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.

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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%).\(^8\) 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.

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).\(^1\)\(^1\) Perined is a nationwide registry that contains validated data from pregnancies with a gestational age (GA) of at least 16 weeks.\(^1\)\(^2\) 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.\(^1\)\(^3\)\(^,\)\(^1\)\(^4\) 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.\(^1\)\(^5\) 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.\(^1\)\(^1\)\(^6\) 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.
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).

**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 | Descriptiona |
|----------|-------|--------------|
| 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. |

aSee Appendix Table A1 for detailed overview of the medication that is included in each category.
2.3 | Outcome assessment

Maternal and obstetric characteristics assessed included age at delivery, neighbourhood socioeconomic status (SES),\textsuperscript{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 outpatient 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 | Use of potentially harmful medication (Cat. 2–6) | No use of potentially harmful medication (Cat. 2–6) | OR (95% CI) use vs. no use |
|-------------------------------------|--------------|-----------------------------------------------|-------------------------------------------------|--------------------------|
|                                     | N = 487 122  | N = 166 484 (34%)                             | N = 320 638 (66%)                                |                          |
| **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)         |
| **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/Westernb             | 16 025 (3)   | 5601 (3)                                      | 10 424 (3)                                      | 1.09 (1.05–1.12)         |
| Otherc                             | 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** |       |                                               |                                                  |                          |
| 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)
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
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%). 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. However, next to the difference in study setting, participants using only vitamin D, folic acid and/or multivitamins during pregnancy were classified as non-medication 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. 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. 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. 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.

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

| Medication (ATC)a | Preconception | First trimester | Second trimester | Third trimester |
|------------------|---------------|----------------|-----------------|----------------|
|                  | N = 487 122   | N = 487 122    | N = 487 122     | N = 483 799    |
|                  | n (%)         | n (%) changeb | n (%) changeb   | n (%) changeb  |
| 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. 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. Metamizole (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; +11%) | 4098 (0.8; +704%) |
| Medication without category assignedb |
| #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. Meclizine, 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;
*Excluding reproductive hormonal drugs (ATC G03);
bAccording 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: ‘preconception, ‘first trimester, and ‘second trimester.

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. 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.\textsuperscript{24} Treating physicians rely on available evidence on risks when making decisions and daily face difficulties balancing drugs’ risks and benefits.\textsuperscript{25} A high proportion of drugs are labelled as “unknown risk”, lacking specific recommendations for use during pregnancy.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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 pREGrant.\textsuperscript{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.\textsuperscript{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. Under-estimated 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 per-conceptional 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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REFERENCES

1. Niebyl J, Simpson J. Teratology and drugs in pregnancy. In Glob Libr Women’s Medicine; 2008. https://doi.org/10.3843/GLOWM.10096.

2. Schatz M. Asthma treatment during pregnancy. Drug Saf. 1997;16(5):342-350.

3. Lawrence JM, Andrade SE, Avalos LA, et al. Prevalence, trends, and patterns of use of antidiabetic medications among pregnant women, 2001-2007. Obstet Gynecol. 2013;121(1):106-114.

4. Lupattelli A, Spigset O, Twigg MJ, et al. Medication use in pregnancy: a cross-sectional, multinational web-based study. BMJ Open. 2014;4(2):e004365.

5. Mitchell AA, Gilboa SM, Werler MM, et al. Medication use during pregnancy, with particular focus on prescription drugs: 1976-2008. Am J Obstet Gynecol. 2011;205(1):51.e1-51.e8.

6. Bakker MK, Jentink J, Vroom F, van den Berg P, de Walle HE, de Jong-van den Berg L. Drug prescription patterns before, during and after pregnancy for chronic, occasional and pregnancy-related drugs in the Netherlands. BJOG. 2006;113(5):559-568.

7. de Waard M, Blomjous BS, Hol ML, et al. Medication use during pregnancy and lactation in a Dutch population. J Hum Lact. 2019;35(1):154-164.

8. Yazici E, Kirkan TS, Aslan PA, Aydin N, Yazici AB. Untreated depression in the first trimester of pregnancy leads to postpartum depression: high rates from a natural follow-up study. Neuropsychiatr Dis Treat. 2015;11:405-411.

9. The Global Health Network - Global Pharmacovigilance. Pharmacovigilance in pregnancy. July 6, 2017.

10. European Medicines Agency. Guideline on the exposure to medicinal products during pregnancy: need for post-authorisation data. EMEA/CHMP/313666/2005 2005.

11. Houben E, Broeders L, Steegers EAP, Herings RMC. Data Resource Profile: The PHARMO Perinatal Research Network. Manuscript submitted, unpublished observations, 2019.

12. Stichting Perinatale Registratie Nederland. 10 jaar Perinatale Registratie Nederland, de grote lijnen. Utrecht: Stichting Perinatale Registratie Nederland; 2011.

13. Steegers EAP, Herings RMC. Dutch trends in the use of potentially harmful medicines during pregnancy. Br J Clin Pharmacol. 2018;79(3):537-544.

14. Stephenson J, Hesslehurst N, Hall J, et al. Before the beginning: nutrition and lifestyle in the preconception period and its importance for future health. The Lancet. 2018;391(10132):1830-1841.

15. Barker M, Dombrowski SU, Colbourn T, et al. Intervention strategies to improve nutrition and health behaviours before conception. The Lancet. 2018;391(10132):1853-1864.

16. Vorstenbosch S, te Winkel B, van Gelder MM, Kant A, Roeleveld N, van Puijenbroek E. Aim and design of pREGnant, the Dutch Pregnancy Drug Register. Drug Saf. 2018;42(1):1-12.

17. Teratologie Informatie Service Lareb. Geneesmiddelen bij zwangerschap 2016 [cited 2018 April 11]. Available from: https://www.lareb.nl/teratologie-nl/zwangerschap/#TOC_Classificatie_en.

18. The Netherlands Institute for Social Research. Available from: https://www.scp.nl/english. Accessed June 9, 2018.

19. Kort D, van Rein N, van der Meer F, et al. Relationship between neighborhood socioeconomic status and venous thromboembolism: results from a population-based study. J Thromb Haemost. 2017;15(12):2352-2360.

20. Ayad M, Costantine MM. Epidemiology of medications use in pregnancy. Semin Perinatol. 2015;39(7):508-511.

21. Tinker SC, Broussard CS, Frey MT, Gilboa SM. Prevalence of prescription medication use among non-pregnant women of childbearing age and pregnant women in the United States – NHANES, 1999–2006. Matern Child Health J. 2015;19(5):1097-1106.

22. Perin. Jaarboeken Zorg in Nederland. Available from: https://www.perined.nl/producten/publicaties/jaarboeken. Accessed August 7, 2019.

23. Mulder B, Bijlsma M, Schuiling-Veninga C, et al. Risks versus benefits of medication use during pregnancy: what do women perceive? Patient Prefer Adherence. 2017;12:1-8.

24. Fransen M, Harris VC, Essink-Bot ML. Low health literacy in ethnic minority patients: understandable language is the beginning of good healthcare. Ned Tijdschr Geneeskd. 2013;157(14):A5581.

25. Houben E, Broeders L, Steegers EAP, Herings RMC. Medication during pregnancy and lactation. In: Strom B, Kimmel S, Hennessy S, eds. PHARMacoepidemiology: Minorities in the Use of Medicines. In: STROM B, KIMMEL S, HENNESSY S, eds. Pharmacoepidemiology. Chichester, UK: John Wiley & Sons; 2012:270-286.

26. WHO. Anatomical Therapeutic Chemical Classification System [www.whocc.no/atc_ddd_index].

27. European Medicines Agency. Guideline on the exposure to medicinal products during pregnancy: need for post-authorisation data. EMEA/CHMP/313666/2005 2005.

28. Stephenson J, Hesslehurst N, Hall J, et al. Before the beginning: nutrition and lifestyle in the preconception period and its importance for future health. The Lancet. 2018;391(10132):1830-1841.

29. Barker M, Dombrowski SU, Colbourn T, et al. Intervention strategies to improve nutrition and health behaviours before conception. The Lancet. 2018;391(10132):1853-1864.

30. Vorstenbosch S, te Winkel B, van Gelder MM, Kant A, Roeleveld N, van Puijenbroek E. Aim and design of pREGnant, the Dutch Pregnancy Drug Register. Drug Saf. 2018;42(1):1-12.

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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               | N.A. (category not included in current study) | N.A.           |
| 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.      |                             |                |
| 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        |
| Aminonide                                     |                             | D07AC11        |
| Mometasone                                    |                             | D07AC13        |
| Fluticasone                                   |                             | D07AC17        |
| Clobetasol                                    |                             | D07AD01        |
| Fenoterol                                     |                             | G02CA03        |
| Fludrocortisone                               |                             | H02AA02        |
| Betamethasone                                 |                             | H02AB01        |
| Dexamethasone                                 |                             | H02AB02        |
| Methylprednisolone                            |                             | H02AB04        |
| Prednisolone                                  |                             | H02AB06        |
| Prednison                                     |                             | 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)
| 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|
|                               | Buproprion                                | N06AX12|
|                               | Venlafaxine                               | N06AX16|
|                               | Buprenorphine                             | N07BC01|
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.

| 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  |
|          | 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  |
|          | Indometacism                | C01EB03  |
|          | Ibuprofen                   | C01EB16  |
|          | Hydrochlorothiazide         | C03AA03  |
|          | Furosemide                  | C03CA01  |
|          | Positonen-Iodine            | D08AG02  |
|          | Iodine                      | D08AG03  |
|          | Positonen-Iodine            | G01AX11  |
|          | Iodine therapy              | H03CA    |
|          | Thiampenicol                | J01BA02  |
|          | Thiampenicol, combinations  | J01BA52  |
|          | Sulfamethoxazole            | J01EC01  |
|          | Sulfadiazine                | J01EC02  |
|          | Sulfamethoxazole and Trimethoprim | J01EE01   |
|          | Sulfametrole and Trimethoprim | J01EE03   |
|          | Fusidic acid                | J01XC01  |
|          | Nitrofurantoin              | J01XE01  |
|          | Phenylbutazone              | M01AA01  |
|          | Indometacism                | M01AB01  |
|          | Proglumetacin               | M01AB14  |
|          | Aceclofenac                 | M01AB16  |
|          | Piroxicam                   | M01AC01  |
|          | Tenoxicam                   | M01AC02  |

(Continues)
| Category | Name                      | ATC     |
|----------|---------------------------|---------|
|          | Meloxicam                 | M01AC06 |
|          | Ibuprofen                 | M01AE01 |
|          | Naproxen                  | M01AE02 |
|          | Ketoprofen                | M01AE03 |
|          | Flurbiprofen              | M01AE09 |
|          | Tiaprofenic acid          | M01AE11 |
|          | Dextropropfen             | 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.

| Name                      | ATC     |
|---------------------------|---------|
| Propylthiouracil          | H03BA02 |
| Carbinazole               | 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.

| Name                      | ATC     |
|---------------------------|---------|
| Doxycycline               | A01AB22 |
| Misoprostol               | A02BB01 |
| Neomycin                  | A07AA01 |
| Nandrolone                | A14AB01 |
| Warfarin                  | B01AA03 |
| Phenprocoumon             | B01AA04 |
| Acenocoumarol             | B01AA07 |
| Captopril                 | C09AA01 |
| Enalapril                 | C09AA02 |
| Lisinopril                | C09AA03 |
| Perindopril               | C09AA04 |
| 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               | J01X04 |
|          | 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