

Medication use during pregnancy in Europe and North America: a systematic review

R Nehard · V Faure Bardon · B Coulm · D Rajendrabose · E Elefant · C Vauzelle · D Beghin · M Latour · MS Brochet · M M.H.J. van Gelder · A Dechartres · B Marin 

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Abstract

Background To describe the mean number of medications used as well as the prevalence of medication use throughout pregnancy in Europe and North America, with a focus on use by trimester, type of medication, and use of harmful medications.

Methods A systematic review was performed searching MEDLINE, EMBASE, Cochrane Library, ClinicalTrials.gov and the WHO ICTRP from database inception to August 1, 2025 (CRD42023411090). We included population-based observational study describing medication use in pregnancy in Europe and North America. Medication use was defined as prescription, dispensing, or reported intake of medication. Two reviewers independently checked citations for eligibility, collected data, and assessed the risk of bias using the JBI Critical Appraisal Checklist. Because of substantial heterogeneity, no meta-analysis was performed. Data were reported as medians and interquartile range [IQR].

Results From 17,304 citations, we included 67 studies over a 50-year period (with study periods ranging from 1971 to 2021) involving around 17 million pregnant women and conducted in North America ($n = 16$, 23.9%), northern Europe ($n = 18$, 26.9%), western Europe ($n = 22$, 32.8%), and southern Europe ($n = 11$, 16.4%). Women used 3.3 [IQR:2.3–6.4] different medications during pregnancy, 75.3% [IQR:59.6–88.4] using at least one medication. The number of medications used seemed higher in western Europe, than in southern Europe, northern Europe and North America (6.4 [IQR:4.2–10.2] vs 2.2 [IQR:1.3–2.7], 2.8 [IQR:2.1–3.3], and 2.4 [IQR:1.7–3.7] respectively). The prevalence of women using any medication during pregnancy was also highest in western Europe (89.9% [IQR:78.9–95.1]), followed by southern Europe (80.4% [IQR:73.1–83.4]), northern Europe (71.7% [IQR:54.3–86.1]), and North America (62.3% [IQR:56.3–74.5]). There was no evidence of temporal trend. Anti-infectives for systemic use and alimentary tract and metabolism classes of medications were the most commonly used. The prevalence of use of medication considered harmful ranged from 0.9% to 7.8%, with the highest estimates for the first trimester.

Conclusion Medication use was frequent during pregnancy in Europe and North America, especially in western Europe. An undeniable proportion of pregnant women were exposed to medications considered harmful. The

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V Faure Bardon and B Coulm contributed equally to this work.

A Dechartres and B Marin contributed equally to this work.



high heterogeneity in medication reporting highlights a strong need for standardized reporting of medication exposure during pregnancy and harmonization of risk classifications.

Trial registration CRD42023411090.

Keywords Medications · Pregnancy · Use · Population-based · Europe · North America · Harmful drugs · Teratogenicity · Fetotoxicity

Abbreviations

OTC Over-the-counter medication

ATC Anatomical Therapeutic Chemical

INN International nonproprietary names

Introduction

Medication use during pregnancy is common, reflecting the need to treat chronic diseases, acute illnesses, and pregnancy-related conditions. Approximately one in six pregnant women have multiple chronic conditions requiring ongoing medical care [1]. On the other hand, in utero exposure to some medications may be harmful for the embryo or fetus.

Understanding of how medications are used during pregnancy is essential for clinicians, researchers, and public health authorities. Comprehensive information on medication use during pregnancy provides an essential basis for monitoring geographical and temporal trends, investigating the factors underlying observed differences (e.g., healthcare systems, drug availability, reimbursement policies, and evolving clinical recommendations), and supporting future research on medication safety.

Although the prevalence of medication use provides an estimate of how many pregnant women are exposed to medications, the number of medications used offers complementary information on medication burden and prescribing practices. Together, these indicators provide a more comprehensive picture of medication use during pregnancy and facilitate comparisons across populations, healthcare systems, and time periods.

A previous systematic review published in 1990 reported a median number of medications used during pregnancy of 4.7 [2], while another, published in 2011, found that the mean number of medications used ranged from 1.7 to 15.8 in developed countries [3]. However, both reviews are now considered outdated, included relatively few studies, and were limited in their geographical coverage and study periods. More recently, Sullivan et al. [4] published a systematic review and meta-analysis reporting a pooled prevalence estimate of prescribed medication use during pregnancy of 56% (95% CI 44–67%). Although this review provided estimates of the prevalence of medication use, important aspects, including the number of medications used, geographical and temporal variations, therapeutic class distributions, the most frequently used medications, and the use of potentially harmful medications, were beyond the scope of their review.

Here, we aimed to systematically review the literature to describe the number of medications used during pregnancy in Europe and North America. Secondary aims were to describe 1) the prevalence of women using at least one medication during pregnancy (overall and by trimester); 2) the number of medications used during each trimester; 3) the variety of pharmacotherapeutic classifications used as well as the most frequently used classes of medications during pregnancy, and 4) the pregnancy risk classifications used in studies as well as the prevalence of medication use within these categories (overall and by trimester).

Material and methods

This systematic review followed the methodology from the Cochrane Handbook (version 6.3, 2022) [5]. The protocol was registered on PROSPERO (April 6, 2023; no. CRD42023411090) and the modifications made to the original protocol are reported and justified in Appendix 1. This article is reported in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement [6].

Search strategy

The search strategy was defined by a multidisciplinary team including epidemiologists and experts in perinatal pharmacoepidemiology. The following electronic databases were searched on August 1, 2025: MEDLINE via PubMed, EMBASE, and the Cochrane Library. A specific search algorithm was developed for each database (Appendix 2). The following registries were also searched on the same date: Clinicaltrials.gov and the WHO International Clinical Trials Registry Platform.

To retrieve any articles that might not have been identified, we hand-searched the tables of contents of the two journals *Pharmacoepidemiology* and *Pharmacoepidemiology and Drug Safety* for the last 5 years. We also searched the abstracts of the main conferences in the field (Appendix 3). Finally, we screened all reference lists for additional references and asked two independent experts in epidemiology and pregnancy medication use (MSB and MvG) to assess the list of included articles and add missing references, if any.

Eligibility criteria

Study design

We included observational studies (cohort and cross-sectional studies) focusing on medication use during pregnancy. We included only population-based studies (i.e., epidemiological investigations based on a sample or the entire population, within well-defined populations, geographic, and time boundaries [7, 8]) to provide accurate estimates of the use of medication during pregnancy. Studies were included regardless of language or publication date. We did not include systematic reviews and meta-analyses but screened their references.

Population

The population of interest was pregnant women living in Europe or North America as defined by the United Nations [9], with no restriction on ethnicity, socioeconomic, or administrative status. We excluded studies focusing on subgroups of pregnant women (e.g., women with a disease or deprived populations).

Medication

Medication definitions were retained as reported by the original studies. Information on the inclusion of vitamins, mineral supplements, over-the-counter (OTC) medications, medication given in hospital, and herbal products was extracted.

Medication use

Medication exposure was assessed using different data sources across studies, including prescription records, pharmacy dispensing databases, and self-reported medication use. Throughout this review, the term medication use is used as a generic term encompassing these different measures of medication exposure unless otherwise specified. Studies were included if they reported medication use during pregnancy (i.e., overall, or at least during

one trimester). Studies were excluded if they assessed medication use only during the preconceptional or postpartum periods, or if the reported estimates of medication use during pregnancy included medication exposure occurring more than one month before conception without separately reporting medication use during pregnancy, as the objective of this review was to characterize medication use during pregnancy rather than across the preconception and pregnancy periods. We did not include papers limited to medication use in hospitals, OTC medication only or a specific type or class of medication.

Study outcomes

The main study outcome was the mean number of different medications used during pregnancy (i.e., calculated over the entire sample of included pregnant women). Secondary outcomes were 1) the mean number of medications used during each pregnancy trimester as well as the prevalence of women using at least one medication during the entire pregnancy and during each trimester; and 2) the types of medications used: prevalence of medication use per pharmacotherapeutic classification (using the pharmacotherapeutic classification adopted by the original study, with no predefined classification imposed), the most frequently used medications during the entire pregnancy (the five most frequent in each study), pregnancy risk classifications applied, and the prevalence of medication use within these categories.

Selection process

Retrieved records were managed by using Zotero v6.0.22 [10]. After duplicate removal, one reviewer identified eligible studies by screening titles and abstracts, then eligible studies were read independently by two authors to confirm inclusion. All disagreements were resolved by discussion with the help of a third reviewer. If a full-text was not available, the authors of the study were contacted to obtain the full text or detailed results. Abstracts and full texts not in English or French were translated by using *Google Translate* to check for eligibility. Authors were also contacted to obtain further clarifications when needed. Studies that used data from the same sources for overlapping periods were considered duplicates when the same outcomes were reported.

Data extraction

Two reviewers independently extracted data from the included studies using a standardized data extraction form. Disagreements were resolved by discussion with a third reviewer. In case of missing or unclear data in the report, we attempted to contact the study authors. If only an abstract or poster presentation of a study was available after contact with the authors, we extracted all relevant information from it.

The following characteristics were collected:

- General study characteristics: title, first author name, publication year, journal of publication, country, geographic area (national, multi-regional, regional), study period, sampling method (full population or sample), medication-use data source (medico-administrative, medical chart, interview/questionnaire), name of databases, database linkage, sample size, inclusion age limits, types of pregnancies/outcomes included (all pregnancies, births [live- and still-births], live birth only), inclusion of consecutive pregnancies, inclusion of multiple pregnancies, specific inclusion/exclusion criteria.
- Population characteristics: maternal age,
- Medication use: medication-use data type (prescription, dispensation, intake); exposure period assessed (entire pregnancy, first trimester, second trimester, third trimester); inclusion of OTC medications; vitamins (including folic acid); minerals; medications received in hospital; number of medication-use estimates reported as mean (standard deviation), median [interquartile range], and proportions considering various use definitions (with or without vitamins and minerals, prescribed only or including OTC medications); medication classifications

used (pharmacotherapeutic and pregnancy risk level); frequency of medication use per pharmacotherapeutic classification; the five most frequently used medications during pregnancy; and frequency of medication use per risk level category and the most used medications in these categories. When numerical data were available only in graphical form in the original papers, they were extracted from the figures using WebPlotDigitizer version 4.6 [11] as recommended by the Cochrane collaboration.

Risk of bias assessment

The risk of bias was independently assessed by two reviewers using the Joanna Briggs Institute Critical Appraisal Checklist for studies reporting prevalence data [12]. This tool was selected because it was specifically developed for the critical appraisal of descriptive studies and was therefore considered the most appropriate for the studies included in this review. Disagreements were resolved by discussion with a third reviewer.

Data synthesis

Specifications regarding data preparation are presented in Appendix 4. Given the substantial clinical and methodological heterogeneity across studies, a pooled meta-analysis was not considered appropriate. Therefore, descriptive analyses were performed as recommended by the Cochrane Handbook [13]: median [interquartile range, IQR] values were calculated overall and by subcontinent. However, random-effects meta-regression was used as an exploratory analysis to investigate whether study-level characteristics (calendar time and geographical region) explained part of the between-study heterogeneity in prevalence estimates. The mean number of medications used and the prevalence of women using at least one medication are presented with forest plots stratified by subcontinent, both for the entire pregnancy period and by trimester. Prevalence estimates (overall and by trimester) were extracted from the original publications and were based on the total number of eligible pregnancies reported in each study. When both numerators and denominators were available, prevalence estimates were recalculated to verify consistency with the published values. When it was not explicitly stated whether estimates referred to all women or only to women using a single medication, values were assigned by default to the “all women” category. Similarly, when it was unclear whether vitamin use was included, estimates were assumed to include vitamins by default.

Mann–Kendall tests were conducted to assess monotonic temporal trends in mean estimates by subcontinent, restricted to regions with at least six available observations ($n \geq 6$), due to limited statistical power with smaller sample sizes [14]. To examine variations in prevalence estimates, random-effects meta-regression models were conducted with the mid-time of the study period and subcontinent as explanatory variables, first in separate univariable models and then in a model including both variables, with an interaction term to assess effect modification. Statistical analyses were performed with R 4.2.1 [15], including the gridExtra, cowplot, ggwordcloud, maps and meta packages [16–20].

Results

Study selection

Our search strategy identified 17,262 unique citations in electronic databases, with 91 reports further assessed for eligibility (Fig. 1). Additional sources including conference abstracts, hand-searches of relevant journals, reference lists, and expert suggestions allowed for identifying an additional 42 reports. After screening of those later, 19 citations were further assessed for eligibility. After two reviewers independently examined these 110 reports, 67 were included.

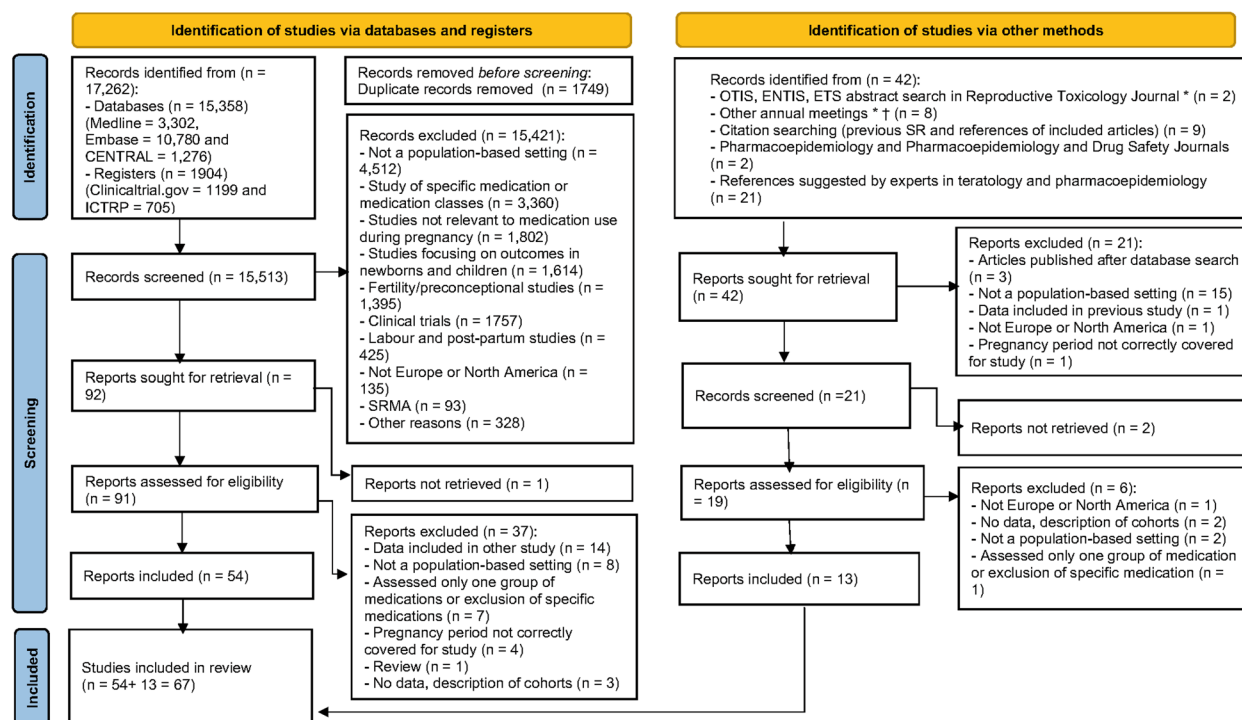


Fig. 1 Flow diagram of included studies. * records not previously identified in databases and registers. † Teratology Society, American College of Obstetricians and Gynaecologists, Society for Maternal Fetal Medicine, Society for Pediatric and Perinatal Epidemiologic Research, International Conference on Pharmaco-Epidemiology and risk management, European Pharmacovigilance Congress, The World Drug Safety Congress Europe and The International Society of Pharmacovigilance annual meetings. LEGEND: OTIS: Organization of Teratology Information Specialists, ENTIS: European Network of Teratology Information Services, ETS: European Teratology Society, SRMA: systematic review and meta-analysis, ICTRP: International Clinical Trials Registry Platform

Study characteristics

The 67 studies included were conducted in 14 countries across four geographical regions: North America (16 studies, 23.9%) [21–36], northern Europe (18 studies, 26.9%) [37–54], western Europe (22 studies, 32.8%) [55–76], and southern Europe (11 studies, 16.4%) [77–87] (Table 1, eTable 1 for a detailed description of individual studies). No studies from eastern Europe were identified. The countries contributing the largest number of studies were France (n = 9) [55–62, 76], Canada (n = 8) [22–29], Italy (n = 7) [77–81, 85, 87] and Denmark (n = 6) [38, 49–51, 53, 54]. Most studies had national (n = 35, 52.2%) or regional (n = 24, 35.8%) coverage, whereas a few were multi-regional (n = 5, 7.5%) and three (4.5%) were set in a single city. The earliest study start date was 1971 and the latest study end was the end of 2021.

The sample size ranged from 292 to 5,253,284 pregnancies (median: 42,382 [IQR:8,628–221,706]) representing around 17 million pregnant women overall. Most studies included only births (live- and still-births, 41.8%) or all types of pregnancy outcomes (31.4%). Medication-use data were from medico-administrative databases (n = 53, 79.1%), questionnaires or interviews (n = 14, 20.9%) or medical charts (n = 10, 14.9%); nine studies (13.4%) used more than one method of data collection. Most data come from pharmacy claims (prescribed and delivered medications) (76.1%).

OTC medications were included in at least 32 studies (47.8%), with unclear inclusion in eight additional studies. Vitamins and minerals were included in at least 39 studies (58.2%), with unclear inclusion in 15 other studies (22.4%). For 30 studies (44.8%), reports explicitly mentioned that medications administered during

Table 1 Synthesis of the main study characteristics reported in the 67 included studies

Characteristics	n (%)
Number of countries	14
Sub-continent	
North America	16 (23.9)
Northern Europe	18 (26.9)
Western Europe	22 (32.8)
Southern Europe	11 (16.4)
Medication use data source †	
Medico-administrative databases	53 (79.1)
Medical charts	10 (14.9)
Questionnaires/interviews	14 (20.9)
Medication use data type	
Prescribed and dispensed medications	51 (76.1)
Consumption (self reported)	12 (17.9)
Prescriptions	4 (6.0)
Type of pregnancy	
All pregnancies	21 (31.4)
Births (live- and stillbirths)	28 (41.8)
Live-births only	9 (13.4)
Pregnancies lasting at least 10/12/16/22/32 weeks or 154 days	9 (13.4)
Therapeutic class presented † (n = 58, 86.6%)	
WHO Anatomical Therapeutic Chemical classification	42 (72.4)
British National Formulary	3 (5.1)
Authors' classification	7 (13.0)
Determined by market authorization	3 (5.1)
Others (EphMRA and MULTILEX)	3 (5.1)
Risk classification † (n = 34, 50.7%)	
Former FDA classification	17 (50.0)
Former Australian classification (ADEC)	7 (20.5)
Author defined/TIS center	8 (23.5)
Briggs classification	6 (17.6)
Swedish (FASS)	5 (14.7)
National market authorizations	4 (11.8)

† Multiple characteristics possible per study

LEGEND: *EPHMA* European Pharmaceutical Market Research Association, *WHO* World Health Organization, *FDA* Food and Drug Administration, *ADEC* Australian Drug Evaluation Committee, *FASS* Swedish classification system (Farmaceutiska Specialiteter i Sverige), *TIS* Teratology Information Service

hospitalization were not included. Such medications were included in 17 studies (25.3%), with unclear inclusion for 16 (23.8%).

Risk of bias within studies

The risk of bias assessment using the Joanna Briggs Institute critical appraisal tool is reported in eTable 2. Items related to “study population”, “coverage of the sample” and “appropriate response rate” received overall a satisfactory evaluation. For only 39 studies (58.2%), conditions were considered as measured in an accurate, reliable, and standardized way. Indeed, the inclusion of vitamins or OTC medications and the denominator for medication use (among all women or only among women who used at least one medication) was unclear in a substantial number of studies. The description of study participants and the appropriateness of statistical analyses were the most penalizing items, receiving 52.2% of negative or unclear answers for both questions.

Number of medications used during pregnancy

Of the 67 included studies, 50.7% ($n = 34$) reported the mean number of medications used during pregnancy (eTable 3). Nevertheless, because of duplicate material ($n = 3$), and inability to calculate the mean value based on the median data reported ($n = 1$) [63], we finally included 30 reports for this outcome: 24 for all pregnant women

[21, 26, 30, 34, 39, 42, 44, 47, 51, 55–60, 63, 64, 70, 72, 73, 75, 78, 79, 84] and 11 for women using at least one medication during pregnancy only [21, 23, 26, 38, 50, 54, 64, 65, 79–81]. Overall, these data concerned approximately five million pregnant women.

Figure 2a displays the forest plot, stratified by subcontinent, for the mean number of medications used among all pregnant women during pregnancy (median of this estimate: 3.3 [IQR:2.3–6.4]). For western Europe, the mean number of medications used ranged from 2.3 to 15.8 (median 6.4 [IQR:4.2–10.2]), while it ranged from 1.3 and 3.7 medications per woman in the other subcontinents: southern Europe (2.2 [IQR:1.3–2.7]), northern Europe (2.8 [IQR:2.1–3.3]), and North America (2.4 [IQR:1.7–3.7]). In Western Europe, a decreasing trend over time was suggested ($\tau = -0.26$), but this trend did not reach statistical significance ($p = 0.27$). Mann–Kendall tests were not performed in the other subcontinents due to the limited number of available data points.

The mean number of medications used was less heterogenous among subcontinents when reported among women using at least one medication during pregnancy (Fig. 2b). eFigure 1 reports the average number of

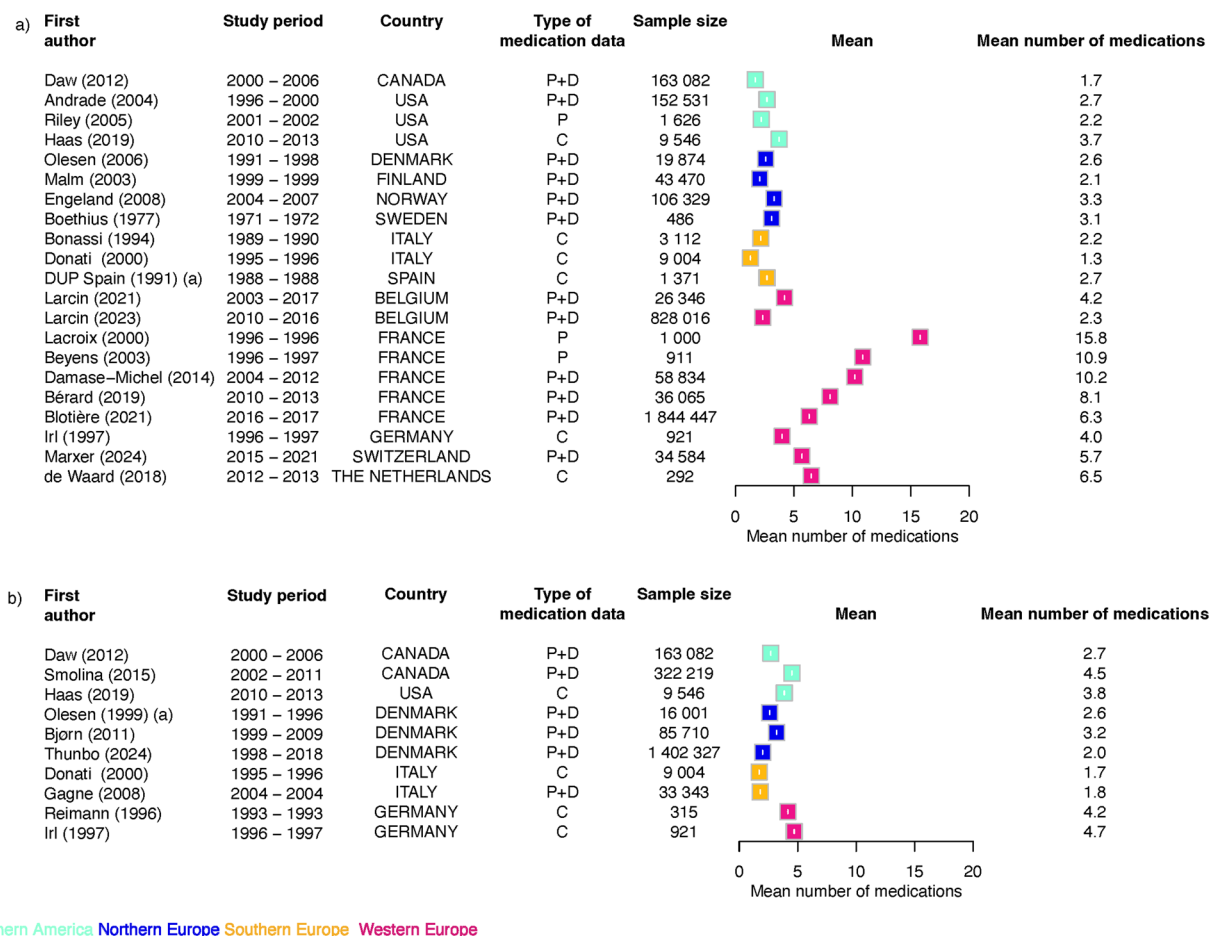


Fig. 2 Mean number of medications used during the entire pregnancy among all women (a) and among women using at least one medication (b) – values including vitamins. Studies are organized by subcontinents, country and midpoint study period. Among all women, median (interquartile range) of the mean number of medications used during pregnancy = 3.3 [2.3–6.4]. When it was not explicitly stated whether estimates referred to all women or only to women using a single medication, values were assigned by default to the “all women” category. Similarly, when it was unclear whether vitamin use was included, estimates were assumed to include vitamins by default. Type of medication data: P=prescription, D=dispensation, C=consumption. *DUP Spain (1991) (a): Medicina Clinica. 1991;96:11–5; Olesen (1999) (a): Eur J Clin Pharmacol. 1999;55:139–44*

medications used by trimester of pregnancy. Most data were from western Europe, which featured the highest number of medications used (up to 7.1), regardless of pregnancy trimester.

Prevalence of use of at least one medication during pregnancy

For 57 studies (85.1%), reports presented data on the prevalence of women using at least one medication during pregnancy (eTable 4). Nevertheless, because of duplicate material $n = 8$) [22, 38, 42, 47, 50, 57, 66, 80], 49 studies involving more than ten million women were considered here (48 studies with data including vitamins and minerals and 17 excluding them).

The overall median prevalence of women using at least one medication (including vitamins and minerals) was 75.3% (59.6–88.4), Fig. 3. The median was highest for western Europe (89.9% [IQR:78.9–95.1], $n = 14$ studies), followed by southern Europe (80.4% [IQR:73.1–83.4], $n = 6$ studies), northern Europe (71.7% [IQR:54.3–86.1], $n = 11$ studies) and North America (62.3% [IQR:56.3–74.5], $n = 10$ studies). In random-effects meta-regression, no significant temporal trend in prevalence was observed ($p = 0.395$). There was no evidence of region-specific temporal trends. Overall, geographical region explained approximately 25% of the between-study heterogeneity (eFigure 2).

In contrast, there was evidence of geographical variation: compared with Western Europe, studies from Northern Europe and North America reported significantly lower prevalences ($p = 0.0002$ and 0.0003 respectively). There was no evidence of differences with Southern Europe ($p = 0.15$).

By subcontinents, the prevalence of women using at least one medication did not differ greatly between trimesters (eFigure 3). Also, subcontinents showed little heterogeneity in the prevalence of medication use excluding vitamins and minerals during pregnancy and by trimester (eFigure 4 and eFigure 5).

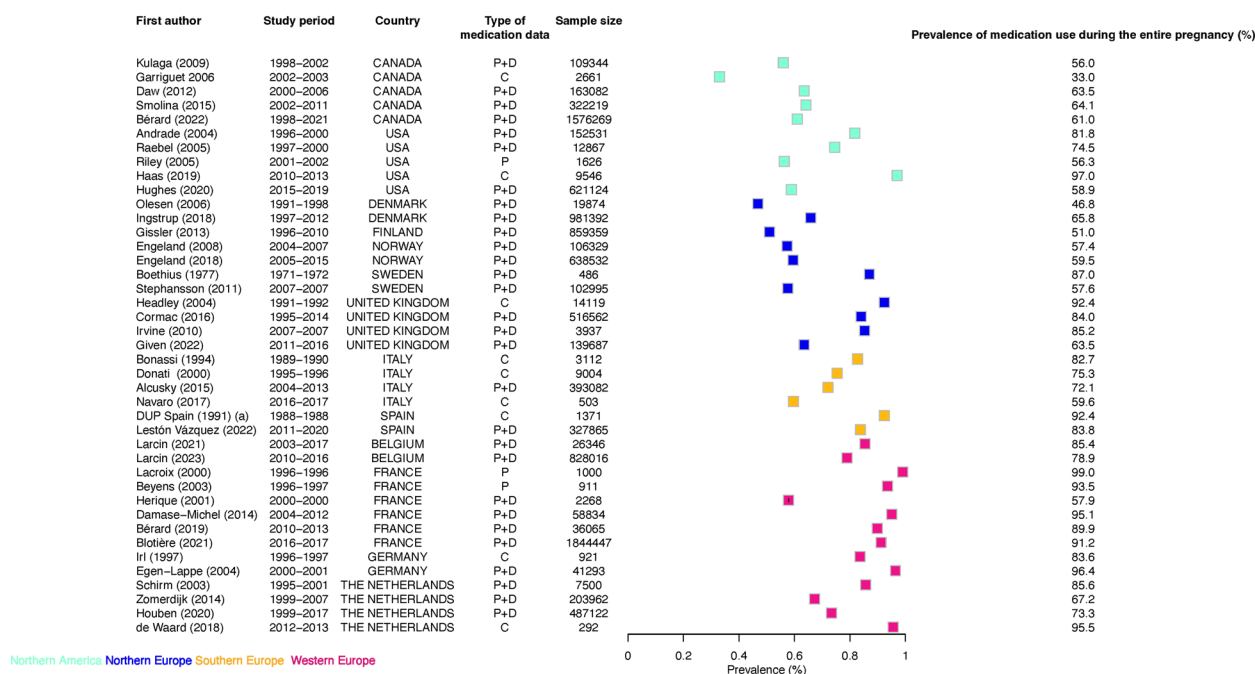


Fig. 3 Prevalences of women using at least one medication at any time during pregnancy – values including vitamins and minerals. Prevalence estimates were calculated using the total number of eligible pregnancies reported in each study as the denominator. Studies are organized by subcontinents, country and midpoint study period. The overall median (interquartile range) of the prevalence of women using at least one medication during pregnancy = 75.3% [59.6–88.4]. When it was unclear whether vitamin use was included, estimates were assumed to include vitamins by default. Type of medication data: P=prescription, D=dispensation, C=consumption. *DUP Spain (1991) (a): Medicina Clinica. 1991;96:11–5*

Medication use by pharmacotherapeutic class

For 58 studies (86.6%), reports indicated the classes of medications used. Most studies used the Anatomical Therapeutic Chemical (ATC) classification ($n = 42$, 72.4%) (Table 1). Overall, 15 studies reported medication use according to the first ATC level classification (Table 2). “Anti-infectives for systemic use” was the most consistently reported medication category within the subcontinents and was the most prevalent in North America. Use of the “alimentary tract and metabolism” class of medications was prevalent in western Europe, along with the “blood and blood forming organs” ATC class, whose use was also highly prevalent in southern Europe. Twenty-two studies reported the most frequent international nonproprietary names (INN) used during pregnancy (eTable 5). In North America, these were amoxicillin, nitrofurantoin, metronidazole, and cefalexin. In northern Europe, these were folic acid, aspirin, penicillin, and paracetamol. In western Europe and southern Europe, the most frequently reported medications were paracetamol and progesterone, respectively.

Pregnancy risk classifications and prevalence of use of medications within these risk categories

Among included studies, 34 (50.8%) reported the use of potentially harmful medications during pregnancy, with the most frequent classifications being the former 1979 US Food and Drug Administration pregnancy risk categories classification ($n = 17$, 50.0%), the former Australian Drug Evaluation Committee classification ($n = 7$, 20.5%), the Swedish Catalogue of Approved Drugs ($n = 5$, 14.7%), and the Briggs classification ($n = 6$, 17.6%). The reported prevalence of use of medications within these risk categories was heterogeneous and ranged from 0.9% to 7.8% (apart from the prevalence of 59.3% reported by Lacroix (2000) [56] (Fig. 4)), with a median prevalence of 4.2% [IQR:3.6–5.2]. Prevalence estimates were more heterogeneous during the first trimester (from 0.3% to 5.5%, eFigure 6) than for the second and third trimesters (0.5% to 2.3%, eFigures 7 and 8). The most frequently used medications reported are listed in eTable 6.

Discussion

This systematic review included 67 population-based studies including around 17 million pregnant women that were conducted in 14 countries from Europe and North America. Medication use during pregnancy was frequent in Europe and North America, with pregnant women using overall a median of 3.3 different medications and 75.3% using at least one medication. Women in western Europe used medications more frequently (90%) and in higher quantities (median 6.4 medications) during pregnancy than those in the other subcontinents. The most-reported therapeutic classes of medication were anti-infectives for systemic use and alimentary tract and metabolism medications. Subcontinents varied in the most frequently used medications, with mostly antibiotics and antiparasitic medications used in North America and paracetamol, folic acid, iron preparations, and progesterone used in Europe. The prevalence of use of medications within the risk categories was highly heterogeneous, ranging from 0.9% to 7.8%, with the highest estimates observed during the first trimester of pregnancy.

The main strength of this study lies in its in-depth description of medication use in North America and Europe over a 50-year period, considering complementary aspects such as the number and prevalence of medication use, the most commonly prescribed drug classes, and the use of potentially harmful medications during pregnancy. Also, our systematic review followed a registered protocol with a search as exhaustive as possible, considering major medical literature databases as well as the grey literature (congress abstracts and registries), hand-searching reference lists, and a review by two experts in perinatal pharmacoepidemiology, thus ensuring the exhaustiveness of included studies. We included only population-based studies because the representativeness of the samples considered provides a more accurate perspective on the use of medications during pregnancy at a population level, thereby enhancing the generalizability and external validity. Moreover, we assessed the methodological

Table 2 Prevalence of use of medications reported in studies according to Anatomical Therapeutic Chemical (ATC) classification level-one categories

Reference	ATC classification															
	Country	Study midpoint date	A	B	C	D	G	H	J	L	M	N	P	R	S	V
North America																
(Daw et al., 2012) [26]	Canada	16/05/2003	7.0	3.6	4.9	13.4	6.1	4.0	30.5	0.2	1.7	12.8	0.1	25.7	3.0	<0.1
(Leong et al., 2019) [28]	Canada	02/07/2007	9.7	3.3	5.3	10.4	10.0	4.5	41.5	0.4	3.7	17.2	4.8	26.2	2.9	<0.1
Northern Europe																
(Olesen et al., 2006) [51]	Denmark	31/12/1994	NA	NA	NA	13.6	15.5	NA	28.4	NA	NA	NA	NA	12.1	NA	NA
(Ingstrup et al., 2018) [53]	Denmark	31/12/2004	9.8	2.6	9.3	14.6	15.0	2.4	35.1	0.3	3.2	5.1	1.8	11.7	7.8	0.1
(Thunbo et al., 2024) [54]	Denmark	01/07/2008	9.3	2.9	7.7	9.7	13.0	4.3	28.4	NA	2.4	7.4	8.9	5.0	NA	NA
(Engeland et al., 2018) [37]	Norway	02/07/2010	11.3	6.2	2.9	7.6	8.6	4.1	29.5	0.3	2.4	8.5	0.6	18.1	6.8	
(Headley et al., 2004) [45]	UK	15/02/1992	29.8	30.2	3.9	9.7	2.8	0.5	5.8	0.0	0.8	31.5	0.1	8.7	0.6	3.1
Southern Europe																
(Gagne et al., 2008) [80]	Italy	01/07/2004	13.4	40.5	4.8	0.2	12.1	5.1	37.2	0.1	1.9	2.1	0.2	7.9	0.3	<0.1
(Ventura et al., 2018)	Italy	02/07/2010	12.0	53.0	3.1	0.4	21.7	11.1	50.7	0.1	3.3	1.6	NA	9.1	0.2	NA
(Navaro et al., 2018) [81]	Italy	15/10/2016	16.0	7.2	4.0	NA	7.9	7.7	12.8	NA	3.5	37.1	NA	3.6	NA	0.2
(Lestón Vázquez et al., 2023) [86]	Spain	01/10/2015	16.4	73.8	3.6	13.5	28.5	45.5	47.4	0.3	16.3	38.3	1.0	15.7	5.2	0.2
Western Europe																
(Larcin et al., 2023) [72]	Belgium	01/04/2013	22.4	18.1	6.8	15.9	37.9	13.3	50.2	0.3	7.7	17.7	0.7	14.3	3.7	7.5
(Beyens et al., 2003) [55]#	France	01/04/1997	78.0	57.0	51.0	48.0	62.0	8.0	51.0	0.2	25.0	62.0	0.8	56.0	7.0	2.0
(Araujo et al., 2021) [57]	France	01/01/2016	75.4	58.7	4.8	37.8	40.3	11.5	42.4	0.3	15.7	64.0	5.1	31.4	7.4	7.4
(Egen-Lappe and Hasford, 2004) [63]	Germany	30/11/2000	72.0	59.0	17.0	19.0	46.0	37.0	27.0	1.0	5.0	10.0	1.0	28.0	6.0	<0.1
Studies are organized by subcontinents, country and midpoint study period. Bold values indicate most prevalent ATC classification																

Studies are organized by subcontinents, country and midpoint study period. Bold values indicate most prevalent ATC classification

LEGEND: A: Alimentary tract and metabolism, B: Blood and blood forming organs, C: Cardiovascular system, D: Dermatologicals, G: Genito-urinary system and sex hormones, H: Systemic hormonal preparations excluding sex hormones and insulins, J: Antineoplastic and immunomodulating agents, L: Antineoplastic and immunomodulating agents, M: Musculo-skeletal system, N: Nervous system, P: Antiparasitic products, insecticides and repellents, R: Respiratory system, S: Sensory organs, V: Various, NA: not available

two further classifications used: Homeopathic products (17%) and phytotherapeutic products (13%)

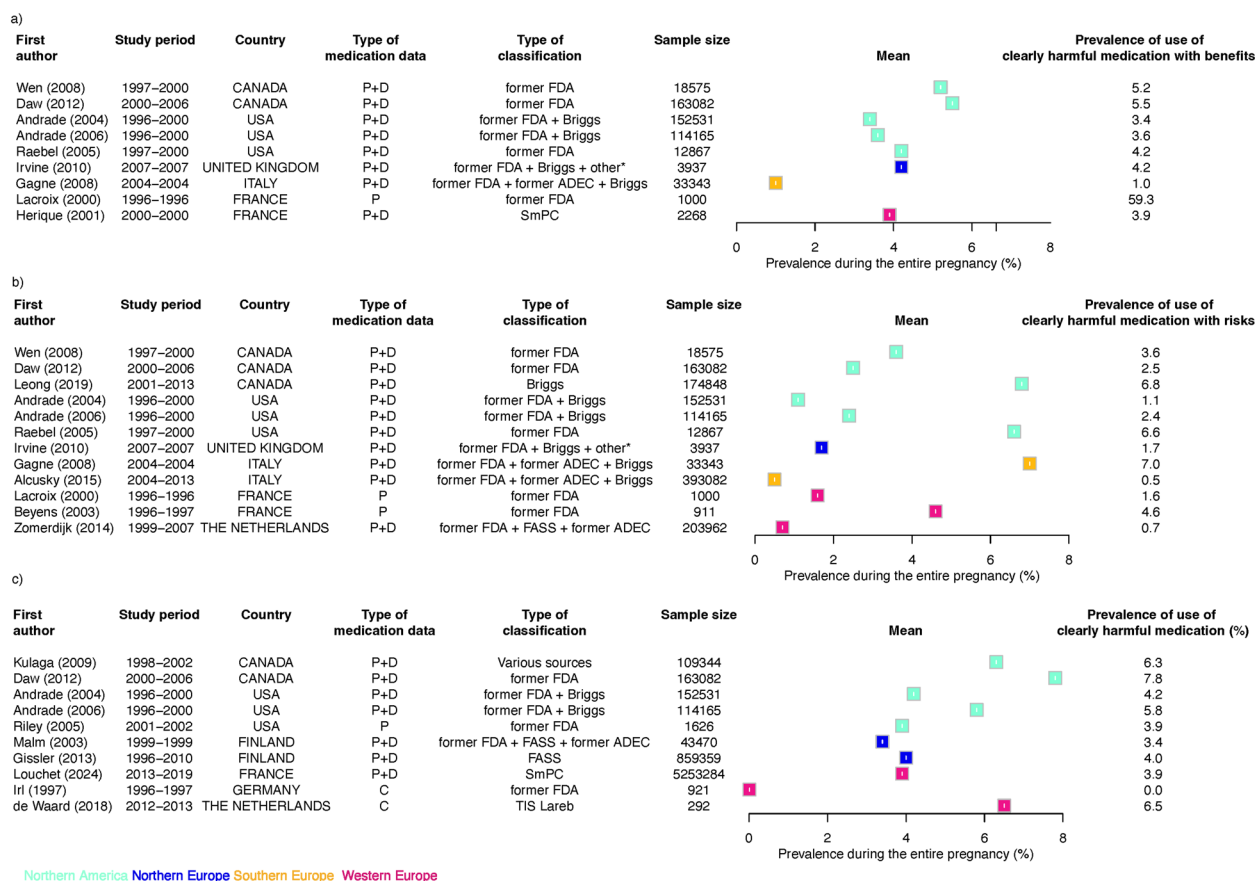


Fig. 4 Prevalence of women using medications considered at risk to the embryo or fetus during the entire pregnancy: **a** clearly harmful medication with maternal benefits outweighing the risks for the embryo/fetus; **b** clearly harmful medication with risks for the embryo/fetus outweighing the maternal benefits; **c** clearly harmful medication. According to the most frequently used classification (former 1979 FDA classification), the data were reclassified following three different levels: harmful medications during pregnancy with a benefit for the mother outweighing the risks for the embryo/fetus (adapted from former FDA D category); harmful medications during pregnancy with a risk for the embryo/fetus outweighing the benefit for the mother (adapted from former FDA X category); and harmful medications (in general) (adapted from former FDA D or X category). The denominator corresponds to the total number of eligible pregnancies reported in each study. Studies are organized by subcontinents and midpoint study period. Among all subcontinents, the median [interquartile range] prevalence of use of clearly harmful medication with the benefits outweighing the risks during the entire pregnancy was 4.2 [3.6–5.2]. This value was 2.5 [1.5–5.1] for the use of clearly harmful medication with the risks outweighing the benefits during the entire pregnancy and 4.1 [3.9–6.3] for the use of clearly harmful medication overall. Type of medication data: P=prescription, D=dispensation, C=consumption. The Lacroix (2000) [56] value of 59.3% women using clearly harmful medication with benefits is not represented on the plot (a). Legend: FDA: Unites States Food and Drug Administration

quality of the studies, which had not been done in previous reviews. Finally, we were able to perform a meta-regression for prevalence of medication use to explore heterogeneity related to time and subcontinents.

Nonetheless, some limitations of our systematic review must be acknowledged. First, the prevalence and number of medications do not inform on the appropriateness of prescribing. To complement these quantitative measures, we also described the most frequently used medications, therapeutic classes, and potentially harmful medications. Second, the heterogeneity in types of medications considered across the studies and the wide variability of medication use estimates did not allow our estimates to be pooled in a meta-analysis. Because of incomplete reporting in the original articles, we were not able to fully explore sources of heterogeneity including pregnancy outcomes considered, calendar time, actual medication consumption and inclusion of OTC medications, vitamins, and minerals. As recommended by the Cochrane handbook [13], we provided an extensive

descriptive analysis of the estimates instead. Meta-regression could not be conducted for the mean number of medications used due to infrequent and heterogeneous reporting of dispersion measures (e.g., standard deviation) across studies; therefore, geographical differences and temporal trends for these outcomes could not be adequately explored. Third, results relied heavily on pharmacy claims/administrative databases, which may reflect dispensing rather than actual medication use, overestimating medication use due to non-adherence. Fourth, the original studies generally did not report whether medications dispensed before pregnancy but extending into the first trimester were considered as medication use during pregnancy. Consequently, this potential source of heterogeneity could not be assessed in the present review. Fifth, risk classification systems used in the included studies do not directly quantify fetal risk, but rather provide a regulatory or evidence-based categorization of potential risk. Therefore, exposure to medications within higher-risk categories should not be interpreted as reflecting actual fetal harm. Sixth, title and abstract screening was performed by a single reviewer for feasibility reasons. Although predefined eligibility criteria were applied throughout the selection process, this approach may have increased the risk of missing potentially eligible studies. Nevertheless, the list of included studies was independently reviewed by two experts in epidemiology and medication use during pregnancy, who suggested additional potentially relevant references, thereby reducing the likelihood of missed studies.

Our review offers a thorough picture of medication use during pregnancy over a 50-year period. In Bonati et al., in 1990 [88], the median number of medications used was 4.7 (range 2.9 to 5.5) in studies published from 1960 to 1988 in the United Kingdom, United States, and Sweden. Most of the medications used were vitamins and iron preparations as well as analgesics, antiemetics, and antacids. Daw et al. updated this search, focusing on “developed countries”, and found a mean number of medications use varied in between 1.7 to 15.8 in studies published from 1989 to 2010 [3]. The recent meta-analysis by Sullivan et al. [4] also quantified the prevalence of prescribed medication use during pregnancy using meta-analysis (2010–2025; worldwide perspective; pooled prevalences of 56% excluding vitamins and minerals and 83% including them). Our review focused on population-based studies from Europe and North America without restrictions to the study period and provides a more extensive characterization of medication use during pregnancy. Consistent with Sullivan et al., our overall median prevalence of medication use including vitamins and minerals was 75.3%, which falls within the range of their pooled estimates. Rather than producing pooled prevalence estimates despite substantial heterogeneity, our review highlights the marked variability in prescribing practices and reporting methods and provides a comprehensive framework for interpreting medication use and identifying priorities for harmonizing future drug utilization studies in pregnancy. The two reviews are complementary, as our findings provide a more detailed characterization of medication use during pregnancy by describing the prevalence of medication use in developed countries overall and by geographical region, the median number of medications used overall and by region, temporal trends in these patterns, trimester-specific patterns, pharmacotherapeutic classes, the most commonly used medications, and exposure to medications considered harmful during pregnancy. Together, these findings provide a comprehensive understanding of medication use during pregnancy and document this important public health issue in great detail.

Our results suggest a higher prevalence and mean number of medications used in pregnancy in western Europe than in other subcontinents, which agrees with Daw et al. [3]. This finding may be explained, at least in part, by the high medication use in France, especially in the early 2000s. For example, Lacroix et al. and Beyens et al. included both reimbursed and non-reimbursed prescribed medications and reported high mean numbers of medications used during pregnancy (15.8 and 10.9, respectively) [55, 56]. These results are not surprising because France has been reported to have a high overall medication consumption. A report from the European Commission identified that in 2014, among 28 country members of the European Union, France ranked tenth in prescribed medications, with a prevalence of medication use for a period of 2 weeks of 52.4%, a proportion above the European Union average of 48.6%. This pattern was even greater for French women of childbearing age (15–44 years), in eighth position with a prevalence of 38.7%, higher than the European Union average of 32.9% [89].

We focused on Europe and North America to obtain estimates relevant to populations that are generally comparable in terms of access to healthcare, medication markets, and regulatory authorities. Nevertheless, important

differences exist among countries in how healthcare is organized and accessible. For example, in the United Kingdom and France, all maternity care is covered by the state or basic health insurance, whereas in more market-based healthcare systems, such as in the United States, maternity care is covered by private health insurers (via employment) or, for women with low income, by Medicaid [90]. Also, although we aimed to report an overview of medication use during pregnancy for North America and Europe, studies were based on 14 countries only and data may differ from other countries in these continents. Notably, no data were available from eastern Europe.

No evidence of a temporal trend was identified in the global picture of the prevalence of drug use or in the mean number of medication used across Europe and North America. This finding is noteworthy given the progressive implementation of several initiatives that might have been expected to reduce medication use during pregnancy, including institutional campaigns from regulatory agencies promoting more restrictive use, updated clinical guidelines issued by professional societies, and counselling provided by teratology information services. These measures may have encouraged more cautious prescribing practices among healthcare providers for pregnant women or women of childbearing age planning pregnancy. Nevertheless, limited statistical power and data availability may have constrained our ability to detect such temporal trends. At the regional level, however, data from France appear to suggest a decrease in the number of medications used over time, a trend that is less apparent in other European countries, where fewer studies are available. Nevertheless, this observation should be interpreted with considerable caution as methodological differences between the French studies may also explain the suggested trend.

We noted a change over time in data collection methods for medication-use studies in pregnancy. In the Bonati et al. review from 1990, most studies used interviews with pregnant women to ascertain medication exposure. The Daw et al. updated review in 2011 additionally captured some reports based on medico-administrative data that were not available when Bonati et al. conducted their review. The use of medico-administrative data in recent years across Europe and North America limits potential information bias as well as selection bias as compared with convenience samples using questionnaires or interviews. However, medico-administrative databases capture medication dispensing rather than actual medication intake. Consequently, medication use may be overestimated because dispensed medications are not necessarily consumed due to non-adherence [91].

This review highlighted the limits of the available data with on the one hand, the need for studies on medication use in countries for which there are few or no data and on the other, the high heterogeneity between studies. The substantial clinical and methodological heterogeneity across studies should be considered when interpreting the findings of this review. Medication use during pregnancy was assessed using prescription records, pharmacy dispensing databases, or self-reported medication use, reflecting the diversity of data sources available in perinatal pharmacoepidemiology. Although these approaches measure different stages of medication exposure and are therefore not directly comparable, considering all of them provides a comprehensive overview of the available literature and illustrates the evolution of data sources used to study medication use during pregnancy. Besides, the definition of medication exposure (i.e. inclusion or exclusion of over-the-counter medications, vitamins, mineral supplements, and hospital-administered medications) varied considerably between studies and was not always clearly reported. Another important source of heterogeneity relates to the pregnancy populations included in the original studies. While some studies considered all pregnancies as the denominator, others were restricted to births or live births. Consequently, studies based only on births or live births may have underestimated early pregnancy medication exposure. Other sources of heterogeneity can also be highlighted such as study period, country, healthcare system. Consequently, comparisons between studies and apparent geographical differences should be interpreted with caution, and the reported estimates should be viewed as reflecting both true differences in medication use and methodological differences between studies.

A lack of transparency was also identified. First, for some studies, results were unclear regarding the denominator for calculating the mean number of medications used during pregnancy (“among all women” or “among women having used at least one medication”) and whether or not vitamins and minerals were included. We attempted to clarify these issues by contacting the authors. Some authors provided answers, but some uncertainties

remained. In addition, how researchers counted different medications varied among studies. Moreover, some medications are available both OTC and by prescription.

Given the high level of heterogeneity in reporting, consensus is needed for the best reporting methods and details as regards sampling method, inclusion and exclusion criteria, population characteristics, statistical methods, medication use estimates, and the correct definition of medication use in drug utilization studies in pregnancy [92]. More specifically, based on the findings of this review, future studies should report key maternal characteristics relevant for data interpretation (e.g., age, parity, and prevalence of chronic diseases), as well as pregnancy outcomes and duration. Although reports usually specify the source of medication information (e.g., self-report, dispensing records, or prescription records), a precise definition of medication exposure should also be provided. Specifically, authors should clearly state whether the analysis included prescribed or dispensed medications only, and whether vitamins, minerals, vaccinations, homeopathic products, over-the-counter medications, and medications administered during hospitalization were included or excluded. They should also specify whether medications dispensed before pregnancy but whose exposure extended into the first trimester were considered as medication use during pregnancy [93], and whether a given international non-proprietary name was counted once or multiple times when prescribed under different brand names. Moreover, in all cases, the numerator, denominator, and prevalence of medication use, based on the number of women or pregnancies, should be reported. The number of different medications used should be reported as the median and interquartile range, both among women with medication use and in the overall study population. These measures should be presented for the complete pregnancy period and for each trimester (using standardized trimester definitions). Indeed, there is a need for well-conducted drug utilization studies focusing on granular time windows in pregnancy considering the varying risks according to the developmental stage of the embryo or foetus. Reports should provide estimates according to pregnancy outcome and with and without vitamins, minerals, OTC medications. Finally, to improve knowledge of medication use during pregnancy, studies should report the most commonly used medications together with their corresponding ATC codes, as well as the medications most frequently considered to be at potential risk, preferably using an evidence-based risk classification.

Future studies should also investigate factors related to indication of use and the availability and reimbursement status of medications. Alignment of these aspects would facilitate the assessment of time trends and geographical differences as well as prescribing habits and the types of healthcare pregnant women receive in different countries. In turn, more advanced data regarding medications during pregnancy could also enable more robust public health campaigns regarding the safe use of medications during pregnancy. Also, although our review shows that an undeniable proportion of pregnant women were exposed to medications considered as harmful, further research on the subject is needed to provide a clearer picture of the benefit–risk balance of medication use and should include maternal indications for medication use as well as gestational age in pregnancy.

Conclusion

Our systematic review confirmed that medication use during pregnancy was frequent in Europe and North America. Studies conducted in western Europe generally reported higher estimates of medication use during pregnancy than studies from the other European subcontinents and North America, although these apparent regional differences should be interpreted with caution. Given the substantial heterogeneity in methods and reporting between studies, it is currently not feasible to accurately characterize or compare medication use among subcontinents and over time. This review highlights a strong need for standardized practices for the presentation of medication exposure during pregnancy as well as the use of a standardized pharmacotherapeutic classification tool and harmonization of current risk classifications.

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Authors' contributions BM, RN and ADC conceived the study. RN developed the search strategy, which was validated by ADC and BM. RN conducted literature search. RN and VFB or BC and DR screened and selected studies. MvG and MSB assessed the list of included articles and added missing references if any. RN and VFB or BC and DR collected data. RN performed data synthesis and wrote the first draft of the manuscript under the direction of ADC and BM with guidance from MvG and with critical input from all authors. All authors read and approved the final submitted version. RN and BM act as guarantors. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Data availability The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate Not applicable.

Consent for publication Not applicable.

Competing interests The authors declare no competing interests.

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Authors and Affiliations

R Nehard¹ · V Faure Bardon^{2,3} · B Coulm¹ · D Rajendrabose⁴ · E Elefant⁴ · C Vauzelle⁴ · D Beghin⁴ · M Latour^{4,5} · MS Brochet⁵ · M M.H.J. van Gelder^{6,7} · A Dechartres⁸ · B Marin^{1,9}

✉ B Marin
benoit.marin@aphp.fr

¹ Département de Santé Publique, Centre de Référence Sur Les Agents Tératogènes (CRAT), Sorbonne Université, INSERM, Institut Pierre Louis d'Epidémiologie Et de Santé Publique, Équipe PEPITES, AP-HP, Hôpital Pitié Salpêtrière, 75013 Paris, France

² Department of Gynecology and Obstetrics, Pitié-Salpêtrière Hospital, AP-HP, Sorbonne University, Paris, France

³ URP FETUS 7328, Federation for Research into Innovative Explorations and Therapeutics in Utero, University of Paris Cité, Paris, France

⁴ Département de Santé Publique, Centre de Référence Sur Les Agents Tératogènes (CRAT), AP-HP.Sorbonne Université, Hôpital Pitié Salpêtrière, F75013 Paris, France

⁵ Department of Pharmacy and Assisted Reproduction Technology Center, Department of Obstetrics and Gynecology, CHU Sainte-Justine, Montreal, QC, Canada

- ⁶ IQ Health Science Department, Radboud University Medical Center, Nijmegen, The Netherlands
- ⁷ PharmacoEpidemiology and Drug Safety Research Group, Department of Pharmacy, Faculty of Mathematics and Natural Sciences, University of Oslo, Oslo, Norway
- ⁸ Département de Santé Publique, Centre de Pharmacoépidémiologie (Cephepi), Unité de Recherche Clinique PSL-CFX, Sorbonne Université, INSERM, Institut Pierre Louis d'Epidémiologie et de Santé Publique, Equipe PEPITES, AP-HP, Hôpital Pitié Salpêtrière, F75013 Paris, France
- ⁹ Centre de Référence Sur Les Agents Tératogènes (CRAT), Batiment Mazarin, APHP.Sorbonne Université. Hôpital Pitié Salpêtrière, 47-83 Boulevard de L'Hôpital, 75013 Paris, France