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ORIGINAL ARTICLE

Dutch trends in the use of potentially harmful medication during pregnancy

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Aims: Recent population-based data on drug utilization around pregnancy are lacking. This study aims to examine the prevalence of drug exposure in the Netherlands during the preconception, pregnancy and postpartum periods, with special emphasis on trends of potentially harmful medication over the years.

Methods: A population-based study was conducted using records from the PHARMO Perinatal Research Network. From 1999 to 2017, the proportion of pregnancies during which women used any medication or potentially harmful medication was assessed, overall and stratified by timing of exposure relative to pregnancy and by the year of delivery.

Results: Overall, 357 226 (73%) and 166 484 (34%) of 487 122 selected pregnancies were exposed to any and potentially harmful medication, respectively. Among these 487 122 pregnancies, preconception prevalence for use of potentially harmful medication was 43%, 24% during the first trimester, 19% during the second, 16% during the third, and 45% postpartum. A declining trend was observed for exposure to any medication, from 84% in 1999 to 68% in 2017. No clear changes were observed over time for the proportion of pregnancies exposed to potentially harmful medication.

Conclusions: Our study shows that the use of potentially harmful medication was high over the last two decades. Although there was a declining trend over the years in overall medication use, during a steady one-third of pregnancies, women used potentially harmful medication. Our findings highlight the need for an increased sense of urgency among both healthcare providers and women of reproductive age regarding potential risks associated with pharmacological treatment during pregnancy.

KEYWORDS

medication safety, pharmacoepidemiology, pregnancy

This study does not contain any new interventions performed with human subjects or patients and does therefore not include a Principal Investigator as the current paper presents a database research with anonymous data.

1 | INTRODUCTION

The potentially harmful effects on the mother, embryo or fetus, and newborn of medication used before, during and after pregnancy are well known and can lead to major birth defects. It is therefore undisputed that safe pharmaceutical care around pregnancy is of vital importance. There are critical time points during a pregnancy when medication is likely to impact pregnancy outcomes. In the first trimester, risk of spontaneous abortion and birth defects are highest because of organogenesis. However, after the first trimester, teratogens can still affect development of fetal organs and tissues such as the brain.[1,2]

Despite this, drug exposure during pregnancy is common in Europe and the US.[3–5] Prior drug utilization studies have revealed an overall prescription rate of up to 79% during pregnancy in the period 1994 to 2013 in the Netherlands.[6,7] A multinational study showed that compared to other (European) countries, prevalence of any medication use during pregnancy was high in the Netherlands (95% vs. on average 81%).[4] For certain chronic conditions like epilepsy or diabetes, medical treatment cannot be easily avoided. In case of potential teratogenicity, switching to alternative (pharmaceutical) treatment, lowering the dose or temporary cessation should be considered. However, it remains a matter of balancing fetal and maternal risks, especially in case of chronic conditions.[8]

The public health importance of monitoring drug use around pregnancy has been recognized from a national as well as from an EU perspective.[9,10] Recent long-term population-based data on drug utilization before, during and after pregnancy in the Netherlands are lacking. Such data would allow for more intense future interventions targeted at preventing use of potentially harmful medication during pregnancy. The objective of the current study was to examine, at a population level, the prevalence of drug exposure during the preconception, pregnancy and postpartum periods in the Netherlands, with special emphasis on potentially harmful medication, and to assess trends over the years.

What is already known about this subject

- The potentially harmful effects on the mother, embryo or fetus, and newborn of some medication used before, during and after pregnancy are well known.
- Despite this, drug exposure during pregnancy is common in Europe and the US.
- Recent long-term population-based data on drug utilization before, during and after pregnancy in the Netherlands are lacking.

What this study adds

- Over all the study years, potentially harmful medication was used during a steady one-third of pregnancies.
- Our findings highlight the need for an increased sense of urgency among both healthcare providers and women of reproductive age regarding the potential risks associated with pharmacological treatment during pregnancy.

2 | METHODS

2.1 | Study design and data sources

This population-based study was performed using the PHARMO Perinatal Research Network (PPRN), which combines records from the Netherlands Perinatal Registry (Perined) and the PHARMO Database Network (PHARMO).[11] Perined is a nationwide registry that contains validated data from pregnancies with a gestational age (GA) of at least 16 weeks.[12] PHARMO comprises a dynamic cohort of participants and includes, among other information, drug-dispensing records from community pharmacies for more than three million individuals (approximately 25% of the Dutch population) collected since 1998.[13,14] The Out-patient Pharmacy Database contains the following information per filled prescription: the Anatomical Therapeutic Chemical (ATC) classification of the drug, dispensing date, dose regimen, prescribing physician, quantity dispensed and estimated duration of use.[15] The Out-patient Pharmacy Database represents the Dutch population that has picked up prescription drugs or has registered with a pharmacy and has been shown to be representative of the general Dutch population in terms of age and gender. The linkage between PHARMO and Perined has been described in detail elsewhere but was generally based on the birth date of the mother and child and their addresses and could be established for about 20% of the pregnancies in Perined.[11,16] Women who gave birth between 1999 and 2017 were selected from the PPRN, including both live and stillbirths (GA ≥22 weeks). No exclusion criteria were applied in order to increase the generalizability of the results. To allow for women's medication use to be assessed during the preconception, pregnancy and postpartum periods, their details needed to be registered in the Out-patient Pharmacy Database from 40 weeks before the conception date (based on ultrasound or first day of the last menstrual period [LMP]) until 40 weeks after the delivery date as recorded in Perined. For the current database research with anonymous data, no Institutional Review Board or ethics committee approval was required.

2.2 | Drug exposure during the preconception, pregnancy and postpartum periods

All drug dispensing records of the women in the PPRN were selected from the Out-patient Pharmacy Database and the length of each dispensing was calculated by dividing the total number of dispensed units by the number of units to be taken per day.

TABLE 1 Overview of medication categories according to the 2016 risk classification system for drugs in pregnancy of the Dutch Teratology Information Service Lareb

Category	Label	Description[a]
1.	Wide experience; can be used	Medicines used in research or in practice without showing a raised prevalence of congenital defects, or (in)direct harmful effects in the embryo, fetus or newborn. This category is not taken into account separately in the current study.
2.	Pharmacological effects; require monitoring	Medicines known or suspected to result in pharmacological effects in the embryo, fetus or newborn. The use of these medicines must be considered carefully. When used, monitoring for side effects is needed.
3.	Pharmacological effects; avoid (temporarily)	Medicines known or suspected to result in pharmacological effects in the embryo, fetus or newborn. These medicines should not be used during this hazardous period; an alternative medicine should be chosen.
4.	Teratogenic effects; require monitoring	Medicines known or suspected to cause a higher prevalence of congenital defects or other permanent damage or that can have harmful pharmacological effects in the embryo, fetus or newborn. Usage must be considered carefully, and if so, monitoring for undesirable effects is needed.
5.	Teratogenic effects; avoid (temporarily)	Medicines known or suspected to cause a higher prevalence of congenital defects or other permanent damage and that can have harmful pharmacological effects in the embryo, fetus or infant. These medicines should not be used during this hazardous period; an alternative medicine should be chosen.
6.	Unknown risk	Medicines of which the risk for the embryo, fetus or newborn cannot be determined because there are insufficient data on their effect in humans. The use of these medicines must be considered carefully and, when possible, another medicine should be chosen.

[a]See Appendix Table A1 for detailed overview of the medication that is included in each category.

Dispensings were converted into treatment episodes of uninterrupted use to be able to determine drug exposure over time. Drug exposure preconception was defined as an active treatment episode within 40 weeks before the conception date. Drug exposure during pregnancy was similarly assessed from on or after the conception date until delivery date and classified by pregnancy trimester: up to the week 12 of amenorrhea (first), 13–27 weeks (second) and 28 weeks to delivery (third). Drug exposure postpartum was assessed during the 40 weeks after delivery. Although the conventional definition of the periconceptional period is shorter, these periods were defined in order to have time windows of similar length and thereby allow comparability of drug exposure between the three periods. Sensitivity analyses were performed in which drug exposure during these periods was based on drug dispensings rather than treatment episodes. Drug exposure to medication not indicated as safe (hereafter referred to as "potentially harmful medication") was classified according to Categories 2–6 of the 2016 risk classification system for drugs in pregnancy of the Dutch Teratology Information Service Lareb (see Table 1 and Appendix Table 1).[17] Although this classification system is directed specifically at drug use during pregnancy, the same classification was applied to the postpartum period in order to visualize periconceptional exposure patterns (i.e. without applying breastfeeding-specific risk classification).

2.3 | Outcome assessment

Maternal and obstetric characteristics assessed included age at delivery, neighbourhood socioeconomic status (SES),[18,19] year of delivery, ethnicity, preconceptional use of medication for chronic conditions (see Appendix Table A2), parity and GA at birth (ultrasound- or LMP-based). The proportion of pregnancies during which potentially harmful as well as any medication was used was determined and stratified by the timing of exposure relative to pregnancy (i.e. preconception, first trimester, second trimester, third trimester and postpartum). Risk classification categories were presented separately and combined as "potentially harmful" (Categories 2–6) and "'known risk" (Categories 2–5) medication. The medication most often used during pregnancy was assessed per medication category (2, 3, 4, 5, 6 and none) and the top 5 presented by pregnancy trimester (excluding reproductive hormonal drugs). In order to assess developments over the years, the proportion of pregnancies during which potentially harmful as well as any medication was used was stratified by the year of delivery. Any medication included all ATC-coded drugs, in case they were dispensed in the out-patient pharmacy and not purchased over-the-counter (including folic acid and vitamin D, although these are nearly always purchased over-the-counter).

2.4 | Statistical analysis

All analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). Logistic regression models were used to calculate unadjusted odds ratios (ORs) and 95% confidence intervals (Cis) to estimate associations between maternal and obstetric characteristics and use of potentially harmful medication. Missing categories were created for SES, ethnicity and parity. Trends over time were tested by Poisson regression at *P*-value <0.05.

TABLE A2 ATC codes for use of medication for chronic conditions

Chronic condition	ATC
Drugs used in diabetes	A10
Corticosteroids, dermatological preparations	D07
Corticosteroids for systemic use	H02
Thyroid therapy	H03
Anti-inflammatory and antirheumatic products	M01
Antimigraine medication	N02C
Antiepileptics	N03A
Antipsychotics	N05A, excl. N05AB04
Antidepressants	N06A
Antiasthmatics	R03

Note: Preconceptional use was defined similar to all other medication classes assessed (i.e. an active treatment episode within 40 weeks before the conception date).

3 | RESULTS

In total, 487 122 pregnancies were selected from the PPRN between 1999 and 2017 for inclusion in the study (Table 2). During 357 226 (73%) of all the pregnancies, women used any medication at least once. Overall, women used potentially harmful medication during 166 484 (34%) of these pregnancies. This was 43% preconception, 24% during the first trimester, 19% during the second trimester, 16% during the third trimester and 45% postpartum (Figure 1). The highest prevalence was observed for medication with unknown risk (Category 6; ranging from 9% to 31%) and the lowest for medication with teratogenic effects that require monitoring (Category 4; ranging from <0.5% to 1%), regardless of the timing relative to pregnancy. Similar periconceptional patterns were observed for any medication with overall higher prevalence (preconception: 71%, first trimester: 58%, second trimester: 55%, third trimester: 53%, postpartum: 80%). Sensitivity analyses in which drug exposure prevalence during these periods was based on drug dispensings rather than treatment episodes showed very similar results: all percentage differences in recalculated prevalences were smaller than 0.5% (data not presented).

Table 2 shows that preconceptional use of medication for chronic conditions was strongly associated with potentially harmful medication use (OR 3.82, 95% CI 3.77–3.86), particularly antipsychotics and drugs used in diabetes. The use of potentially harmful medication was observed to a significantly larger extent among women of non-Dutch ethnicity compared with Dutch women (OR Moroccan/Turkish: 1.41, 95% CI 1.38–1.44; OR other European/Western: 1.09, 95% CI 1.05–1.12; OR Other: 1.25, 95% CI 1.22–1.28).

An overall declining trend over the years for any medication use was observed, from 84% in 1999 to 68% in 2017 (Figure 2). However, no clear long-term linear trend is apparent for the potentially harmful medication categories presented in this figure. Combining this information, the proportion of "potentially harmful medication" relative to "any medication" increased from 39% in 1999 to about 50% from 2011 onwards (data not presented in figure). Pregnancies during which women used potentially harmful medication were predominantly in Category 6 (63%), followed by Category 3 (33%), Category 2 (29%), Category 5 (11%) and Category 4 (1%).

The top five medications used in each category are presented in Table 3. The table shows that among drugs with pharmacological effects that require monitoring (Category 2), the nervous system drugs (psycholeptics and psychoanaleptics) were at the top. A marked increase for temazepam was observed in the third trimester, which is used for short-term treatment of insomnia and is one of the preferred choices during pregnancy. Nitrofurantoin, which should be avoided only around the due date, was most often used within Category 3, including drugs with pharmacological effects that should be (temporarily) avoided, followed by ibuprofen (contraindicated in third trimester), naproxen (contraindicated in third trimester), acetylsalicylic acid (contraindicated in third trimester at daily dose >80 mg) and promethazine (should be avoided in last weeks of pregnancy, however known for its sedating side effect in favour of other sleep medication). Overall, the prevalence of drugs with teratogenic effects that require

TABLE 2 Maternal and obstetric characteristics of included pregnancies, stratified by use of potentially harmful medication during pregnancy

Characteristic	Study cohort *N* = 487 122 *n* (%)	Use of potentially harmful medication (Cat. 2–6) *N* = 166 484 (34%) *n* (%)	No use of potentially harmful medication (Cat. 2–6) *N* = 320 638 (66%) *n* (%)	OR (95% CI) use vs. no use
Age at delivery (years)				
≤20	7837 (2)	2900 (2)	4937 (2)	1.18 (1.13–1.24)
21–30	213 153 (44)	70 742 (42)	142 411 (44)	1 (reference)
31–40	254 949 (52)	87 868 (53)	167 081 (52)	1.06 (1.05–1.07)
≥41	11 183 (2)	4974 (3)	6209 (2)	1.61 (1.55–1.68)
Mean ± SD	31 ± 5	31 ± 5	31 ± 5	1.06 (1.06–1.07)[a]
SES				
Low	171 623 (35)	61 490 (37)	110 133 (34)	1.12 (1.11–1.14)
Normal	151 123 (31)	50 165 (30)	100 958 (31)	1 (reference)
High	162 414 (33)	54 114 (33)	108 300 (34)	1.01 (0.99–1.02)
Unknown	1962 (<0.5)	715 (<0.5)	1247 (<0.5)	-
Year of delivery				
1999–2003	74 812 (15)	24 833 (15)	49 979 (16)	1 (reference)
2004–2008	134 370 (28)	45 639 (27)	88 731 (28)	1.04 (1.02–1.05)
2009–2013	142 759 (29)	51 685 (31)	91 074 (28)	1.14 (1.12–1.16)
2014–2017	135 181 (28)	44 327 (27)	90 854 (28)	0.98 (0.96–1.00)
Ethnicity				
Dutch	388 723 (80)	128 584 (77)	260 139 (81)	1 (reference)
Moroccan/Turkish	35 400 (7)	14 550 (9)	20 850 (7)	1.41 (1.38–1.44)
Other European/Western[b]	16 025 (3)	5601 (3)	10 424 (3)	1.09 (1.05–1.12)
Other[c]	44 609 (9)	17 036 (10)	27 573 (9)	1.25 (1.22–1.28)
Unknown	2365 (<0.5)	713 (<0.5)	1652 (1)	-
Medication for chronic conditions[d]	150 232 (31)	83 418 (50)	66 814 (21)	3.82 (3.77–3.86)
Drugs used in diabetes	2677 (1)	2360 (1)	317 (<0.5)	14.53 (12.92–16.34)
Corticosteroids, dermatological preparations	47 269 (10)	25 508 (15)	21 761 (7)	2.48 (2.44–2.53)
Corticosteroids for systemic use	7036 (1)	5004 (3)	2032 (1)	4.86 (4.61–5.12)
Thyroid therapy	8517 (2)	4362 (3)	4155 (1)	2.05 (1.96–2.14)
Anti-inflammatory and antirheumatic products	70 340 (14)	37 632 (23)	32 708 (10)	2.57 (2.53–2.61)
Antimigraine medication	8730 (2)	6136 (4)	2594 (1)	4.69 (4.48–4.91)
Antiepileptics	2937 (1)	2508 (2)	429 (<0.5)	11.42 (10.30–12.65)
Antipsychotics	3185 (1)	2913 (2)	272 (<0.5)	20.92 (18.48–23.69)
Antidepressants	19 583 (4)	16 563 (10)	3020 (1)	11.62 (11.17–12.08)
Antiasthmatics	24 602 (5)	14 153 (9)	10 449 (3)	2.76 (2.69–2.83)
Parity				
0	219 670 (45)	76 845 (46)	142 825 (45)	1 (reference)
1	24 802 (5)	7884 (5)	16 918 (5)	0.87 (0.84–0.89)
2	161 309 (33)	52 764 (32)	108 545 (34)	0.90 (0.89–0.92)
≥3	81 295 (17)	28 975 (17)	52 320 (16)	1.03 (1.01–1.05)
Unknown	46 (<0.5)	16 (<0.5)	30 (<0.5)	-

(Continues)

TABLE 2 (Continued)

Characteristic	Study cohort *N* = 487 122 *n* (%)	Use of potentially harmful medication (Cat. 2–6) *N* = 166 484 (34%) *n* (%)	No use of potentially harmful medication (Cat. 2–6) *N* = 320 638 (66%) *n* (%)	OR (95% CI) use vs. no use
GA at birth (weeks)				
≤24	1875 (<0.5)	803 (<0.5)	1072 (<0.5)	1.48 (1.35–1.62)
25- < 28	1455 (<0.5)	648 (<0.5)	807 (<0.5)	1.58 (1.43–1.76)
28- < 33	5679 (1)	2327 (1)	3352 (1)	1.37 (1.30–1.44)
33- < 37	29 385 (6)	11 702 (7)	17 683 (6)	1.30 (1.27–1.34)
≥37	448 728 (92)	151 004 (91)	297 724 (93)	1 (reference)
Mean ± SD	39.2 ± 2.2	39.0 ± 2.4	39.3 ± 2.1	0.75 (0.75–0.76)[a]

OR = odds ratio; CI = confidence interval; SD = standard deviation; SES = neighbourhood socioeconomic status; GA = gestational age;
[a]OR for 5 units change;
[b]Including North American and Canadian;
[c]Creole, Hindu, Asia and other;
[d]Medication use for chronic conditions was assessed preconception (see Appendix Table 2 for definitions).

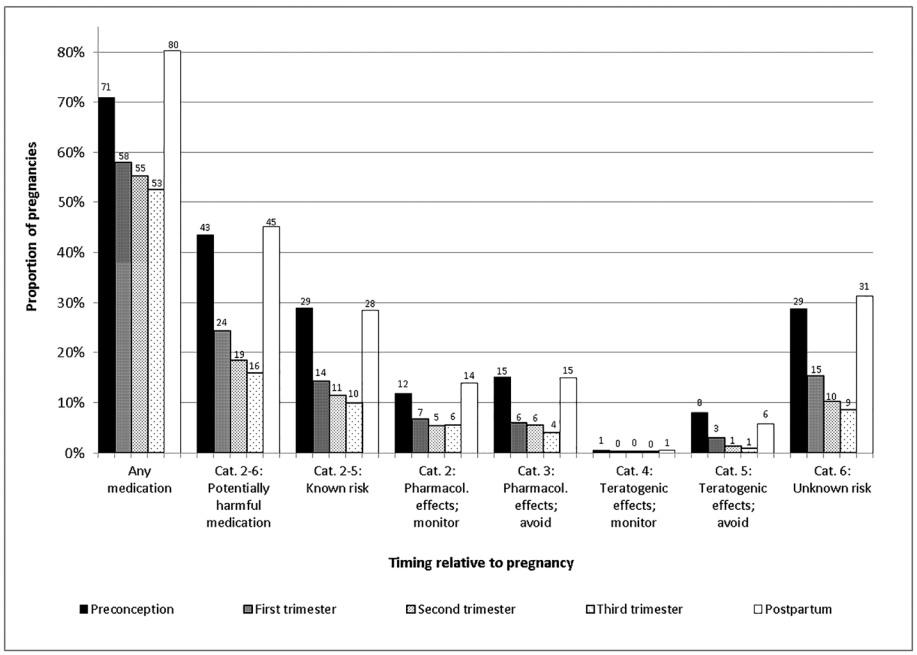

FIGURE 1 Medication use during the preconception, pregnancy and postpartum periods categorized according to the 2016 risk classification system for drugs in pregnancy of the Dutch Teratology Information Service Lareb
All trends over time were statistically significant at *P*-value <0.05

monitoring (Category 4) was low across all trimesters (≤0.1%). Of those Category 5 drugs with teratogenic effects that should be (temporarily) avoided, doxycycline (should be avoided in second and third trimester) was most often used, followed by minocycline (contraindicated in second and third trimester), valproic acid (contraindicated during pregnancy, unless other epilepsy treatment is inadequate), acenocoumarol (should be avoided from 6 weeks GA onwards) and enalapril (contraindicated in second and third trimester). In Category 6 including drugs with unknown risk, a clear decrease in prevalence was observed reflecting patients who switched or stopped nonpreferred treatment. For cabergoline, used to suppress lactation, a high increase was observed in the third trimester. Among medication without a category assigned, pregnancy-related drugs were most apparent. For example, a clear increase was observed in meclozine use in the first trimester, which is prescribed for nausea and vomiting in pregnancy. Use of ferrous fumarate also increased over the trimesters, which is recommended for maternal anaemia.

4 | DISCUSSION

This study shows a high prevalence of exposure to potentially harmful medication during pregnancy in the Netherlands from 1999 to 2017. Over all the study years, potentially harmful medication was

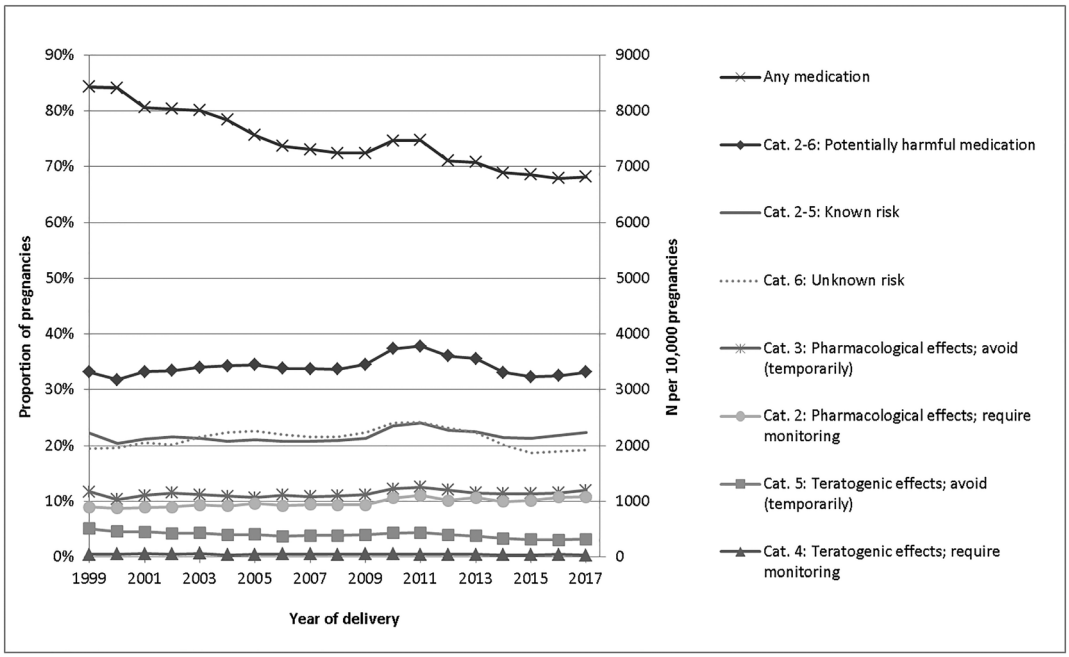

FIGURE 2 Trends in medication use during pregnancy, categorized according to 2016 risk classification system for drugs in pregnancy of the Dutch Teratology Information Service Lareb

used during approximately one-third of pregnancies, including drugs with known and unknown risks to a similar extent. Although there was a declining trend in overall medication use, no such trend was observed for potentially harmful medication, indicating an increasing share of potentially harmful medication relative to all medication used. Most notably, potentially harmful medication use was significantly higher among women with preconceptional use of medication for chronic conditions and women of non-Dutch ethnicity. Exposure was most common during the first trimester for all risk categories. Although in particular the use of drugs with known teratogenic effects dropped most markedly in the second and third trimester, exposure to harmful medications such as non-steroidal anti-inflammatory drugs (NSAIDs), tetracyclines or valproic acid remained common.

The current study findings are in line with those in previous Dutch studies on medication exposure during pregnancy. Our estimate of overall medication use was somewhat lower than observed in a study published in 2006 (73% vs. 79%).[6] This is probably due to differences in patient selection (e.g. their restriction to first pregnancies), as well as the extension of our study into more recent years. A recent Dutch, tertiary academic centre study of pregnant and lactating women showed that 68.2% used prescribed medication.[7] However, next to the difference in study setting, participants using only vitamin D, folic acid and/or multivitamins during pregnancy were classified as nonmedication users, contrary to the current study. We observed a decreasing trend for any medication use over the years. Similar recent studies focusing on Dutch population-based trends are limited. Increasing multinational trends were described in two papers published in the last decade, and attributed to older maternal age and associated pre-existing medical conditions that require pharmacotherapy.[5,20] In addition to international differences, the study period differed and the main focus was on the number of medications used (i.e. polypharmacy) rather than the binomial outcome of medication use applied in this study. Focusing on potentially harmful medication specifically, other recently reported rates were somewhat higher than those presented here.[7] As well as the different make-up of their study population, they used a questionnaire design taking into account over-the-counter drugs. Studies assessing medication use during preconception, pregnancy and postpartum periods and classified per risk category are limited. In a Dutch study from 2006, decreasing exposure to potentially harmful medication was reported from 30% in the first trimester to 14% in the third trimester, increasing to 45% postpartum.[6] This is very similar to the patterns we observed for all risk categories together. Contrary to the current study, an increase in overall prescription rates during pregnancy trimesters was observed. This can be attributed to their exclusion of contraceptive prescriptions, the main drugs used before pregnancy.[21]

Our results have important implications for public health. The unchanged high use of medication with known risks suggests a potential deficit of risk perception among healthcare providers and pregnant women. The increased relative share of potentially harmful medication together with the decline in overall medication use implies that patients with high-risk conditions requiring pharmaceutical treatment continue their therapy, supported also by the strong associations with chronic medication use in this study. This is in line with the abovementioned increase in maternal age and pre-existing medical conditions (e.g. diabetes) over the years, as recorded in the

TABLE 3 Top 5 medications used during pregnancy trimesters according to 2016 risk classification system for drugs in pregnancy of the Dutch Teratology Information Service Lareb

	Preconception	First trimester	Second trimester	Third trimester
	N = 487 122	N = 487 122	*N* = 487 122	*N* = 483 799
Medication (ATC)[a]	*n* (%)	*n* (%; change[c])	*n* (%; change[d])	*n* (%; change[e])
Cat. 2: Pharmacological effects; require monitoring				
#1. Temazepam (N05CD07)	6347 (1)	2402 (0.5; −62%)	2016 (0.4; −16%)	5328 (1; +166%)
#2. Oxazepam (N05BA04)	9781 (2)	3999 (0.8; −59%)	2774 (0.6; −31%)	2541 (0.5; −8%)
#3. Paroxetine (N06AB05)	5328 (1)	3756 (0.8; −30%)	2875 (0.6; −23%)	2529 (0.5; −11%)
#4. Betamethasone (D07AC01)	5338 (1)	2566 (0.5; −52%)	1901 (0.4; −26%)	1406 (0.3; −26%)
#5. Prednisolone (H02AB06)	3705 (0.8)	1644 (0.3; −56%)	1570 (0.3; −5%)	1487 (0.3; −5%)
Cat. 3: Pharmacological effects; avoid (temporarily)				
#1. Nitrofurantoin (J01XE01)	23 101 (5)	10 851 (2; −53%)	14 904 (3; +37%)	9852 (2; −33%)
#2. Ibuprofen (M01AE01)	25 081 (5)	6784 (1; −73%)	3216 (0.7; −53%)	2344 (0.5; −27%)
#3. Naproxen (M01AE02)	17 088 (4)	4472 (0.9; −74%)	1836 (0.4; −59%)	1358 (0.3; −26%)
#4. Acetylsalicylic acid (B01AC06)	842 (0.2)	2514 (0.5; +199%)	3174 (0.7; +26%)	2878 (0.6; −9%)
#5. Promethazine (R06AD02)	1266 (0.3)	840 (0.2; −34%)	1167 (0.2; +39%)	1416 (0.3; +22%)
Cat. 4: Teratogenic effects; require monitoring				
#1. Carbamazepine (N03AF01)	591 (0.1)	485 (<0.1; −18%)	474 (<0.1; −2%)	457 (<0.1; −3%)
#2. Valproic acid (N03AG01)	589 (0.1)	446 (<0.1; −24%)	393 (<0.1; −12%)	367 (<0.1; −6%)
#3. Propylthiouracil (H03BA02)	314 (<0.1)	373 (<0.1; +19%)	393 (<0.1; +5%)	289 (<0.1; −26%)
#4. Lithium (N05AN01)	299 (<0.1)	271 (<0.1; −9%)	242 (<0.1; −11%)	259 (<0.1; +8%)
#5. Thiamazole (H03BB02)	460 (<0.1)	258 (<0.1; −44%)	207 (<0.1; −20%)	139 (<0.1; −32%)
Cat. 5: Teratogenic effects; avoid (temporarily)				
#1. Doxycycline (J01AA02)	17 909 (4)	3625 (0.7; −80%)	1704 (0.3; −53%)	1178 (0.2; −30%)
#2. Minocycline (J01AA08)	1651 (0.3)	623 (0.1; −62%)	374 (<0.1; −40%)	315 (<0.1; −15%)
#3. Valproic acid (N03AG01)	589 (0.1)	446 (<0.1; −24%)	393 (<0.1; −12%)	367 (<0.1; −6%)
#4. Acenocoumarol (B01AA07)	510 (0.1)	347 (<0.1; −32%)	351 (<0.1; +1%)	288 (<0.1; −17%)
#5. Enalapril (C09AA02)	391 (<0.1)	258 (<0.1; −34%)	193 (<0.1; −25%)	119 (<0.1; −38%)
Cat. 6: Unknown risk				
#1. Desloratadine (R06AX27)	12 018 (2)	4855 (1.0; −60%)	2571 (0.5; −47%)	1721 (0.4; −33%)
#2. Ketoconazole (D01AC08)	7046 (1)	3986 (0.8; −43%)	3367 (0.7; −16%)	2453 (0.5; −27%)
#3. Levocetirizine (R06AE09)	9555 (2)	4382 (0.9; −54%)	2548 (0.5; −42%)	1666 (0.3; −34%)
#4. Mometasone (R01AD09)	7372 (2)	4207 (0.9; −43%)	2773 (0.6; −34%)	1831 (0.4; −34%)
#5. Cabergoline (G02CB03)	1291 (0.3)	448 (<0.1; −65%)	513 (0.1; +15%)	4098 (0.8; +704%)
Medication without category assigned[b]				
#1. Ferrous fumarate (B03AA02)	11 519 (2)	7465 (2; −35%)	24 705 (5; +231%)	45 553 (9; +86%)
#2. Miconazole (G01AF04)	25 417 (5)	15 827 (3; −38%)	27 272 (6; +72%)	28 675 (6; +6%)
#3. Amoxicillin (J01CA04)	23 321 (5)	11 769 (2; −50%)	20 160 (4; +71%)	19 530 (4; −2%)
#4. Meclozine, combinations (R06AE55)	1439 (0.3)	27 419 (6; +1805%)	19 263 (4; −30%)	3140 (0.6; −84%)
#5. Folic acid (B03BB01)	16 747 (3)	22 168 (5; +32%)	19 257 (4; −13%)	9521 (2; −50%)

Note: Top 5 determined during entire pregnancy combining first, second and third trimester;
[a]Excluding reproductive hormonal drugs (ATC G03);
[b]According to the 2016 risk classification system for drugs in pregnancy of the Dutch Teratology Information Service Lareb;
Percentage change in proportion that used medication calculated relative to: [c]preconception, [d]first trimester, and [e]second trimester.

annual Perined reports and substantiated in this study cohort.[22] Healthcare providers, including pharmacists, have to recognize and shoulder their responsibility for drug use surveillance among women of reproductive age. A recent Dutch study has shown that pregnant women perceived most drugs relatively low in risk and high in benefit. This should be taken into account when counselling them.[23] The

higher use among women of non-Dutch ethnicity suggests that these patients in particular have difficulty obtaining, understanding and implementing health information as demonstrated also in previous research.[24] Treating physicians rely on available evidence on risks when making decisions and daily face difficulties balancing drugs' risks and benefits.[25] A high proportion of drugs are labelled as "unknown risk", lacking specific recommendations for use during pregnancy.[26] As exposure rates were highest in early pregnancy, which can be expected as sometimes pregnancy is still unknown, preconception counselling of the general population would in theory make women more aware of the risks of certain pharmacological treatments in relation to pregnancy. This could help to improve prevention of potentially harmful medication use. However, the implementation of preconception care in European countries is still very limited.[26–28] In order to achieve speedy and scalable benefits to public health, it was recently suggested that an advocacy coalition of groups interested in preconception health should be developed to harness the political will and leadership necessary to turn high-level policy into effective coordinated action.[29]

These results highlight the need for an expansion of medication-risk knowledge and communication by means of targeted preventive interventions, research and education programmes, so that specific recommendations can be made for medication use during pregnancy. Novel insights on the consequences of drug exposure during pregnancy should and can be gained, for example from the nearly 20 years of follow-up data currently available in the PPRN and other registries such as pREGnant.[30] Next to that, drug-centric research would enable assessment of dose–response relationships and provide insight on patient-level pregnancy-centred treatment patterns and alternatives (i.e. individualized care). Based on the current results, NSAIDs, tetracyclines, valproic acid or, more generally, medication for chronic conditions would be eligible for prioritization in such studies. Future research should focus on the challenge of actually achieving the desired risk perception, responsibility and activism in the context of risk management.

This observational study used nearly 20 years of data from a large population-based cohort, combining drug dispensing and pregnancy records and was shown to be representative of the Dutch population.[11] The timing of drug exposure relative to pregnancy staging could be accurately assessed based on LMP, ultrasound, exact delivery date, drug dispensing dates and intended duration of use. A limitation of Perined is that first trimester miscarriages were unable to be included, thereby potentially underestimating miscarriage-inducing medication.

A common challenge in using administrative data is defining drug exposure or compliance. Treatment episodes based on dispensing records can only approximate actual exposure and, particularly during pregnancy, drugs may be discontinued. Drug exposure could therefore have been overestimated, although sensitivity analyses using dispensing dates showed similar exposure rates. Underestimated drug exposure is likely because hospital-administered drugs and over-the-counter drugs sold outside pharmacies were not captured.

Of importance in this study was the use of a risk classification system for drugs in pregnancy that did not take into account individualized care in which drug risks are balanced with benefits. Also, the proportion of drugs with unknown risks was relatively high and therefore a statement could only be made on potentially harmful medication. In addition, risk classifications have evolved and been revised over time, and we specifically designed our study to use recent insights. Although some risk classification categories only apply during specific parts of pregnancy, no distinction was made between pregnancy trimesters for the trends in medication use during pregnancy over time. To put this into perspective, we also determined periconceptional patterns of exposure to risk classification categories. The risks of medication used in relation to breastfeeding were beyond the scope of this paper.

Our study shows that the use of potentially harmful medication was high over the last two decades, especially among ethnic minorities and women with chronic medical conditions. Although there was a declining trend over the years in overall medication use, during a steady one-third of pregnancies women used potentially harmful medication. Our findings highlight the need for an increased sense of urgency among both healthcare providers and women of reproductive age regarding the potential risks associated with pharmacological treatment during pregnancy. In order to be able to make specific recommendations, medication-risk knowledge needs to be expanded and readily accessible. Political will and leadership are needed to turn high-level policy on preconception care into effective coordinated action.

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COMPETING INTERESTS

There are no competing interests to declare.

CONTRIBUTORS

E.H. and R.H. had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors contributed to the plan and design of the study. E.H. performed the data analyses and drafted the manuscript. All authors contributed to the interpretation of the results and critical revision of the manuscript for important intellectual content and approved the final version of the manuscript. E.H. and R.H. are the guarantors of this paper. The corresponding author attests that all listed authors meet all ICMJE authorship criteria and that no others meeting the criteria have been omitted.

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APPENDIX A

TABLE A1 ATC codes for medication categories according to the 2016 risk classification system for drugs in pregnancy of the Dutch Teratology Information Service Lareb

Category	Name	ATC
1. Wide experience; can be used *Medicines used in research or in practice without showing a raised prevalence of congenital defects, or (in)direct harmful effects in the embryo, fetus or newborn.*	N.A. (category not included in current study)	N.A.
2. Pharmacological effects; require monitoring *Medicines known or suspected to result in pharmacological effects in the embryo, fetus or newborn. The use of these medicines must be considered carefully. When used, monitoring for side effects is needed.*	Dexamethasone	A01AC02
	Epinephrine	A01AD01
	Atropine	A03BA01
	Prednisolone	A07EA01
	Betamethasone	A07EA04
	Quinidine	C01BA01
	Lidocaine	C01BB01
	Propranolol	C07AA05
	Metoprolol	C07AB02
	Atenolol	C07AB03
	Labetalol	C07AG01
	Nifedipine	C08CA05
	Betamethasone	D07AC01
	Desoximetasone	D07AC03
	Diflucortolone	D07AC06
	Amcinonide	D07AC11
	Mometasone	D07AC13
	Fluticasone	D07AC17
	Clobetasol	D07AD01
	Fenoterol	G02CA03
	Fludrocortisone	H02AA02
	Betamethasone	H02AB01
	Dexamethasone	H02AB02
	Methylprednisolone	H02AB04
	Prednisolone	H02AB06
	Prednisone	H02AB07
	Triamcinolone	H02AB08
	Hydrocortisone	H02AB09
	Cortisone	H02AB10
	Rifampicin	J04AB02
	Trastuzumab	L01XC03
	Trastuzumab emtansine	L01XC14
	Ciclosporin	L04AD01
	Azathioprine	L04AX01
	Suxamethonium	M03AB01
	Atracurium	M03AC04
	Rocuronium bromide	M03AC09
	Mivacurium chloride	M03AC10
	Cisatracurium	M03AC11
	Enflurane	N01AB04

(Continues)

TABLE A1 (Continued)

Category	Name	ATC
	Isoflurane	N01AB06
	Desflurane	N01AB07
	Sevoflurane	N01AB08
	Thiopental	N01AF03
	Fentanyl	N01AH01
	Alfentanil	N01AH02
	Sufentanil	N01AH03
	Remifentanil	N01AH06
	Ketamine	N01AX03
	Etomidate	N01AX07
	Propofol	N01AX10
	Nitrous Oxide	N01AX13
	Morphine	N02AA01
	Hydromorphone	N02AA03
	Nicomorphine	N02AA04
	Oxycodone	N02AA05
	Dihydrocodeine	N02AA08
	Dihydrocodeine, combinations	N02AA58
	Pethidine	N02AB02
	Fentanyl	N02AB03
	Dextromoramide	N02AC01
	Pentazocine	N02AD01
	Buprenorphine	N02AE01
	Dihydrocodeine and Paracetamol	N02AJ01
	Dihydrocodeine and Acetylsalicylic acid	N02AJ02
	Dihydrocodeine and other non-opioid analgesics	N02AJ03
	Tramadol	N02AX02
	Haloperidol	N05AD01
	Oxazepam	N05BA04
	Lorazepam	N05BA06
	Temazepam	N05CD07
	Zopiclone	N05CF01
	Zolpidem	N05CF02
	Imipramine	N06AA02
	Clomipramine	N06AA04
	Amitriptyline	N06AA09
	Nortriptyline	N06AA10
	Fluoxetine	N06AB03
	Citalopram	N06AB04
	Paroxetine	N06AB05
	Sertraline	N06AB06
	Fluvoxamine	N06AB08
	Escitalopram	N06AB10
	Bupropion	N06AX12
	Venlafaxine	N06AX16
	Buprenorphine	N07BC01

TABLE A1 (Continued)

Category	Name	ATC
	Methadone	N07BC02
	Fenoterol	R03AC04
	Salbutamol	R03CC02
	Fenoterol	R03CC04
	Theophylline	R03DA04
	Aminophylline	R03DA05
	Prednisolone	S01BA04
	Timolol	S01ED01
	Betaxolol	S01ED02
	Levobunolol	S01ED03
	Carteolol	S01ED05
	Ciclosporin	S01XA18
	Diazoxide	V03AH01
3. Pharmacological effects; avoid (temporarily) *Medicines known or suspected to result in pharmacological effects in the embryo, fetus or newborn. These medicines should not be used during this hazardous period; an alternative medicine should be chosen.*	Tetracycline	A01AB13
	Magnesium silicate	A02AA05
	Atropine	A03BA01
	Liquid paraffin	A06AA01
	Senna glycosides	A06AB06
	Acetylsalicylic acid	B01AC06
	Carbasalate calcium	B01AC08
	Amiodarone	C01BD01
	Norepinephrine	C01CA03
	Phenylephrine	C01CA06
	Ephedrine	C01CA26
	Indometacin	C01EB03
	Ibuprofen	C01EB16
	Hydrochlorothiazide	C03AA03
	Furosemide	C03CA01
	Positonen-Iodine	D08AG02
	Iodine	D08AG03
	Positonen-Iodine	G01AX11
	Iodine therapy	H03CA
	Thiamphenicol	J01BA02
	Thiamphenicol, combinations	J01BA52
	Sulfamethoxazole	J01EC01
	Sulfadiazine	J01EC02
	Sulfamethoxazole and Trimethoprim	J01EE01
	Sulfametrole and Trimethoprim	J01EE03
	Fusidic acid	J01XC01
	Nitrofurantoin	J01XE01
	Phenylbutazone	M01AA01
	Indometacin	M01AB01
	Proglumetacin	M01AB14
	Aceclofenac	M01AB16
	Piroxicam	M01AC01
	Tenoxicam	M01AC02

(Continues)

TABLE A1 (Continued)

Category	Name	ATC
	Meloxicam	M01AC06
	Ibuprofen	M01AE01
	Naproxen	M01AE02
	Ketoprofen	M01AE03
	Flurbiprofen	M01AE09
	Tiaprofenic acid	M01AE11
	Dexketoprofen	M01AE17
	Nabumetone	M01AX01
	Nimesulide	M01AX17
	Ibuprofen	M02AA13
	Diclofenac	M02AA15
	Nimesulide	M02AA26
	Acetylsalicylic acid	N02BA01
	Carbasalate calcium	N02BA15
	Chlorpromazine	N05AA01
	Ephedrine	R01AA03
	Pseudoephedrine	R01BA02
	Flurbiprofen	R02AX01
	Combinations	R05CA10
	Promethazine	R06AD02
	Chloramphenicol	S01AA01
	Ketorolac	S01BC05
	Phenylephrine	S01FB01
	Phenylephrine	S01GA05
	X-Ray contrast media, iodinated	V08A
4. Teratogenic effects; require monitoring *Medicines known or suspected to cause a higher prevalence of congenital defects or other permanent damage or that can have harmful pharmacological effects in the embryo, fetus or newborn. Usage must be considered carefully, and if so, monitoring for undesirable effects is needed.*	Propylthiouracil	H03BA02
	Carbimazole	H03BB01
	Thiamazole	H03BB02
	Phenobarbital	N03AA02
	Primidone	N03AA03
	Phenytoin	N03AB02
	Carbamazepine	N03AF01
	Valproic acid	N03AG01
	Topiramate	N03AX11
	Lithium	N05AN
5. Teratogenic effects; avoid (temporarily) *Medicines known or suspected to cause a higher prevalence of congenital defects or other permanent damage and that can have harmful pharmacological effects in the embryo, fetus or infant. These medicines should not be used during this hazardous period; an alternative medicine should be chosen.*	Doxycycline	A01AB22
	Misoprostol	A02BB01
	Neomycin	A07AA01
	Nandrolone	A14AB01
	Warfarin	B01AA03
	Phenprocoumon	B01AA04
	Acenocoumarol	B01AA07
	Captopril	C09AA01
	Enalapril	C09AA02
	Lisinopril	C09AA03
	Perindopril	C09AA04

TABLE A1 (Continued)

Category	Name	ATC
	Ramipril	C09AA05
	Quinapril	C09AA06
	Benazepril	C09AA07
	Cilazapril	C09AA08
	Fosinopril	C09AA09
	Zofenopril	C09AA15
	Losartan	C09CA01
	Eprosartan	C09CA02
	Valsartan	C09CA03
	Irbesartan	C09CA04
	Candesartan	C09CA06
	Telmisartan	C09CA07
	Olmesartan medoxomil	C09CA08
	Acitretin	D05BB02
	Isotretinoin	D10BA01
	Alitretinoin	D11AH04
	Nomegestrol and Estradiol	G03AA14
	Lynestrenol	G03AC02
	Progesterone	G03DA04
	Norethisterone	G03DC02
	Lynestrenol	G03DC03
	Cyproterone	G03HA01
	Danazol	G03XA01
	Demeclocycline	J01AA01
	Doxycycline	J01AA02
	Lymecycline	J01AA04
	Tetracycline	J01AA07
	Minocycline	J01AA08
	Tigecycline	J01AA12
	Tobramycin	J01GB01
	Gentamicin	J01GB03
	Kanamycin	J01GB04
	Neomycin	J01GB05
	Amikacin	J01GB06
	Spectinomycin	J01XX04
	Methotrexate	L01BA01
	Fluorouracil	L01BC02
	Megestrol	L02AB01
	Medroxyprogesterone	L02AB02
	Tamoxifen	L02BA01
	Mycophenolic acid	L04AA06
	Thalidomide	L04AX02
	Methotrexate	L04AX03
	Lenalidomide	L04AX04
	Pomalidomide	L04AX06
	Penicillamine	M01CC01

(Continues)

TABLE A1 (Continued)

Category	Name	ATC
	Dihydroergotamine	N02CA01
	Ergotamine	N02CA02
	Dihydroergotamine, combinations	N02CA51
	Valproic acid	N03AG01
	Topiramate	N03AX11
	Nicotine	N07BA01
	Quinine	P01BC01
6. Unknown risk *Medicines of which the risk for the embryo, fetus or newborn cannot be determined because there are insufficient data on their effect in humans. The use of these medicines must be considered carefully and, when possible, another medicine should be chosen.*	In total, 733 substances were included in this category according to the 2016 risk classification system for drugs in pregnancy of the Dutch Teratology Information Service Lareb (examples: ciprofloxacin, infliximab, ketanserin, midazolam).	

Note: Adapted from 2016 risk classification system for drugs in pregnancy of the Dutch Teratology Information Service Lareb.[17]