from 2.44% to 4.42% and from 0.17% to 0.78%, respectively). More specifically, in the third trimester, ibuprofen was the most frequently dispensed NSAID, with 0.52% of pregnancies exposed, followed by diclofenac with 0.34%. A possible reason for the use of ibuprofen, diclofenac, and indomethacin during the third trimester is that these NSAIDs can be used as tocolytics (30). A network metaanalysis indicated that prostaglandin inhibitors (e.g., ibuprofen) can be used as a first choice tocolytic agent, followed by calcium channel blockers as the second alternative. While our

data show that the majority of dispensations of the most frequently dispensed NSAIDs during pregnancy occurred in the hospital, where the occurrence of ductus arteriosus can be monitored, a significant number were dispensed by community pharmacists where the absence of monitoring represents a clear concern.

The use of the permanent sample (EPS) database to study medication use during pregnancy:

Strength and limitations

The EPS database has some advantages. The database is a random sample representative of the Belgian population. Pregnant women who have given birth can be extracted using their delivery reimbursement codes. Maternal exposure to medications can then be determined because the database contains information about the ATC codes of the medications dispensed, the quantities of medications dispensed, the dispensing dates. Since data are available from 2002, this database offers the opportunity to retrospectively study habits in drug prescription. However, it also presents important limitations, including missing key information such as the exact date of the beginning of the pregnancy. In this study, the start of the first trimester was estimated by subtracting 270 days from the delivery date. By doing this, we might have included medications dispensed before the beginning of the pregnancy and might miss medications dispensed for pregnancies lasting more than 270 days. We assumed that the medications dispensed were used by the mother during the same trimester period, because this information was not available in the database. The medications recorded from public pharmacies only included those reimbursed by health insurers, but some medications are available over the counter. This might have led to an underestimation of medication use during pregnancy. This is, for example, the case of NSAIDs also available over the counter. In Belgium, before 2008, self-employed persons had a different benefit insurance scheme, so we decided not to include them in the three study periods. We do not think that this affected the generalizability of our study, as in the two last study periods, we compared the data with and without the inclusion of self-employed persons, and the prevalence of the use of medications remained very similar.

CONCLUSION

The study results indicate that the use of prescribed and dispensed medications during pregnancy is increasing in Belgium. Progesterone exposure during pregnancy may be higher in Belgium compared to in other contexts. The use of antibiotics remained high during the three study periods. The dispensation of ibuprofen and ketorolac was shown to increase, despite recommendations to avoid

these medications during pregnancy. A welcome observation was the increase in dispensation of recommended vaccines between 2003 and 2017. Having accurate information about the use of medications during pregnancy should allow the development of better target campaigns to make pregnant women aware of the potential risks associated with medication use during pregnancy. The use of the permanent sample database EPS was useful as an exploratory approach to characterize trends in prescription medication habits during pregnancy in Belgium.

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AUTHOR CONTRIBUTIONS

Lionel Larcin performed the statistical analysis and wrote the draft of the manuscript. Murielle Lona and Güngör Karakaya contributed to the data acquisition and interpretation of data. Alexis Van Espen has been involved in the data extraction and statistical analysis. Christine Damase-Michel contributed to interpretation of data and revisions of the manuscript. Fati Kirakoya-Samadoulougou formulated research goals and objectives, supervised statistical analysis, interpretation of results and revisions of the manuscript. All authors have contributed to the design of the study and approved the final version of the manuscript.

ETHICS STATEMENT

The authors state that no ethical approval was needed.

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TABLES:

Table 1. Ages and regions of residence of pregnant mothers in Belgium in the three study periods between 2003 and 2017.

	Period 2003–2005 (N = 7779)	Period 2009–2011 (N = 8345)	Period 2015–2017 (N = 7788)
Variables	% (*n*)	% (*n*)	% (*n*)
Maternal age			
≤20 years	3.6 (277)	3 (248)	2.2 (168)
21–30 years	55.7 (4335)	54.8 (4572)	51.2 (3991)
31–40 years	39 (3038)	40.1 (3351)	44.1 (3433)
≥41 years	1.7 (129)	2.1 (175)	2.5 (197)
Region of residence			
Flanders	46.4 (3612)	47.9 (4001)	48.8 (3804)
Wallonia	41 (3189)	39.4 (3286)	37.8 (2945)
Brussels region	12.6 (978)	12.7 (1058)	13.3 (1039)

Table 2. Prevalence of at least one medication dispensed during pregnancy in Belgium between 2003 and 2017.

	Period 2003–2005		Period 2009–2011		Period 2015–2017		
	N	% (*n*)	N	% (*n*)	N	% (*n*)	*p*-Value
Overall	7779	78.3 (6093)	8345	83.3 (6951)	7788	86.7 (6755)	<0.001 *
Maternal age (years)							<0.001 **
≤20 years	277	78.7 (218)	248	83.1 (206)	168	89.9 (151)	
21–30 years	4335	77.3 (3353)	4572	82.6 (3776)	3991	85.9 (3430)	
31–40 years	3038	79.1 (2402)	3351	84.1 (2817)	3433	87 (2986)	
≥41 years	129	93 (120)	175	86.9 (152)	197	95.4 (188)	
Region of residence							<0.001 **
Flanders	3612	73.7 (2661)	4001	80.7 (3228)	3804	85 (3232)	
Wallonia	3189	82.9 (2644)	3286	86.1 (2830)	2945	88.7 (2611)	
Brussels region	978	80.6 (788)	1058	84.3 (892)	1039	87.7 (911)	

* χ^2 for trends across the three periods.
** Pearson's χ^2 (only for 2015–2017).

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Table 3. Prevalence of the most frequently dispensed medications during pregnancy in Belgium between 2003 and 2017.

	Period 2003–2005 (N = 7779)				Period 2009–2011 (N = 8345)				Period 2015–2017 (N= 7788)			
	Pregnancies exposed % (n)				Pregnancies exposed % (n)				Pregnancies exposed % (n)			
Medication (ATC code)	All	T1	T2	T3	All	T1	T2	T3	All	T1	T2	T3
progesterone (G03DA04)	**20 (1559)**	8.4 (655)	7.8 (603)	10.9 (848)	**23.6 (1971)**	10.4 (869)	8.5 (706)	12.8 (1072)	**25.5 (1988)**	11.7 (912)	8.7 (681)	13.4 (1041)
electrolytes (B05BB01)	**19.2 (1496)**	3.3 (256)	2.6 (205)	14.8 (1148)	**22 (1832)**	5.1 (422)	2.6 (216)	16.3 (1358)	**25.6 (1991)**	6 (468)	3.2 (246)	19.2 (1495)
amoxicillin (J01CA04)	**20.2 (1573)**	6.1 (474)	7.9 (618)	9.5 (742)	**19.5 (1631)**	6.2 (519)	7.4 (616)	8.8 (730)	**17.1 (1329)**	5.7 (443)	5.9 (463)	7.8 (605)
paracetamol (N02BE01)	**10.1 (785)**	1.5 (119)	1.4 (107)	7.7 (598)	**14.1 (1176)**	4.3 (356)	2.6 (217)	8.7 (725)	**17.8 (1387)**	6 (465)	3.5 (274)	10.4 (807)
miconazole (G01AF04)	**15.1 (1175)**	3.3 (253)	5.2 (402)	7.7 (600)	**14 (1167)**	2.9 (239)	5.1 (424)	7.4 (617)	**12.4 (962)**	2.5 (196)	4.4 (342)	6.4 (497)
solution for injection (V07AB40)	**9.6 (743)**	1.3 (101)	0.8 (59)	7.7 (602)	**13.7 (1140)**	3 (250)	1.1 (88)	10.1 (846)	**17.2 (1341)**	4.5 (354)	1.6 (123)	12.3 (957)
chlorhexidine (D08AC02)	**11.3 (877)**	1 (80)	1.4 (108)	9.4 (727)	**12.7 (1056)**	1.6 (134)	1.4 (118)	10.2 (855)	**13.9 (1079)**	2.1 (166)	1.9 (145)	11 (857)
carbohydrates (B05BA03)	**13.4 (1043)**	1.4 (107)	1.7 (129)	11 (855)	**11.1 (929)**	1.2 (96)	1 (84)	9.3 (779)	**10.8 (840)**	1.4 (108)	0.7 (57)	9 (699)
Amoxicillin and beta-lactamase inhibitor (J01CR02)	**12.5 (969)**	3.7 (287)	4.1 (321)	6.2 (479)	**10.5 (879)**	3.4 (281)	3.3 (277)	4.8 (399)	**8.8 (686)**	3.2 (246)	3 (230)	3.8 (299)
fosfomycin (J01XX01)	**6.1 (472)**	1 (78)	2 (156)	3.5 (274)	**9.8 (820)**	1.8 (149)	2.9 (243)	6 (498)	**13.2 (1029)**	2.4 (183)	4.8 (370)	7.6 (590)
oxytocin (H01BB02)	**9 (702)**	0.1 (6)	<0.01 (1)	9 (696)	**9 (752)**	0.1 (9)	0 (0)	8.9 (744)	**9.9 (772)**	0.1 (4)	0 (0)	9.9 (768)
lidocaïne (N01BB02)	**7.9 (612)**	1.1 (88)	1 (79)	5.8 (454)	**9.1 (756)**	1.7 (145)	1 (80)	6.6 (548)	**10.2 (797)**	2.1 (160)	0.8 (62)	7.7 (596)
sufentanil (N01AH03)	**7.3 (570)**	0.7 (53)	0.2 (15)	6.6 (511)	**8.5 (712)**	0.8 (65)	0.4 (33)	7.5 (623)	**9.3 (723)**	0.7 (52)	0.2 (16)	8.5 (661)
phytomenadione (B02BA01)	**7.5 (581)**	0 (0)	0 (0)	7.5 (581)	**8.6 (721)**	<0.1 (1)	0 (0)	8.6 (720)	**8.8 (684)**	<0.1 (1)	0 (0)	8.8 (683)
ropivacaine (N01BB09)	**5.1 (399)**	<0.01 (1)	<0,01 (2)	5.1 (397)	**5.8 (481)**	0.2 (15)	<0.1 (2)	5.6 (464)	**6.4 (495)**	0.2 (12)	0.1 (5)	6.1 (478)
influenza. purified antigen (J07BB02)	**0.2 (13)**	<0.1 (5)	<0.1 (3)	<0.1(5)	**4.3 (362)**	0.5 (39)	2.1 (179)	1.7 (144)	**12.2 (952)**	1 (79)	5.2 (408)	6 (467)
pertussis. purified antigen (J07AJ52)	**0 (0)**	0 (0)	0 (0)	0 (0)	**1.1 (90)**	<0.1 (3)	0.1 (9)	0.9 (78)	**11 (857)**	<0.1 (2)	0.8 (61)	10.2 (794)
ranitidine (A02BA02)	**3.5 (275)**	0.6 (46)	0.5 (42)	2.7 (2019)	**6.2 (516)**	1.4 (117)	1.6 (130)	3.9 (326)	**9 (702)**	1.8 (142)	2.1 (161)	6.3 (492)
levothyroxine sodium (H03AA01)	**2.7 (210)**	1.7 (131)	1.8 (137)	2.1 (160)	**5.5 (457)**	2.8 (230)	3.1 (256)	4.5 (378)	**8.2 (642)**	4.5 (350)	5.3 (409)	6.2 (483)
immunoglobulin anti-d rh (J06BB01)	**4.2 (328)**	0.4 (27)	1.8 (136)	2.4 (190)	**7.6 (637)**	0.5 (42)	1.4 (116)	6.4 (532)	**7.6 (593)**	0.6 (44)	1.1 (85)	6.7 (525)
butylscopolamine (A03BB01)	**6 (464)**	0.9 (73)	1.3 (102)	4.1 (318)	**5.4 (453)**	0.7 (54)	0.7 (60)	4.2 (354)	**6 (468)**	0.7 (57)	0.8 (61)	4.7 (366)
povidone iodine (D08AG02)	**4.5 (346)**	0.5 (38)	1 (79)	3.1 (240)	**5 (420)**	1 (86)	1.3 (107)	2.9 (245)	**5.4 (421)**	1.2 (96)	0.9 (72)	3.4 (262)

Table 4. Most frequently dispensed nonsteroidal anti-inflammatory drugs (NSAID) dispensed during pregnancy in Belgium**.**

		The 6 most frequently dispensed NSAIDs					
	Pregnancy period	ibuprofen (M01AE01)	diclofenac (M01AB05)	ketoralac (M01AB15)	naproxen (M01AE02)	indomethacin (M01AB01)	piroxicam (M01AC01)
Pregnancies exposed % (*n*) 2003–2005 (*N* = 7779)	all	2.74 (213)	4.1 (322)	0.46 (36)	1.7 (129)	0.43 (34)	1.25 (97)
	T1	1.8 (140)	1.12 (87)	0.13 (10)	0.89 (69)	0.013 (1)	0.85 (66)
	T2	0.48 (37)	0.44 (34)	0.03 (2)	0.22 (17)	0.14 (11)	0.17 (13)
	T3	0.67 (52)	2.64 (205)	0.31 (24)	0.64 (50)	0.33 (26)	0.3 (23)
	T3–last week	0.33 (26)	0.6 (46)	0.013 (1)	0.18 (14)	0.24 (19)	0.1 (8)
	Last week	0.33 (26)	2.04 (159)	0.3 (23)	0.46 (36)	0.06 (5)	0.19 (15)
	All without last week	**2.44 (190)**	**2.15 (167)**	**0.17 (24)**	**1.22 (95)**	**0.37 (29)**	**1.05 (82)**
Pregnancies exposed % (*n*) 2009–2011 (*N* = 8345)	all	4.46 (372)	4.77 (398)	0.93 (78)	1.05 (88)	0.53 (44)	0.49 (41)
	T1	2.8 (234)	1.79 (149)	0.42 (35)	0.78 (65)	0.03 (3)	0.43 (36)
	T2	0.74 (62)	0.46 (38)	0.1 (8)	0.11 (9)	0.11 (9)	0.02 (2)
	T3	1.11 (93)	2.62 (219)	0.43 (36)	0.2 (17)	0.38 (32)	0.05 (4)
	T3–last week	0.51 (43)	0.54 (45)	0.03 (3)	0.05 (4)	0.33 (28)	0.05 (4)
	Last week	0.6 (50)	2.08 (174)	0.4 (33)	0.16 (13)	0.05 (4)	0 (0)
	All without last week	**3.88 (324)**	**2.79 (233)**	**0.55 (46)**	**0.89 (75)**	**0.48 (40)**	**0.49 (41)**
Pregnancies exposed % (*n*) 2015–2017 (*N* = 7788)	all	5.61 (437)	4.38 (341)	1.1 (86)	0.64 (50)	0.45 (35)	0.4 (31)
	T1	3.53 (275)	2 (156)	0.71 (55)	0.58 (45)	0.012 (1)	0.36 (28)
	T2	0.56 (44)	0.3 (23)	0.05 (4)	0.06 (5)	0.14 (11)	0.06 (5)
	T3	1.84 (143)	2.25 (175)	0.35 (27)	0.03 (2)	0.32 (25)	0.012 (1)
	T3–last week	0.5 (40)	0.33 (26)	0.012 (1)	0.012 (1)	0.31 (24)	0.012 (1)
	Last week	1.32 (103)	1.91 (149)	0.33 (26)	0.012(1)	0.012 (1)	0 (0)
	All without last week	**4.42 * (344)**	**2.54 (198)**	**0.78 * (61)**	**0.63* (49)**	**0.41 (32)**	**0.4* (31)**

* Trend test across three study periods significant