Medication use in pregnancy: a multinational perspective

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ABSTRACT

Objectives: Inter-country comparability between studies on medication use in pregnancy is difficult due to dissimilarities in study design and methodology. This study aimed to examine patterns and determinants of medications use in pregnancy from a multinational perspective, with emphasis on type of medication utilized and indication for use.

Design: Cross-sectional, internet-based study performed within the period from 1-Oct-2011 to 29-Feb-2012. Uniform collection of drug utilization data was performed via an anonymous online questionnaire.

Setting: Multinational study in Europe (Western, Northern, and Eastern), North and South America, and Australia.

Participants: Pregnant women and new mothers with children less than one year of age.

Primary and secondary outcome measures: Prevalence and determinants of medication use for acute illnesses, chronic disorders and over-the-counter (OTC) medication use.

Results: The study population included 9,459 women whereof 81.2% reported use of at least one medication (prescribed or OTC) during pregnancy. OTC medication use occurred in 66.9% of the pregnancies. The extent of self-reported medicated illnesses and types of medication used by indication varied across regions, especially in relation to urinary tract infections, depression or OTC nasal sprays. Women with higher age or lower educational level, housewives, or women with an unplanned pregnancy were those most often reporting use of chronic medication. Immigrant women in Western (aOR: 0.55, 95% CI: 0.34-0.87) and

Northern Europe (aOR: 0.50, 95% CI: 0.31-0.83) were less likely to report chronic medication use during pregnancy than non-immigrants.

Conclusions: There is a substantial inter-region variability in the extent of medication use during pregnancy. In certain subgroups of the population there is a specific need for information about medications in pregnancy. Future research should focus on this specific group of women, but also address more insights into the outcome of sub-optimal medication of severe conditions in pregnancy.

ARTICLE SUMMARY

Strengths and limitations of this study

- Uniform data collection of drug utilization data across all participating countries allows for intercountry comparability of the prevalence of medication use during pregnancy, up to now impeded by differences in study design and methodology.
- The study adds a multinational perspective on OTC medication use during pregnancy to the limited number of studies quantifying the extent of self-medication during pregnancy.
- Lack of validity of the self-reported diagnoses since all disorders and related medication use were self-reported by the study participants.
- An internet survey as a study method impedes calculation of a conventional response rate and may cause selection bias of the target population.

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COMPETING INTERESTS: None declared

INTRODUCTION

Ethical reasons preclude inclusion of pregnant women in the vast majority of pre-marketing clinical trials.[1] As a consequence, most medications are placed onto the market without a directly established safety profile in human pregnancy.[2] So far, few medications have been shown to be major teratogens, yet the risk of minor teratogenicity or of more subtle effects on fetal development still have to be determined for most of them.[3] Despite this, medication use during pregnancy is common. Mitchell et al. found that use of medications, either prescribed or purchased over-the-counter (OTC), occurred in 88.8% of all pregnancies in the USA.[4] In Europe, prevalence estimates of prescribed medication use vary considerably across countries, ranging from 26% in Serbia to 93% in France.[5-10] Such inter-country variability could, at least in part, be caused by differences in study design, methodology and exposure ascertainment across studies.[11] Uniform collection of drug utilization data during pregnancy between countries may overcome such drawbacks, allowing for inter-country comparability of prevalence estimates and shedding light on differences in prenatal care in the various countries.

Prior studies have addressed research priorities in this area such as presenting results on an individual drug level according to the indication of use, quantifying the extent of OTC and prescribed medication use during pregnancy, and taking into account inter-country comparability.[4] Only a few studies have individually examined maternal factors associated with specific types of medication use during pregnancy.[11-14]

The objectives of the current study were to examine patterns of medication use in pregnancy from a multinational perspective, with special emphasis on type of medication utilized, including OTC medications, and self-reported indications for use, and to identify maternal

background factors potentially associated with the use of specific types of medication during pregnancy.

METHODS

Study design and data collection

This is a multinational, cross-sectional, internet-based study. Pregnant women at any gestational week and mothers with children less than one year of age were eligible to participate. Member countries of the European Network of Teratology Information Services (ENTIS), The Organization of Teratology Information Specialists (OTIS) in North America, MotherSafe in Australia and European institutions conducting public health research were invited to take part in the project. Of these, 18 countries participated (Australia, Austria, Canada, Croatia, Finland, France, Iceland, Italy, Netherlands, Norway, Poland, Russia, Serbia, Slovenia, Sweden, Switzerland, United Kingdom and USA). Data originating from some South and Central American countries were also collected through OTIS. Because of the low number of participants on the individual country level, the region of Central America was excluded and countries in South America were aggregated into one region. Data selection to achieve the final study sample was performed as depicted in Figure 1. Participants were categorized according to the reported country of residency and grouped into six regions: Western Europe, Northern Europe, Eastern Europe, North America, South America and Australia.

Data were collected through an anonymous on-line questionnaire administered by Quest Back (http://www.questback.com) and accessible for a period of two months in each participating country within the period 1-Oct-2011 to 29-Feb-2012. The questionnaire was open to the public via utilization of banners (invitations to participate in the study) on national websites and/or social networks commonly visited and consulted by pregnant women and/or new

mothers. Detailed information about recruitment tools utilized and internet penetration rates is summarized in Appendix 1.

The questionnaire was first developed in Norwegian and English and then translated into the other relevant languages. A pilot study was carried out in September 2011 (n=47) and elicited no major change to the questionnaire. Collected data were scrutinized for the presence of potential duplicates (based on reported country of residency, socio-demographic characteristics, date and exact time of questionnaire completion) but none were identified.

Exposure variables

Maternal socio-demographics (i.e. region of residency, age, educational level, mother tongue, working status, previous children, marital status and unplanned pregnancy) and life-style characteristics (i.e. smoking status before and during pregnancy and alcohol consumption after awareness of pregnancy) constituted the exposure variables. To assess external validity, we compared socio-demographic and life-style characteristics of our study population on an individual country level with those of the general birthing population in the same country. Reports of National Statistics Bureaus or previous national studies were utilized for this purpose. The ratio between the number of respondents and the estimated number of live births in the 2-months period was also examined for each country (Appendix 2).

Outcome variables

Use of prescribed medication for acute/short-term illnesses or chronic/long-term disorders and OTC medication use during pregnancy constituted the outcome variables. Participants were first confronted with a list of the most common acute/short-term illnesses (i.e. nausea, heartburn, constipation, common cold, urinary tract infections (UTIs), other infections, pain in the neck/back/pelvic girdle, headache, sleeping problems) and the most prevalent

chronic/long-term disorders (i.e. asthma, allergy, hypothyroidism, rheumatic disorders, diabetes, epilepsy, depression, anxiety, cardiovascular disease, other disorders) and asked whether they suffered/had suffered from these conditions during pregnancy. In case of an affirmative response, women were questioned about medication use for each individual indication as a free-text entry. Use of OTC medications was also recorded. Recall was aided with a list of five OTC categories: painkillers, nasal spray/drops, antinauseants, antacids and laxatives, along with examples of brand name products of relevance in each country. Timing of exposure (gestational weeks 0-12 (1st trimester), 13-24 (2nd trimester) and 25-delivery (3rd trimester)) could be reported for each of the medication use questions.

We defined a medicine as a single product containing one or more active ingredients. We initially identified the main active ingredient(s) and formulation of the reported medicinal products either in the relevant national medicines database or in the "Martindale" textbook.[15] All recorded medications were coded into the corresponding Anatomical Therapeutic Chemical (ATC) codes at the ATC 5th level (i.e. the substance level) whenever possible, otherwise into the 2nd- 4th levels as appropriate, in accordance with the World Health Organization ATC index.[16] The OTC status of medications was crosschecked with the prescription policies within each country. Whenever a prescription medication was reported under the OTC question, this record was omitted from the analysis of OTC use but counted in the estimation of total medication use (including prescription and OTC). Iron, mineral supplements, vitamins, herbal remedies and any type of alternative medicine were recorded separately and excluded from the estimation of medication use.

Ethics

All participants gave informed consent by answering "Yes" to the question "Are you willing to participate in the study?" The study was approved by the Regional Ethics Committee,

Region South-East in Norway. Ethical approval or study notification to the relevant national Ethics Boards was achieved in specific countries as required by national legislation. All data were handled and stored anonymously.

Statistical analysis

Descriptive statistics were utilized as appropriate. Univariate and multivariate logistic regression analyses were used to examine the association between maternal characteristic and three categorical outcome measures (Yes/No): Medication use for acute/short-term illnesses; medication use for chronic/long-term disorders; OTC medication use. P-values of <0.05 were considered statistically significant. Data are presented as adjusted odds ratios (aOR) with 95% confidence intervals (CI). The analyzed explanatory variables included all maternal socio-demographics and life-style characteristics. After fitting the univariate logistic regression model for all explanatory variables, the multivariate model was built and adjusted for all remaining covariates. The Hosmer and Lemeshow test was used to assess goodness of fit of the final multivariate model.[17] Analogue sub-analyses on individual region level were performed. In these instances, region of residency was not included in the model. All statistical analyses were performed by using the Statistical Package for the Social Sciences (SPSS) version 20.0 (IBM® SPSS® Statistics).

RESULTS

Population characteristics

A total of 9,615 women accessed the on-line questionnaire whereof 98.6% completed it. The participant flow-chart to achieve final study population (n=9,459) is depicted in Figure 1. A total of 5,089 women (53.8%) were pregnant at the time of completion of the questionnaire whereas 4,370 women (46.2%) had delivered their babies within the previous year.

Overall, the birthing population in each participating country was reflected quite well by the sample with respect to age, parity and smoking habits (Appendix 2). However, there was a difference in terms of educational level; on average, the women in the study had higher education than the general birthing population in each country. In addition, participants in Sweden, Austria, Iceland and Italy were slightly more often primiparous, whereas the responders in Australia, USA, Netherlands, Slovenia and Croatia were somewhat older than the general birthing population.

Total medication use

After exclusion of vitamins, mineral supplements and iron, use of at least one medication either prescribed or OTC at any time during pregnancy was reported by 7,678 out of 9,459 women (81.2%). Figure 2 depicts prevalence estimates of total medication use during pregnancy by region and country of residence, with specific rates according to inclusion or exclusion of vitamins, mineral supplements and iron. The extent of OTC medication use is also outlined. The highest prevalence of total medication use during pregnancy was observed in The Netherlands (95.1%), Iceland (93.0%) and Finland (92.3%). The overall prevalence estimates of medication use in pregnancy according to timing and drug class (ATC level 1 and 2) are presented in Appendix 3. Medications for the nervous system (ATC class N) were the most commonly used during pregnancy (57.5%), mostly due to paracetamol (acetaminophen) and its combinations.

Medication use according to indication

Headache, heartburn, pain, nausea and UTIs constituted the leading indications for use of medication during pregnancy among the acute/short-term illnesses analyzed. Hypothyroidism, asthma, allergy and depression were the leading indications for chronic/long-term medication use. Observed prevalence rates of these disorders, overall and by region of residency, are

presented in Appendices 4 and 5, respectively, along with rates of total and specific medication use. Table 1 outlines prevalence estimates of OTC medication use during pregnancy by region and indication for use. Only the most common medication groups reported are presented. Inter-region variations in rates and types of medication used during pregnancy were observed both for acute/short-term illnesses (e.g. nausea and UTIs), chronic/long-term disorders (e.g. asthma and depression) and OTC medications (e.g. nasal spray).

Table 1: Use of OTC medication at any time during pregnancy by ATC level, indication for use and region (n=9,459) [*†]

	REGION						
OTC medication use, overall and by drug groups	**Western Europe n=3,201** *n (%)*	**Northern Europe n=2,820** *n (%)*	**Eastern Europe n=2,342** *n (%)*	**North America n=533** *n (%)*	**South America n=346** *n (%)*	**Australian n=217** *n (%)*	**Total n=9,459** *n (%)*
OTC painkillers, total	**1,714 (53.5)**	**1,773 (62.9)**	**734 (31.3)**	**284 (53.3)**	**127 (36.7)**	**151 (69.9)**	**4,783 (50.6)**
By drug group							
Paracetamol (incl. combinations) (N02BE)	1,655 (51.7)	1,735 (61.5)	630 (26.9)	263 (49.3)	87 (25.1)	146 (67.3)	4,516 (47.7)
Non-steroideal antiinflammatory drugs (M01A)	70 (2.2)	182 (6.5)	68 (2.9)	40 (7.5)	59 (17.1)	7 (3.2)	426 (4.5)
Acetylsalicylic acid (incl. combinations) (N02BA)	7 (0.2)	11 (0.4)	32 (1.4)	2 (0.4)	2 (0.6)	1 (0.5)	55 (0.6)
Metamizole (N02BB02)	-	6 (0.2)	31 (1.3)	1 (0.2)	12 (3.5)	-	50 (0.5)
OTC antacids, total	**1,011 (31.6)**	**883 (31.3)**	**583 (24.9)**	**129 (24.2)**	**48 (13.9)**	**76 (35.0)**	**2,730 (28.9)**
By drug group							
Antacids (aluminium, salts combinations, antiflatulents)	472 (14.7)	550 (19.5)	508 (21.7)	47 (8.8)	36 (10.4)	54 (24.9)	1,667 (17.6)
Alginic acid complex/sucralfate/bismuth (A02BX)	606 (18.9)	421 (14.9)	87 (3.7)	4 (0.8)	1 (0.3)	17 (7.8)	1,136 (12.0)
H_2 receptor antagonists (A02BA)	20 (0.6)	20 (0.7)	16 (0.7)	57 (10.1)	10 (2.9)	17 (7.8)	137 (1.4)
Antacids with calcium (A02AC)	23 (0.7)	12 (0.4)	10 (0.4)	69 (12.9)	2 (0.6)	10 (4.6)	126 (1.3)
Proton pump inhibitors (A02BC)	38 (1.2)	52 (1.8)	-	10 (1.9)	2 (0.6)	5 (0.3)	107 (1.1)
OTC nasal sprays/drops, total	**272 (8.5)**	**742 (26.3)**	**451 (19.3)**	**35 (6.6)**	**7 (2.0)**	**14 (6.5)**	**1,521 (16.1)**
By drug group							
Sympathomimetic nasal decongestants (R01AA/R01BB)	204 (6.4)	683 (24.2)	365 (15.6)	20 (3.8)	3 (0.9)	4 (1.8)	1,279 (13.5)
Nasal corticosteroids (R01AD)	31 (1.0)	49 (1.7)	12 (0.5)	5 (0.9)	2 (0.6)	10 (4.6)	109 (1.2)
Nasal immunostimulants (low dose interferon) (L03A)	-	-	28 (1.2)	-	-	-	28 (0.3)
OTC laxatives, total	**240 (7.5)**	**227 (8.0)**	**237 (10.1)**	**50 (9.4)**	**8 (2.3)**	**19 (8.8)**	**781 (8.3)**
By drug group							
Osmotically acting laxatives (A06AD)	159 (5.0)	171 (6.1)	197 (8.4)	2 (0.4)	2 (0.6)	8 (3.7)	539 (5.7)
Contact laxatives (A06AB)	28 (0.9)	44 (1.6)	18 (0.8)	7 (1.3)	6 (1.7)	2 (0.9)	105 (1.1)

OTC medication use, overall and by drug groups	REGION						
	Western Europe	**Northern Europe**	**Eastern Europe**	**North America**	**South America**	**Australian**	**Total**
	n=3,201	**n=2,820**	**n=2,342**	**n=533**	**n=346**	**n=217**	**n=9,459**
	n (%)	***n (%)***	***n (%)***	***n (%)***	***n (%)***	***n (%)***	***n (%)***
Enemas (A06AG)	3 (0.1)	25 (0.9)	34 (1.5)	4 (0.8)	-	2 (0.9)	68 (0.7)
Softeners, emollients (A06AA)	8 (0.2)	-	-	38 (7.1)	-	6 (2.8)	52 (0.5)
OTC antinauseants, total	**263 (8.2)**	**273 (9.7)**	**41 (1.8)**	**60 (11.3)**	**28 (8.1)**	**40 (18.4)**	**705 (7.5)**
By drug group							
First generation antihistamines (R06A)	141 (4.4)	256 (9.1)	7 (1.5)	55 (10.3)	5 (1.4)	5 (2.3)	469 (5.0)
Metoclopramide/domperidone/bromopride (A03FA)	113 (3.5)	5 (0.2)	18 (0.8)	2 (0.4)	19 (5.5)	27 (12.4)	184 (1.9)
Total OTC medication use	**2,163 (67.6)**	**2,155 (76.4)**	**1,347 (57.5)**	**342 (64.2)**	**156 (45.1)**	**168 (77.4)**	**6,331 (66.9)**

*Countries are grouped into regions as shown in Figure 1.

†Sums of percentages do not add up to total medication use as only most common medication groups are presented. Rates do not include mineral supplements, vitamins, iron, and herbal or alternative medicine products.

Abbreviations: OTC: Over-The-Counter medications.

Determinants of medication use

Determinants of medication use during pregnancy according to type of medication utilized are presented in table 2. Use of chronic/long-term medications during pregnancy was reported in a significant larger extent by women in Northern Europe (aOR:1.68, 95% CI:1.46-1.94), North America (aOR:1.80, 95% CI:1.42-2.28) and Australia (aOR:2.76, 95% CI:2.03-3.76) compared to women in Western Europe. Older women or housewives, those with low education or with an unplanned pregnancy, were the ones most often reporting use of chronic/long-term medication. Sub-analysis on individual region level revealed that women not having the official language of the country of residency as mother tongue were less likely to report chronic/long-term medication use in Western (aOR: 0.55, 95% CI: 0.34-0.87) and Northern Europe (aOR: 0.50, 95% CI: 0.31-0.83), but not in the other regions.

Table 2: Determinants of medication use in pregnancy (n=9,459)*

	Medication use					
	For acute/short-term illnesses (n=6,469)		For chronic/long-term disorders (n=1,604)		OTC (n=6,331)	
	n (%)	*aOR (95% CI)*	*n (%)*	*aOR (95% CI)*	*n (%)*	*aOR (95% CI)*
Region of residency†						
Western Europe	2,224 (69.5)	Reference	462 (14.4)	Reference	2,163 (67.6)	Reference
Northern Europe	1,954 (69.3)	0.96 (0.86-1.08)	593 (21.0)	**1.68 (1.46-1.94)**	2,155 (76.4)	**1.54 (1.36-1.74)**
Eastern Europe	1,474 (62.9)	**0.69 (0.61-0.78)**	322 (13.7)	1.03 (0.87-1.21)	1,347 (57.5)	**0.60 (0.53-0.67)**
North America	403 (75.6)	**1.28 (1.03-1.60)**	119 (22.3)	**1.80 (1.42-2.28)**	342 (64.2)	**0.81 (0.66-0.99)**
South America	250 (82.3)	1.03 (0.79-1.34)	38 (11.0)	0.70 (0.48-1.01)	156 (45.1)	**0.34 (0.27-0.44)**
Australia	164 (75.6)	1.29 (0.93-1.79)	70 (32.3)	**2.76 (2.03-3.76)**	168 (77.4)	**1.57 (1.12-2.20)**
Maternal age (years)						
≤20	232 (70.5)	1.22 (0.93-1.60)	761 (14.7)	**0.58 (0.39-0.87)**	205 (62.3)	1.05 (0.81-1.36)
21-30	3,531 (68.2)	Reference	33 (10.0)	Reference	3,461 (66.8)	Reference
31-40	2,576 (68.6)	0.90 (0.82-1.00)	764 (20.4)	**1.44 (1.27-1.63)**	2,531 (67.4)	**0.85 (0.77-0.94)**
≥41	130 (66.3)	0.73 (0.54-1.00)	46 (23.5)	**1.61 (1.13-2.29)**	134 (68.4)	0.86 (0.62-1.19)
Previous children						
No	3,082 (65.5)	Reference	735 (15.6)	Reference	2,949 (62.6)	Reference
Yes	3,387 (71.3)	**1.34 (1.22-1.47)**	869 (18.3)	1.08 (0.96-1.21)	3,382 (71.2)	**1.58 (1.44-1.74)**
Marital status						
Married/cohabiting	6,066 (68.5)	Reference	1,503 (17.0)	Reference	5,960 (67.3)	Reference
Single/divorced/others	403 (66.3)	0.91 (0.75-1.10)	101 (16.6)	1.06 (0.83-1.35)	371 (61.0)	0.91 (0.75-1.10)
Working status						
Employed, but not as HCP	3,737 (66.8)	Reference	905 (16.2)	Reference	3,667 (65.6)	Reference
HCP	934 (74.4)	**1.41 (1.23-1.63)**	240 (19.1)	1.13 (0.96-1.33)	944 (75.2)	**1.42 (1.23-1.64)**
Student	592 (69.1)	1.11 (0.94-1.31)	128 (14.9)	1.04 (0.84-1.30)	578 (67.4)	1.10 (0.93-1.30)
Housewife	608 (72.6)	1.14 (0.96-1.35)	170 (20.3)	**1.34 (1.10-1.63)**	577 (68.9)	1.05 (0.88-1.24)
Job seeker	281 (66.0)	0.96 (0.78-1.20)	66 (15.5)	1.03 (0.78-1.36)	258 (60.6)	0.85 (0.68-1.05)
Other than above	311 (65.2)	0.91 (0.75-1.12)	94 (19.7)	**1.29 (1.01-1.65)**	302 (63.3)	0.91 (0.74-1.12)
Educational level						

	Medication use					
	For acute/short-term illnesses (n=6,469)		For chronic/long-term disorders (n=1,604)		OTC (n=6,331)	
	n (%)	*aOR (95% CI)*	*n (%)*	*aOR (95% CI)*	*n (%)*	*aOR (95% CI)*
High school	1,864 (68.7)	Reference	428 (15.8)	Reference	1,779 (65.6)	Reference
Less than high school	331 (72.7)	1.17 (0.93-1.49)	92 (20.2)	**1.51 (1.15-1.97)**	317 (69.7)	**1.32 (1.04-1.67)**
More than high school	3,574 (68.4)	0.99 (0.89-1.11)	916 (17.5)	1.04 (0.91-1.20)	3,489 (66.8)	1.07 (0.96-1.19)
Others, unspecified	700 (65.7)	0.82 (0.70-0.96)	168 (15.8)	0.94 (0.77-1.16)	746 (70.0)	1.13 (0.97-1.33)
Alcohol use after awareness of pregnancy						
No	5,270 (67.1)	Reference	1,322 (16.8)	Reference	5,133 (65.3)	Reference
Yes	1,144 (75.7)	**1.59 (1.39-1.81)**	270 (17.9)	1.11 (0.95-1.29)	1,150 (76.1)	**1.95 (1.71-2.23)**
Smoking during pregnancy						
No	5,835 (68.5)	Reference	1,441 (16.9)	Reference	5,716 (67.0)	Reference
Yes, but less than before pregnancy	530 (69.0)	1.08 (0.91-1.27)	130 (16.9)	1.01 (0.82-1.25)	511 (66.5)	1.06 (0.90-1.26)
Yes, the same or more than before pregnancy	88 (67.7)	0.95 (0.64-1.40)	28 (21.5)	1.19 (0.74-1.90)	89 (68.5)	1.21 (0.81-1.82)
Planned pregnancy						
Yes	5,836 (68.4)	Reference	1,427 (16.7)	Reference	5,727 (67.2)	Reference
No	616 (68.4)	0.96 (0.82-1.12)	173 (19.2)	**1.29 (1.06-1.56)**	587 (65.1)	1.00 (0.85-1.17)
First language different from the official main language in the country of residency						
No	6,089 (68.5)	Reference	1,530 (17.2)	Reference	5,972 (67.1)	Reference
Yes	363 (67.2)	0.93 (0.76-1.12)	71 (13.1)	**0.66 (0.50-0.86)**	347 (64.3)	0.89 (0.74-1.08)

Abbreviation: HCP: health care provider.

*Numbers may not add up due to missing values. Missing values are less than 5% of the total. Mineral supplements, vitamins, iron, herbal or alternative medicine products are not included in the medication use estimates.

†Countries are grouped into regions as shown in Figure 1.

DISCUSSION

This is the first internet-based study examining patterns and determinants of medication use during pregnancy on a multinational level. In specific countries (Australia, Canada, France, Russia, The Netherlands, and the USA) the study sample was a small proportion of the general birthing population; hence the generalizability of our findings for these specific countries should be interpreted with caution. In all regions, approximately eight out of ten women reported use of at least one medication, either prescribed or OTC, during the course of their pregnancy. This finding is in line with previous research conducted in Europe, North America, South America and Australia,[4,18-23] though our estimates were somewhat higher in some of the Eastern European countries, e.g. Serbia, than those observed in a previous study.[5] Different recruitment strategies, i.e. internet-based in our study versus maternity care unit-/community pharmacy-based in the previous study could explain such discrepancy.

Overall, analgesics, antacids, nasal decongestants/antiallergics and systemic antibiotics were the medication groups dominating the drug utilization scenario, as also shown by previous research.[4,18-20] However, our study also provides insights into the proportion of medicated women among those suffering from a specific illness during pregnancy across the six regions. We found that approximately seven out of ten women who reported UTIs were treated with antibiotics during pregnancy. This related to all regions, except Eastern Europe where it was only four out of ten women. Since women may perceive dysuria without ascertainment of bacteriuria in the urine as UTI, an over-reporting of the illness could have occurred. Yet, a sub-optimal treatment of UTIs during pregnancy in Eastern Europe cannot be ruled out. The inter-country variability in the types of antibiotics used for UTIs could simply be explained by differences in prescribing practice,[24] presence of screening for bacteriuria in early pregnancy, or specific antibiotic resistance patterns.

Even though nausea was the condition affecting most women in all six regions, the corresponding proportions of medicated nausea were generally low. This scenario is probably due to two main factors: a) the predominantly mild character of nausea and the possibility of non-pharmacological management (e.g. dietary advices); b) the reluctance of general practitioners to prescribe antinauseants even though safety profile assessments are in place.[25,26] As also shown in previous studies,[4,27] use of serotonin antagonists in North America and Australia is increasing also in pregnancy compared to the other regions, eliciting the need of sound studies assessing the safety profile of this drug group in pregnancy.

In most regions, the self-reported prevalence of hypothyroidism was somewhat higher than the reported hormone substitution rate. Because of its known association with adverse pregnancy outcomes,[28] the unexpected finding of potential sub-optimal treatment of hypothyroidism during pregnancy deserves attention. It could probably be due to a lack of information about hypothyroidism typology and its diagnostic ascertainment in our study.

In our study, depression was self-reported and not based on any psychometric assessment, thus the observed substantial inter-regional variability in the extent of this disorder and related medication use could have certainly been affected by women's attitudes in reporting. Our estimate of medication use for depression in Australia was higher than that observed in a recent study (10.6% versus 2.1%).[29] However, the similarity in self-reported depression itself (11.5% versus 15.6%) suggests that our population might mostly comprise women who did not discontinue their pharmacological therapy once they became pregnant. Our estimates for North America and Western Europe were in line with recent literature showing an increase in antidepressant use in pregnancy during the last years.[4,30]

In most regions approximately 60-70% of women reported use of at least one OTC medication during the course of their pregnancy, mostly for pain conditions, heartburn and

upper airways disorders, indicating a substantially high rate of self-medication during pregnancy. This estimate aligns with previous research carried out in North America.[31] Of note, self-medication with OTC sympathomimetic nasal decongestants was more extensive in Northern and Eastern Europe than in the remaining regions; this could be explained by the time of the year when the data collection was performed.

Region of residency was an important factor associated with medication use during pregnancy. As also shown by Cleary et al.,[32] we found that rates of medication use among women originally from Eastern Europe and South America were significantly lower than those observed in Western Europe, North America and Australia. Such geographical differences could be due to culture, variations in prenatal care assistance or access to medications in the various regions and the related costs.

Women working as health care providers, those consuming alcohol during pregnancy and those with previous children were those more likely to use short-term and OTC medications, possibly reflecting higher confidence in self-treatment and use of medications in general in the former instance, and less anxiety for the pregnancy outcome in the latter two instances. One factor negatively associated with chronic/long-term medication use was not having the official language of the country of residency as mother tongue. This tendency was detected in Western and Northern Europe, rising concerns about the potential health risks for immigrant women in these two regions. As shown by Hameen-Anttila et al., 57% of pregnant women have perceived information needs about medications during pregnancy.[33] Thus, identification of potential users or non-users of medication during pregnancy might be of clinical relevance, allowing tailored evidence-based information about medication safety or outcome of sub-optimal medication of severe medical conditions in pregnancy.

Strengths and limitations

The main strength is that data collection was performed uniformly across all participating countries, allowing for inter-country comparison of the prevalence of medication use during pregnancy. By quantifying the extent of self-medication with OTC drugs and medication use according to self-reported indication, it was possible to determine the leading causes for medication use among pregnant women. Categorization of maternal characteristics positively associated with the various types of medications used during pregnancy enabled us to identify which groups of women are more likely to need information about medication use during pregnancy. The utilization of an anonymous web-based questionnaire enabled us to reach a large proportion of the birthing population in several countries worldwide. However, we cannot exclude the possibility that the women who decided to participate in the study differed from the general birthing population in other ways that our analysis could not control for.

One main limitation of the study is the lack of validity of the self-reported diagnoses. All disorders were self-reported by the participants and hence dependent on the women's perception of the medical condition. Similarly, information about medication use during pregnancy was dependent on the accuracy of the women's reporting and recall. For new mothers, data were registered retrospectively; hence a risk of recall bias cannot be ruled out. The questionnaire was only available through internet websites; by using this kind of approach a conventional response rate cannot be calculated. However, recent epidemiological studies indicate reasonable validity of web-based recruitment methods.[34,35] Also, the penetration rate of the internet either in households or at work is relatively high among women in childbearing age.[36-40] Hence, the degree to which our findings can be extrapolated to the target population is based on the representativeness of the respondents to the general birthing populations in each country. The sample in each country had a somewhat

higher educational level than the general birthing populations. Inclusion of pregnant women at any gestational week might have inflated the prevalence of non-users of medications during pregnancy. Also, women with specific disorders or in need of information about medication use during pregnancy might have been more likely to consult internet websites and therefore participate in this study.

CONCLUSIONS

Use of medications for acute and chronic disorders as well as use of OTC medications, were common during pregnancy. The extent of medicated illnesses and types of medications used for the different indications varied across the six regions. This was especially relevant for acute/short-term illnesses such as nausea and UTIs, but also for chronic/long-term disorders such as hypothyroidism or depression. Women with higher age or lower educational level, housewives, or women with an unplanned pregnancy were those most often reporting use of chronic/long-term medication and may therefore be more in need of information about medication during pregnancy. Moreover, maternal-fetal health among immigrants residing in Western and Northern Europe might be jeopardized. Future research should definitely focus on this specific group of women, but also address more insights into the outcome of sub-optimal medication of severe conditions in pregnancy.

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AUTHOR'S CONTRIBUTION: AL, OS and HN conceived the idea for the study and participated in its design and coordination. AL drafted the manuscript and analyzed the data. MJT, KZ, ACM, MEM, MD, AP, KHA, AR, RGJ, MO, DK, GR, HJ, AP and IB contributed to the data collection. All authors contributed to the interpretation of the results and revised the manuscript critically for important intellectual content. All the authors read and approved the final manuscript.

DATA SHARING STATEMENT: No additional data are available. Researchers can apply for data access for subprojects within the overall aims of the main study 'Medication Use in Pregnancy—an International Study'.

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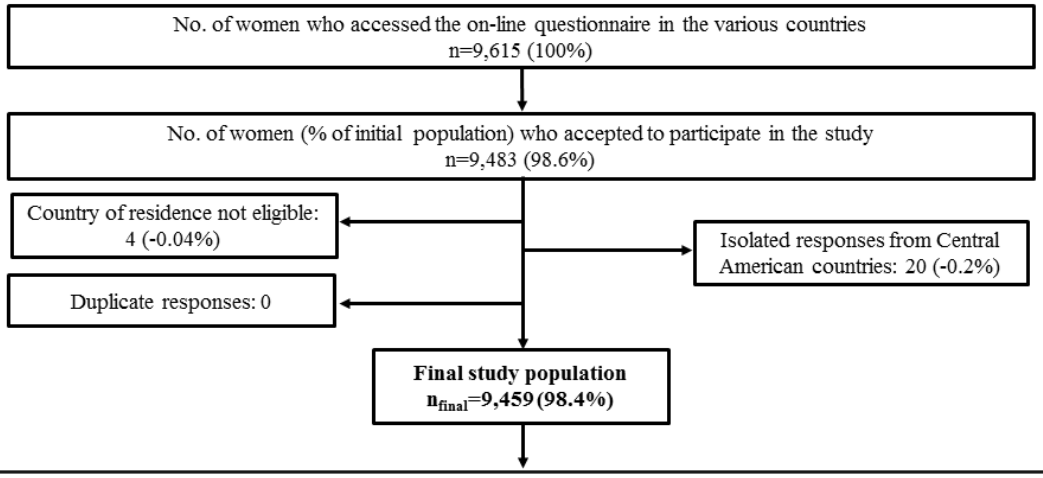
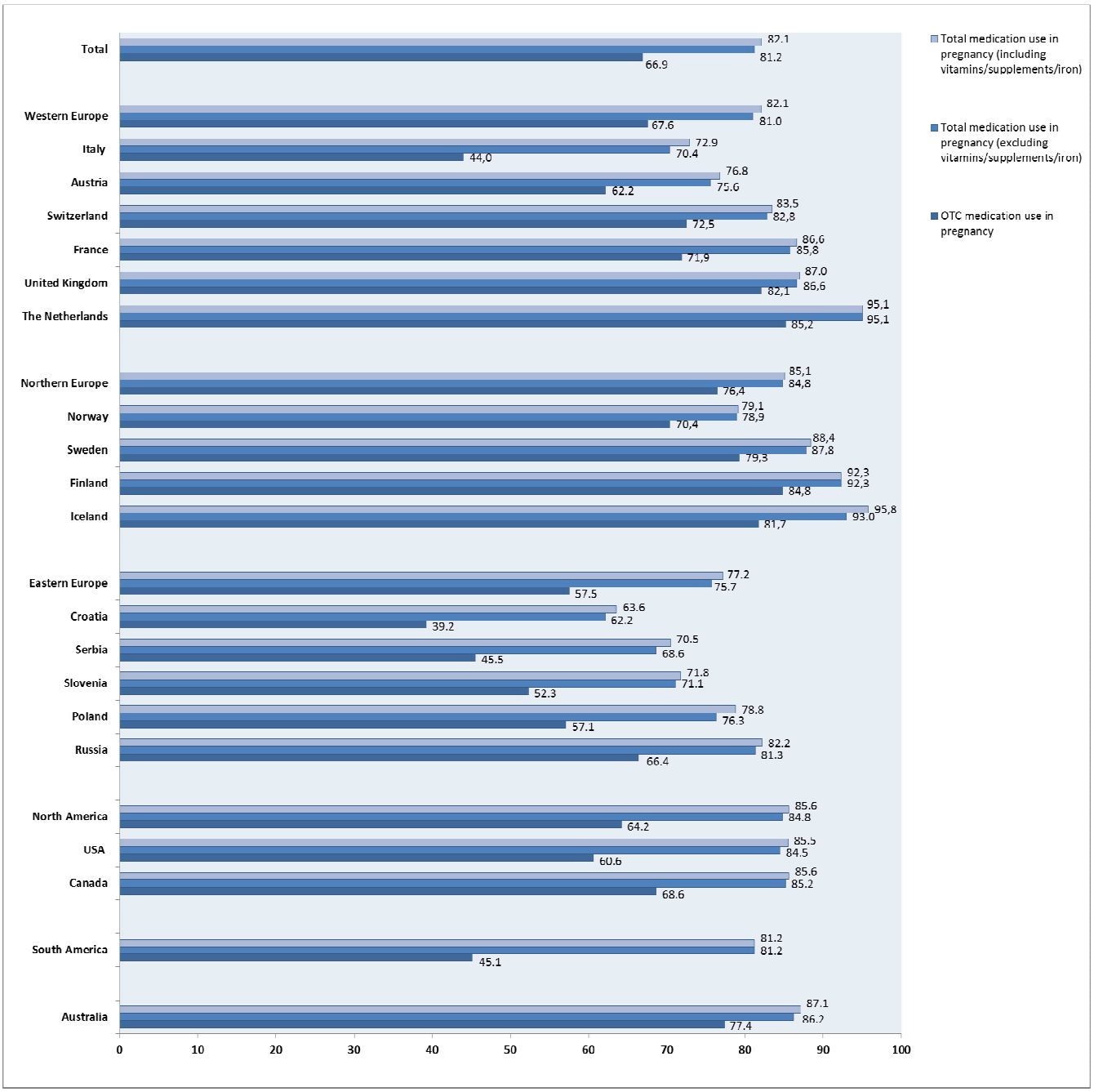
Figure 1: Participant flow-chart to achieve the final sample analyzed



No. (%) of participating women according to region of residency (n=9,459)					
Western Europe n=3,201 (33.8)	**Northern Europe n=2,820 (29.8)**	**Eastern Europe n=2,342 (24.8)**	**North America n=533 (5.6)**	**South America n=346 (3.7)**	**Australia n=217 (2.3)**
United Kingdom (n=1,120) Italy (n=926) Switzerland (n=618) France (n=374) The Netherlands (n=82) Austria (n=81)	Norway (n=1,288) Sweden (n=887) Finland (n=574) Iceland (n=71)	Russia (n=1,008) Poland (n=679) Croatia (n=286) Serbia (n=220) Slovenia (n=149)	USA (n=297) Canada (n=236)	Uruguay (n=151) Paraguay (n=63) Argentina (n=47) Peru (n=18) Bolivia (n=17) Venezuela (n=17) Colombia (n=12) Chile (n=12) Ecuador (n=4) Brazil (n=5)	Australia (n=217)

Figure 2: Proportion of respondents reporting use of any medication - prescribed and/or OTC - during pregnancy (%), including and excluding vitamins, mineral supplements and iron, and proportion of respondents reporting OTC medication use during pregnancy, according to region and country of residency



Appendix 1: Websites used for recruitment and internet penetration rates in each participating country

Country	*Website used for recruitment*	*Internet penetration rates*[*]
	Western Europe	
United Kingdom	*Targeted email to pregnancy forum subscribers*: www.bounty.com *Pregnancy Forums*: www.pregnancyforum.co.uk; www.pregnancyforum.org.uk	93%[1]
Italy	*Pregnancy Forums*: www.gravidanzaonline.it; www.forumsalute.it; www.mammole.it; www.pianetamamma.it; www.miobambino.it *Targeted email to pregnancy forum subscribers*: www.gravidanzaonline.it	70%[1]
Switzerland	www.bebe-bebe.com; www.swissmom.ch	84.2%[2]
France	www.aufeminin.com (*Including ipad application to website subscribers*)	91%[1]
The Netherlands	www.lareb.nl; www.gezondzwangerzijn.nl; www.babybytes.nl	98%[1]
Austria	www.schwangerschaft.at; www.schwangerschafts-blog.at; www.fratz.at; www.netdoctor.at; www.babycenter.at; www.baby-boom.at; www.ekiz-dachverband.at; www.babyguide.at	93% [1]
	Northern Europe	
Norway	www.barnimagen.com; www.klikk.no; www.jormorsiri.no; www.tryggmamamedisin.no	99%[1]
Sweden	www.barntotal.se; www.minbebis.com; www.se.babycenter.com; www.socmed.gu.se	99%[1]
Finland	www.vauva.fi; www.meidanperhe.fi; www.kaksplus.fi	99%[1]
Iceland	*Pregnancy Forums*: www.bland.is	100%[1]
	Eastern Europe	
Russia	www.babyblog.ru; www.littleone.ru *Pregnancy Forums*: www.woman.ru; www.9months.ru; www.bemam; www.280dney.ru; www.iampregnant.ru www.pregnancy.org.ua; www.baby.ru; www.mama66.ru; www.spuzom.ru	47.7%[2]
Poland	www.zzief.umlub.pl *Pregnancy Forums*: www.ebrzuszek.pl; www.babyboom.pl; www.zapytajpolozna.pl; www.planujemydziecko.pl; www.twoja-ciaza.com.pl	84%[1]
Croatia	www.cybermed.hr	80%[1] (data from 2010)

Country	*Website used for recruitment*	*Internet penetration rates*[*]
Serbia	www.ringeraja.rs	52%[1](data from 2009)
Slovenia	*Pregnancy Forums*: www.med.over.net	92%[1]

[*]Indicates the frequency of internet access - at least once a week, including every day - among individuals aged 25- 34 years. Differences between men and women were relatively small. Slightly more than two thirds of men (70%) and 65% of women used the Internet regularly.

Country	*Website used for recruitment*	*Internet penetration rates*
North America		
USA/Canada	www.otispregnancy.org; Facebook page of OTIS; www.babyontheway.com.ca; www.justmommies.com *Pregnancy Forums*: www.babyandbump.com www.babycentre.com.ca; www.thecradle.com; www.talk.sheknows.com; www.parenting.com	Canada: 94%[3] [**] USA: 80.2%[4] [§]
South America	www.otispregnancy.org; Facebook page of OTIS *Pregnancy Forums*: www.semanaasemana.com; www.univision.com; www.elembarazo.net	South America: 48.2%[2]

[**] Indicates individuals aged 16-45 years who used the internet for personal use.
[§]Indicates individuals > 18 years old, access from anywhere; household internet for women is equal to 68.1%; higher percentages are observed for people aged 25-54 years.

Country	*Website used for recruitment*	*Internet penetration rates*[§§]
Australia	www.mothersafe.org.au; www.bubhub.com.au *Pregnancy Forums*: www.abds.org.au; www.birth.com.au	83%[5]

[§§]Indicates households with access to the internet at home.

Sources of internet penetration rates:

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Appendix 2: Socio-demographic characteristics of the study population and general birthing population on individual country[¶]

Appendix 2a: Socio-demographic characteristics in Western European countries (United Kingdom (UK), Italy and Switzerland)

	Study sample in the UK n=1,120 (%)	General birthing population in UK* LB=723,165[1] (%)	Study sample in Italy n=926 (%)	General birthing population in Italy LB=546,606[2] (%)	Study sample in Switzerland n=618 (%)	General birthing population in Switzerland LB=80,808[2] (%)
Mean Age ± sd	30.5 ±- 5.2	29.6[1]	32.3 ± 5.0	31.3[3]	31.6 ± 4.3	31.4[4]
Marital status						
In marriage	63.3	53.2[1]	68.8	75.1[2]	80.0	80.7[4]
Outside marriage	36.7	46.8[1]	31.2	31.5[2]	20.0	19.3[4]
Parity						
No previous children	48.0[†]	41.9[1 †]	59.7	48.7[5]	53.2	-
Educational level						
Less than high school	0.6	16.5[1]	7.0	25.2[6]	11.0	11.7[6]
High school	27.9	37.2[1]	47.2	49.2[6]	13.6	49.2[6]
More than high school	52.1	46.3[1]	44.3	25.6[6]	47.2	39.1[6]
Other	19.3	-	1.5	-	28.2	-
Women smoking before pregnancy	25.2	25.7[7]	34.2	33.3[3]	25.1	25.4[7]
Women smoking during pregnancy	7.1[‡]	13.2[8 ‡]	10.5	22.7[9]	5.5	6.6[10]
Use of alcohol during pregnancy	28.3	24.0[11 §]	17.9	17.7[9]	20.7	29.9[10]
No. of respondents/No. live births [**]	0.9%		1.0%		4.6%	

Abbreviations: LB: Number of live births per year.

[¶]No Statistics Bureaus reports/studies were found for South America.

[*]The figures shown here are statistic estimates for England and Wales. Scotland and Northern Ireland have separate statistical reports. Since more than 85% of the study population in UK were resident in England and about 8% in Wales, we are only showing national statistic data for these two parts of the UK.

[†]Among married women only – as provided by the Statistics Bureau in the UK.

‡Among women resident in England only (as provided by the Statistics Bureau in the UK, data on 4th Quarter of 2011).
§Women reporting at least one occasion during pregnancy of consuming more than four drinks in a day.
**The ratio "No. of respondents/No. live births" is calculated as the proportion (%) of pregnancies included in the study among live births in the country in two months (period of data collection).

Appendix 2b: Socio-demographic characteristics in Western European countries (France, The Netherlands and Austria)

	Study sample in France n=374 (%)	General birthing population in France LB=824,263[2] (%)	Study sample in The Netherlands n=81 (%)	General birthing population in The Netherlands LB=180,060[2] (%)	Study sample in Austria n=82 (%)	General birthing population in Austria LB=78,109[2] (%)
Mean Age ± sd	29.6 ± 4.9	30.1[12]	32.0 ± 6.4	31.0[13]	30.6 ± 4.6	30.0[14]
Marital status						
In marriage	48.9	45.0[2]	69.1	58.2[13]	48.8	59.6[15]
Outside marriage	51.1	55.0[2]	30.8	41.8[13]	51.2	40.4[15]
Parity						
No previous children	52.9	44.2[16]	38.3	46.4[13]	63.4	47.96[15]
Educational level						
Less than high school	1.6	15.4[6]	9.9	15.9[6]	9.8	13.3[6]
High-school	25.1	37.4[6]	66.7	40.2[6]	32.9	64.1[6]
More than high school	57.0	47.2[6]	23.5	43.9[6]	40.2	22.7[6]
Other	16.3	-	-	-	17.1	-
Women smoking before pregnancy	39.3	39.0[16]	34.6	29.5[7]	31.7	32.1[17]
Women smoking during pregnancy	14.2	28.0[16]	14.8	17.1[18]	4.9	-
Use of alcohol during pregnancy	11.5	52.0[19]	11.1	16-35[13]	13.4	-
No. of respondents/No. live births *	0.3%		0.3%		0.6%	

Abbreviations: LB: Number of live births per year.

*The ratio "No. of respondents/No. live births" is calculated as the proportion (%) of pregnancies included in the study among live births in the country in two months (period of data collection).

Appendix 2c: Socio-demographic characteristics in Northern European countries (Norway, Sweden and Finland)

	Study sample in Norway n=1,228 (%)	General birthing population in Norway LB=60,220[2] (%)	Study sample in Sweden n=887 (%)	General birthing population in Sweden LB=111,770[2] (%)	Study sample in Finland n=574 (%)	General birthing population in Finland LB=59,961[2] (%)
Mean Age ± sd	29.0 ± 4.6	29.8 ± 5.3[20]	29.8 ± 5.3	30.3[21]	29.0±5.1	30.1[22]
Marital status						
In marriage	39.1	46.0[20]	40.7	45.8[2]	59.4	57.8[22]
Outside marriage	60.9	53.4[20]	59.3	54.2[2]	40.6	42.0[22]
Unknown	-	0.6[20]			-	0.2[22]
Parity						
No previous children	41.4	42.4[20]	63.1	44.9[21]	35.5	42.2[22]
Educational level		-				
Less than high school	4.5	14.7[6]	5.2	11.1[6]	8.2	7.1[6]
High-school	28.0	31.4[6]	30.0	38.2[6]	36.4	44.5[6]
More than high school	46.9	53.9[6]	60.6	50.6[6]	52.6	48.4[6]
Other	20.7	-	4.2	-	2.8	-
Women smoking before pregnancy	33.5	36.5[7]	25.0	27.2[7]	36.7	19.7[7]
Women smoking during pregnancy	6.8	7.0[20]	5.4	6.5[21]	11.7	15.2[22]
Use of alcohol during pregnancy	4.1	7.4[23]	7.2	5.9[24]	13.9	-
No. of respondents/No. live births *	12.2%		4.8%		5.7%	

Abbreviations: LB: Number of live births per year.

*The ratio "No. of respondents/No. live births" is calculated as the proportion (%) of pregnancies included in the study among live births in the country in two months (period of data collection).

Appendix 2d: Socio-demographic characteristics in Northern European countries (Iceland)

	Study sample in Iceland n=70	General birthing population in Iceland LB=4,492[2]
	(%)	(%)
Age range (years)		
15-20	11.3	5.1[25]
21-25	16.9	19.3[25]
26-30	42.3	34.2[25]
31-35	15.5	27.3[25]
36-40	12.7	11.7[25]
≥41	1.4	2.4[25]
Marital status		
In marriage	31.0	35.0[25]
Outside marriage	69.0	65.0[25]
Parity		
No previous children	47.9	38.1[25]
Educational level		
Less than high school	25.4	21.4[6]
High-school	18.3	30.5[6]
More than high school	43.7	48.1[6]
Other	12.7	-
Women smoking before pregnancy	40.8	35.5[7]
No. of respondents/No. live births *	9.3%	

Abbreviations: LB: Number of live births per year.

*The ratio "No. of respondents/No. live births" is calculated as the proportion (%) of pregnancies included in the study among live births in the country in two months (period of data collection).

Appendix 2e: Socio-demographic characteristics in Eastern European countries (Russia and Poland)

	Study sample in Russia n=1,008	General birthing population in Russia LB=1,796,629[2]	Study sample in Poland n=679	General birthing population in Poland LB=388,416[2]
	(%)	(%)	(%)	(%)
Mean Age ± sd	27.7 ± 4.8	27.4[26]	27.1 ± 4.1	28.6[27 *]
Marital status				
In marriage	85.3	73.9[26]	85.0	79.4[27]
Outside marriage	14.7	26.1[26]	15.0	20.6[27]
Parity				
No previous children	57.9	-	40.6	50.1[27]
Educational level				
Less than high school	1.6	-	1.9	8.7[27]
High-school	9.3	-	31.1	49.6[27]
More than high school	75.1	-	65.1	41.6[27]
Other	14.0	-	1.9	-
Women smoking before pregnancy	46.1	30.8[28]	49.2	25.0[29]
Women smoking during pregnancy	9.6	4.3-6.5[30,31]	12.8	22-30[29]
Use of alcohol during pregnancy	26.0	60.0[32]	9.6	15.3[33]
No. of respondents/No. live births [†]	0.3%		1.0%	

Abbreviations: LB: Number of live births per year.

[*]Median age of women at birth, not mean age.

[†]The ratio "No. of respondents/No. live births" is calculated as the proportion (%) of pregnancies included in the study among live births in the country in two months (period of data collection).

Appendix 2f: Socio-demographic characteristics in Eastern European countries (Croatia, Serbia and Slovenia)

	Study sample in Croatia n=286	General birthing population in Croatia LB=41,197[2]	Study sample in Serbia n=220	General birthing population in Serbia LB=65,598[2]	Study sample in Slovenia n=149	General birthing population in Slovenia LB=21,947[2]
	n (%)	(%)	n (%)	(%)	n (%)	(%)
Mean Age ± sd	29.1 ± 4.5*	27.7[34]	29.2 ± 3.9*	28.7[35]	31.7 ± 4.5	30.4[36]
Marital status						
In marriage	83.9	86.7[34]	90.1	76.1[35]	47.0	43.2[36]
Outside marriage	16.1	13.3[34]	9.9	23.9[35]	53.0	56.8[36]
Unknown	-	-	-	-	-	-
Parity						
No previous children	50.7	46.9[34]	46.8	51.1[35]	45.6	48.5[36]
Educational level						
Less than high school	1.0	3.1[34]	0.9	15.9[37]	2.0	8.5[36]
High-school	36.7	52.5[34]	33.6	54.9[37]	24.8	48.5[36]
More than high school	61.2	44.4[34]	61.8	29.2[37]	69.1	43.0[36]
Other	1.0	-	3.6	-	4.0	-
Women smoking before pregnancy	50.0	34.4[34]	49.1	29.9[38]	32.9	34.4[7]
Women smoking during pregnancy	18.8	23.1[39]	18.2	18.4[40]	6.7	9.6-11.2[41]
Use of alcohol during pregnancy	12.6	15.5[42]	15.0	-	32.2	-
No. of respondents/No. live births †	4.2%		2.0%		4.1%	

Abbreviations: LB: Number of live births per year.

*Mean age for first child (as it is available from the Statistics Bureau reports in Croatia and Serbia).

†The ratio "No. of respondents/No. live births" is calculated as the proportion (%) of pregnancies included in the study among live births in the country in two months (period of data collection).

Appendix 2g: Socio-demographic characteristics in North American countries (USA, Canada) and Australia.

	Study sample in The USA n=297	General birthing population in USA[43] LB=3,999,386	Study sample in Canada n=236	General birthing population in Canada[44] LB=377,636	Study sample in Australia n=217	General birthing population in Australia[45] LB=301,617
	n (%)	(%)	n (%)	(%)	n (%)	(%)
Age range (years)						
15-19	4.7	9.3[43]	2.1	3.9[44]	2.3	3.8[45]
20-24	18.2	23.8[43]	25.0	14.6[44]	8.8	13.8[45]
25-29	28.3	28.3[43]	30.1	30.2[44]	31.8	27.9[45]
30-34	29.3	24.1[43]	30.5	32.2[44]	27.6	31.7[45]
35-39	15.2	11.6[43]	11.0	15.6[44]	22.1	18.4[45]
40-44	4.0	2.7[43]	1.3	3.1[44]	6.9	4.0[45]
≥45	0.3	0.2[43]	-	0.2[44]	0.5	0.2[45]
Mean Age ± sd	29.3 ± 6.1	-	28.3 ± 5.2	29.6[44]	31.1 ± 5.7	30.7[45]
Marital status						
In marriage	67.0	59.2[46]	42.4	60.4[44]	70.5	65.8[45]
Outside marriage	33.0	39.9[46]	57.6	28.8[44]	29.5	34.2[45]
Unknown	-	0.9[46]	-	10.8[44]	-	-
Parity						
No previous children	41.1	40.1[43]	48.3	43.3[44]	47.9	43.8[45]
Educational level						
Less than high school	2.7	17.4[47]	1.3	8.4[48]	0.5	20.6[49]
High-school	25.3	24.4[47]	24.6	-	29.0	
More than high school	62.0	58.2[47]	67.8	69.6[48]	63.1	56.0[50]
Other	10.1	-	6.4	-	7.4	-
Women smoking before pregnancy	28.3	21.5[51]	29.2	22.0[52]	29.1	29.9[53]
Women smoking during pregnancy	8.1	10.2[54]	16.1	13.4[48]	14.3	14.5[55]
Use of alcohol during pregnancy	17.5	15.5[51]	16.1	10.5[48]	27.2	29.0[56]

	Study sample in The USA n=297 n (%)	General birthing population in USA[43] LB=3,999,386 (%)	Study sample in Canada n=236 n (%)	General birthing population in Canada[44] LB=377,636 (%)	Study sample in Australia n=217 n (%)	General birthing population in Australia[45] LB=301,617 (%)
No. of respondents/No. live births*	0.04%		0.4%		0.4%	

Abbreviations: LB: Number of live births per year.

*The ratio "No. of respondents/No. live births" is calculated as the proportion (%) of pregnancies included in the study among live births in the country in two months (period of data collection).

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Appendix 3: Overall medication use on 1st and 2nd ATC level according to timing of use in pregnancy (n=9,459)*

Anatomical Therapeutic Chemical (ATC) classification index 1st and 2nd levels		Anytime during pregnancy n (%)	1st trimester n (%)	2nd trimester n (%)	3rd trimester n (%)
A	**Alimentary tract and metabolism**	**4,275 (45.2)**	**2,786 (29.5)**	**3,390 (35.8)**	**3,160 (33.4)**
A01	Stomatological preparations	62 (0.7)	42 (0.4)	52 (0.5)	46 (0.5)
A02	*Drugs for acid related disorders*	3,242 (34.3)	2,034 (21.5)	2,634 (27.8)	2,615 (27.6)
A03	Drugs for functional gastrointestinal disorders	650 (6.9)	543 (5.7)	512 (5.4)	381 (4.0)
A04	Antiemetics and antinauseants	136 (1.4)	124 (1.3)	114 (1.2)	81 (0.9)
A05	Bile and liver therapy	24 (0.3)	15 (0.2)	17 (0.2)	16 (0.2)
A06	*Laxatives*	978 (10.3)	696 (7.4)	835 (8.8)	735 (7.8)
A07	Antidiarrheals, intestinal antiinflammatory/antiinfective agents	89 (0.9)	61 (0.6)	69 (0.7)	57 (0.6)
A09	Digestives, incl. enzymes	9 (0.1)	7 (0.1)	8 (0.1)	3 (0.0)
A10	Drugs used in diabetes	85 (0.9)	57 (0.6)	58 (0.6)	45 (0.5)
-	Unsecified medications for nausea	6 (0.1)	5 (0.1)	4 (0.0)	3 (0.0)
B	**Blood and blood forming organs**	**148 (1.6)**	**89 (0.9)**	**102 (1.1)**	**79 (0.8)**
B01	*Antithrombotic agents*	135 (1.4)	78 (0.8)	95 (1.0)	72 (0.8)
B02	Antihemorrhagics	5 (0.1)	4 (0.0)	2 (0.0)	3 (0.0)
B05	Blood substitutes and perfusion solutions	7 (0.1)	5 (0.1)	5 (0.1)	2 (0.0)
B06	Other hematological agents	3 (0.0)	2 (0.0)	2 (0.0)	3 (0.0)
C	**Cardiovascular system**	**202 (2.1)**	**132 (1.4)**	**161 (1.7)**	**133 (1.4)**
C01	Cardiac therapy	7 (0.1)	4 (0.0)	5 (0.1)	4 (0.1)
C02	*Antihypertensives*	56 (0.6)	34 (0.4)	42 (0.4)	31 (0.3)
C03	Diuretics	6 (0.1)	5 (0.1)	3 (0.0)	2 (0.0)
C04	Peripheral vasodilators	3 (0.0)	3 (0.0)	3 (0.0)	3 (0.0)
C05	Vasoprotectives	44 (0.5)	24 (0.3)	35 (0.4)	31 (0.3)
C07	*Beta blocking agents*	74 (0.8)	51 (0.5)	59 (0.6)	51 (0.5)
C08	Calcium channel blockers	21 (0.2)	16 (0.2)	18 (0.2)	13 (0.1)
C09	Agents acting on the renin-angiotensin system	4 (0.0)	2 (0.0)	2 (0.0)	2 (0.0)
C10	Lipid modifying agents	5 (0.1)	3 (0.0)	4 (0.0)	4 (0.0)
-	Unspecified medications for hypertension	4 (0.0)	3 (0.0)	3 (0.0)	2 (0.0)

Anatomical Therapeutic Chemical (ATC) classification index 1st and 2nd levels		Anytime during pregnancy n (%)	1st trimester n (%)	2nd trimester n (%)	3rd trimester n (%)
D	**Dermatologicals**	**162 (1.7)**	**116 (1.2)**	**127 (1.3)**	**103 (1.1)**
D01	*Antifungals for dermatological use*	38 (0.4)	28 (0.3)	33 (0.3)	27 (0.3)
D02	Emollients and protectives	14 (0.1)	11 (0.1)	12 (0.1)	10 (0.1)
D03	Preparations for treatment of wounds and ulcers	4 (0.0)	3 (0.0)	3 (0.0)	3 (0.0)
D04	Antipruritics, incl. antihistamines, anesthetics, etc.	6 (0.1)	3 (0.0)	5 (0.1)	4 (0.0)
D05	Antipsoriatics	3 (0.0)	1 (0.0)	1 (0.0)	1 (0.0)
D06	Antibiotics and chemotherapeutics for dermatological use	21 (0.2)	15 (0.2)	16 (0.2)	13 (0.1)
D07	*Corticosteroids, dermatological preparations*	56 (0.6)	40 (0.4)	39 (0.4)	31 (0.3)
D08	Antiseptics and disinfectants	14 (0.1)	9 (0.1)	10 (0.1)	9 (0.1)
D09	Medicated dressings	5 (0.1)	5 (0.1)	5 (0.1)	3 (0.0)
D10	Anti-acne preparations	4 (0.0)	4 (0.0)	4 (0.0)	2 (0.0)
D11	Other dermatological preparations	1 (0.0)	-	1 (0.0)	1 (0.0)
-	Unspecified medications for skin disorders	5 (0.1)	4 (0.0)	4 (0.0)	3 (0.0)
G	**Genito urinary system and sex hormones**	**488 (5.2)**	**318 (3.4)**	**394 (4.2)**	**303 (3.2)**
G01	*Gynecological antiinfectives and antiseptics*	406 (4.3)	255 (2.7)	337 (3.6)	258 (2.7)
G02	Other gynecologicals	13 (0.1)	10 (0.1)	10 (0.1)	8 (0.1)
G03	Sex hormones and modulators of the genital system	68 (0.7)	55 (0.6)	50 (0.5)	36 (0.4)
G04	Urologicals	12 (0.1)	8 (0.1)	7 (0.1)	8 (0.1)
H	**Systemic hormonal preparations, excl. sex hormones and insulins**	**486 (5.1)**	**304 (3.2)**	**346 (3.7)**	**262 (2.8)**
H01	Pituitary and hypothalamic hormones and analogues	4 (0.0)	4 (0.0)	3 (0.0)	4 (0.0)
H02	Corticosteroids for systemic use	93 (1.0)	64 (0.7)	78 (0.8)	63 (0.7)
H03	*Thyroid therapy*	397 (4.2)	242 (2.6)	273 (2.9)	201 (2.1)
J	**Antiinfectives for systemic use**	**1,381 (14.6)**	**874 (9.2)**	**1,107 (11.7)**	**943 (10.0)**
J01	*Antibacterials for systemic use*	1,325 (14.0)	840 (8.9)	1,061 (11.2)	908 (9.6)
J02	Antimycotics for systemic use	23 (0.2)	16 (0.2)	21 (0.2)	17 (0.2)
J05	Antivirals for systemic use	39 (0.4)	27 (0.3)	30 (0.3)	26 (0.3)
J06	Immune sera and immunoglobulins	4 (0.0)	2 (0.0)	3 (0.0)	4 (0.0)
J07	Vaccines	10 (0.1)	5 (0.1)	8 (0.1)	5 (0.1)

Anatomical Therapeutic Chemical (ATC) classification index 1st and 2nd levels		Anytime during pregnancy n (%)	1st trimester n (%)	2nd trimester n (%)	3rd trimester n (%)
L	**Antineoplastic and immunomodulating agents**	**134 (1.4)**	**83 (0.9)**	**117 (1.2)**	**97 (1.0)**
L01	Antineoplastic agents	4 (0.0)	3 (0.0)	4 (0.0)	1 (0.0)
L03	*Immunostimulants*	96 (1.0)	58 (0.6)	86 (0.9)	78 (0.8)
L04	Immunosuppressants	34 (0.4)	22 (0.2)	27 (0.3)	18 (0.2)
M	**Musculo-skeletal system**	**571 (6.0)**	**416 (4.4)**	**437 (4.6)**	**380 (4.0)**
M01	*Antiinflammatory and antirheumatic products*	515 (5.4)	378 (4.0)	396 (4.2)	342 (3.6)
M02	Topical products for joint and muscular pain	54 (0.6)	37 (0.4)	41 (0.4)	41 (0.4)
M03	Muscle relaxants	8 (0.1)	8 (0.1)	4 (0.0)	1 (0.0)
M05	Drugs for treatment of bone diseases	1 (0.0)	-	1 (0.0)	-
M09	Other drugs for disorders of the musculo-skeletal system	2 (0.0)	2 (0.0)	2 (0.0)	2 (0.0)
-	Unspecified medications for headache	2 (0.0)	1 (0.0)	1 (0.0)	1 (0.0)
N	**Nervous system**	**5,441 (57.5)**	**3,638 (38.5)**	**4,247 (44.9)**	**3,449 (36.5)**
N01	Anesthetics	13 (0.1)	10 (0.1)	7 (0.1)	8 (0.1)
N02	*Analgesics*	5,297 (56.0)	3,562 (37.7)	4,171 (44.1)	3,387 (35.8)
N03	Antiepileptics	76 (0.8)	46 (0.5)	49 (0.5)	42 (0.4)
N05	*Psycholeptics*	210 (2.2)	173 (1.8)	164 (1.7)	138 (1.5)
N06	*Psychoanaleptics*	275 (2.9)	211 (2.2)	213 (2.3)	179 (1.9)
N07	Other nervous system drugs	6 (0.1)	4 (0.0)	5 (0.1)	3 (0.0)
-	Unspecified analgesics/medications for the nervous system	52 (0.5)	38 (0.4)	43 (0.5)	35 (0.4)
P	**Antiparasitic products, insecticides and repellents**	**26 (0.3)**	**20 (0.2)**	**22 (0.2)**	**16 (0.2)**
P01	*Antiprotozoals*	25 (0.3)	20 (0.2)	22 (0.2)	16 (0.2)
P02	Anthelmintics	1 (0.0)	-	-	-
R	**Respiratory system**	**2,609 (27.6)**	**1,878 (19.9)**	**2,047 (21.6)**	**1,702 (18.0)**
R01	*Nasal preparations*	1,547 (16.4)	1,079 (11.4)	1,229 (13.0)	1,046 (11.1)
R02	Throat preparations	167 (1.8)	110 (1.2)	131 (1.4)	122 (1.3)
R03	*Drugs for obstructive airway diseases*	396 (4.2)	269 (2.8)	304 (3.2)	242 (2.6)
R05	Cough and cold preparations	152 (1.6)	103 (1.1)	125 (1.3)	101 (1.1)
R06	*Antihistamines for systemic use*	912 (9.6)	777 (8.2)	740 (7.8)	580 (6.1)

Anatomical Therapeutic Chemical (ATC) classification index 1st and 2nd levels		Anytime during pregnancy n (%)	1st trimester n (%)	2nd trimester n (%)	3rd trimester n (%)
R07	Other respiratory system products	3 (0.0)	2 (0.0)	3 (0.0)	3 (0.0)
-	Unspecified medications of the respiratory system	142 (1.5)	101 (1.1)	118 (1.2)	99 (1.0)
S	**Sensory organs**	**45 (0.5)**	**33 (0.3)**	**38 (0.4)**	**28 (0.3)**
S01	*Ophthalmologicals*	33 (0.3)	24 (0.3)	28 (0.3)	23 (0.2)
S02	Otologicals	5 (0.1)	3 (0.0)	4 (0.0)	2 (0.0)
S03	Ophthalmological and otological preparations	3 (0.0)	2 (0.0)	2 (0.0)	2 (0.0)
-	Unspecified medications for eye disorders	5 (0.1)	4 (0.0)	5 (0.1)	2 (0.0)
V	**Various**	15 (0.2)	10 (0.1)	11 (0.1)	9 (0.1)
Total medication use (any ATC)		**7,678 (81.2)**	**4,710 (49.8)**	**5,538 (58.5)**	**4,663 (49.3)**

*The most common medication groups within each ATC class are in italics. Exposure timing is defined as follows: 1st trimester (gestational weeks 0-12), 2nd trimester (gestational week 13-24), 3rd trimester (gestational week 25 and up to childbirth).

Appendix 4: Prevalence of acute/short-term illnesses and most common medications used at any time during pregnancy by ATC level, indication for use and region (n=9,459) [*†]

	REGION						
Prevalence of acute/short-term illnesses in pregnancy and related medication use, overall and by drug groups	**Western Europe n=3,201** *n (%)*	**Northern Europe n=2,820** *n (%)*	**Eastern Europe n=2,342** *n (%)*	**North America n=533** *n (%)*	**South America n=346** *n (%)*	**Australia n=217** *n (%)*	**Total n=9,459** *n (%)*
Prevalence of headache	1,699 (53.1)	1,657 (58.8)	1,138 (48.6)	373 (70.0)	197 (56.9)	147 (67.7)	5,211 (55.1)
Medication use for headache, total	**1,027 (32.1)**	**1,057 (37.5)**	**522 (22.3)**	**226 (42.4)**	**121 (35.0)**	**109 (50.2)**	**3,062 (32.4)**
By drug group							
Paracetamol (incl. combinations) (N02BE)	994 (31.1)	1,009 (35.8)	372 (15.9)	206 (38.6)	92 (26.6)	101 (46.5)	2,774 (29.3)
Non-steroidal antiinflammatory drugs (M01A)	28 (0.9)	78 (2.8)	37 (1.6)	18 (3.0)	18 (5.2)	2 (0.9)	179 (1.9)
Acetylsalicylic acid (incl. combinations) (N02BA)	7 (0.2)	4 (0.1)	81 (3.5)	1 (0.2)	4 (1.2)	2 (0.9)	99 (1.0)
Opioid analgesics (N02A)	14 (0.4)	46 (1.6)	3 (0.1)	3 (0.6)	-	13 (6.0)	79 (0.8)
Selective serotonin (5-HT_1) agonists (N02CC)	6 (0.2)	22 (0.8)	2 (0.1)	3 (0.6)	-	1 (0.5)	34 (0.4)
Prevalence of heartburn	2,196 (68.6)	1,875 (66.5)	1,425 (60.8)	374 (70.2)	248 (71.7)	141 (65.0)	6,259 (66.2)
Medication use for heartburn, total	**984 (30.7)**	**885 (31.4)**	**525 (22.4)**	**202 (37.9)**	**88 (25.4)**	**72 (33.2)**	**2,756 (29.1)**
By drug group							
Antacids (aluminium, salts combinations, antiflatulents)	384 (12.0)	503 (17.8)	440 (18.8)	51 (9.6)	63 (18.2)	20 (9.2)	1,461 (15.4)
Alginic acid complex/sucralfate/bismuth (A02BX)	569 (17.8)	332 (11.8)	86 (3.7)	4 (0.8)	3 (0.9)	14 (6.5)	1,008 (10.7)
Proton pump inhibitors (A02BC)	77 (2.4)	86 (3.0)	4 (0.2)	13 (2.4)	3 (0.9)	7 (3.2)	190 (2.0)
Antacid with calcium (A02AC)	20 (0.6)	13 (0.5)	10 (0.4)	123 (23.1)	2 (0.6)	9 (4.1)	177 (1.9)
H_2 receptor antagonists (A02BA)	27 (0.8)	27 (1.0)	7 (0.3)	45 (8.4)	5 (1.4)	38 (17.5)	149 (1.6)
Prevalence of pain	2,150 (67.2)	2,067 (73.3)	1,484 (63.4)	369 (69.2)	248 (71.7)	157 (72.4)	6,475 (68.5)
Medication use for pain, total	**533 (16.7)**	**426 (15.1)**	**147 (6.3)**	**110 (20.6)**	**80 (23.1)**	**59 (27.2)**	**1,355 (14.3)**
By drug group							
Paracetamol (incl. combinations) (N02BE)	444 (13.9)	374 (13.3)	65 (2.8)	99 (18.6)	44 (12.7)	55 (25.3)	1,081 (11.4)
Non-steroidal antiinflammatory drugs (M01A)	19 (0.6)	36 (1.3)	21 (0.9)	11 (2.1)	24 (6.9)	3 (1.4)	114 (1.2)
Opioid analgesics (N02A)	39 (1.2)	51 (1.8)	2 (0.1)	4 (0.8)	-	12 (5.5)	108 (1.1)

Prevalence of acute/short-term illnesses in pregnancy and related medication use, overall and by drug groups	REGION						
	Western Europe n=3,201 *n (%)*	Northern Europe n=2,820 *n (%)*	Eastern Europe n=2,342 *n (%)*	North America n=533 *n (%)*	South America n=346 *n (%)*	Australia n=217 *n (%)*	Total n=9,459 *n (%)*
Prevalence of nausea	2,324 (72.6)	2,244 (79.6)	1,503 (64.2)	409 (76.7)	238 (68.8)	173 (79.7)	6,891 (72.9)
Medication use for nausea, total	**413 (12.9)**	**380 (13.5)**	**140 (6.0)**	**128 (24.0)**	**71 (20.5)**	**39 (18.0)**	**1,171 (12.4)**
By drug group							
First generation antihistamines (R06A)	150 (4.7)	259 (9.2)	21 (0.9)	84 (15.9)	9 (2.6)	4 (1.8)	527 (5.6)
Metoclopramide/domperidone/bromopride (A03FA)	134 (4.2)	69 (2.4)	27 (1.2)	10 (1.9)	45 (13.0)	25 (11.5)	310 (3.3)
Serotonin antagonists (A04AA)	4 (0.1)	8 (0.3)	1 (0.0)	28 (5.3)	1 (0.3)	11 (5.1)	53 (0.6)
Prevalence of UTI	513 (16.0)	327 (11.6)	452 (19.3)	93 (17.4)	92 (26.6)	25 (11.5)	1,502 (15.9)
Medication use for UTI, total	**315 (9.8)**	**221 (7.8)**	**192 (8.2)**	**56 (10.5)**	**63 (18.2)**	**17 (7.8)**	**864 (9.1)**
By drug group							
Unspecified penicillins (J01C-)	94 (2.9)	99 (3.5)	46 (2.0)	16 (3.0)	17 (4.9)	1 (0.5)	273 (2.9)
NOS Antibacterials for systemic use (J01-)	116 (3.6)	85 (3.0)	25 (1.1)	20 (3.8)	14 (4.0)	6 (2.8)	266 (2.8)
Penicillins with extended spectrum ± beta-lactamase inhibitors (J01CA/J01CR)	85 (2.7)	78 (2.8)	44 (1.9)	14 (2.6)	17 (4.9)	1 (0.5)	239 (2.5)
Nitrofurantoin (J01XE)	7 (0.2)	25 (0.9)	54 (2.3)	10 (1.9)	3 (0.9)	1 (0.5)	100 (1.1)
Cephalosporins (J01D)	20 (0.6)	10 (0.4)	36 (1.5)	2 (0.4)	11 (3.2)	6 (2.8)	85 (0.9)
Total prevalence of any acute/short-term illness	**3,159 (98.7)**	**2,803 (99.4)**	**2,299 (98.2)**	**523 (98.1)**	**341 (98.6)**	**214 (98.6)**	**9,339 (98.7)**
Total medication use for any acute/short-term illness	**2,224 (69.5)**	**1,954 (69.3)**	**1,474 (62.9)**	**403 (75.6)**	**250 (72.3)**	**164 (75.6)**	**6,469 (68.4)**

*Countries are grouped into regions as shown in Figure 1.

†Sums of percentages do not add up to total medication use as only most common medication groups are presented. Rates do not include mineral supplements, vitamins, iron, and herbal or alternative medicine products.

Abbreviations: UTI: Urinary tract infection; NOS: Not otherwise specified.

Appendix 5: Prevalence of chronic/long-term disorders and most common medications used at any time during pregnancy by ATC level, indication for use and region (n=9,459) [*†]

	REGION						
Prevalence of chronic/long-term disorders in pregnancy and related medication use, overall and by drug groups	**Western Europe n=3,201** *n (%)*	**Northern Europe n=2,820** *n (%)*	**Eastern Europe n=2,342** *n (%)*	**North America n=533** *n (%)*	**South America n=346** *n (%)*	**Australia n=217** *n (%)*	**Total n=9,459** *n (%)*
Prevalence of hypothyroidism	130 (4.1)	118 (4.2)	105 (4.5)	22 (4.1)	11 (3.2)	6 (2.8)	392 (4.1)
Medication use for hypothyroidism, total	**118 (3.7)**	**113 (4.0)**	**96 (4.1)**	**21 (3.9)**	**9 (2.6)**	**6 (2.8)**	**363 (3.8)**
By drug group							
Thyroid hormone, levothyroxine (H03AA01)	117 (3.7)	112 (4.0)	89 (3.8)	21 (3.9)	9 (2.6)	6 (2.8)	354 (3.7)
Prevalence of asthma	163 (5.1)	193 (6.8)	58 (2.5)	43 (8.1)	12 (3.5)	24 (11.1)	493 (5.2)
Medication use for asthma, total	**122 (3.8)**	**133 (4.7)**	**38 (1.6)**	**35 (6.6)**	**8 (2.3)**	**24 (11.1)**	**360 (3.8)**
By drug group							
Inhalant selective beta-2 agonists (R03AC)	94 (2.9)	66 (2.3)	26 (1.1)	32 (6.0)	7 (2.0)	24 (11.1)	249 (2.6)
Adrenergics and other drugs for COPD (R03AK)	33 (1.0)	46 (1.6)	10 (0.4)	3 (0.6)	2 (0.6)	7 (3.2)	101 (1.1)
Inhalant glucocorticoids (R03BA)	28 (0.9)	40 (1.4)	13 (0.6)	12 (2.3)	-	4 (1.8)	97 (1.0)
Systemic selective beta-2 agonists (R03CC)	-	30 (1.1)	-	2 (0.4)	-	-	32 (0.3)
Prevalence of allergy	205 (6.4)	372 (13.2)	163 (7.0)	51 (9.6)	20 (5.8)	23 (10.6)	834 (8.8)
Medication use for allergy, total	**66 (2.1)**	**171 (6.1)**	**65 (2.8)**	**24 (4.5)**	**13 (3.8)**	**17 (7.8)**	**356 (3.8)**
By drug group							
Second generation antihistamines (R06A)	29 (0.9)	104 (3.7)	27 (1.2)	17 (3.2)	4 (1.2)	5 (2.3)	186 (2.0)
Nasal corticosteroids (R01AD)	11 (0.3)	32 (1.1)	17 (0.7)	-	-	7 (3.2)	67 (0.7)
First generation antihistamines (R06A)	13 (0.4)	29 (1.0)	10 (0.4)	9 (1.7)	6 (1.7)	4 (1.8)	71 (0.8)
Prevalence of depression	95 (3.0)	144 (5.1)	29 (1.2)	52 (9.8)	4 (1.2)	25 (11.5)	349 (3.7)
Medication use for depression, total	**61 (1.9)**	**100 (3.5)**	**11 (0.5)**	**29 (5.4)**	**1 (0.3)**	**23 (10.6)**	**225 (2.4)**
By drug group							
SSRI antidepressants (N06AB)	44 (1.4)	82 (2.9)	6 (0.3)	14 (2.6)	-	14 (6.5)	160 (1.7)
SNRIs/mianserin/trazodone/mirtazapine/bupropionAnxiolytic	9 (0.3)	11 (0.4)	1 (0.0)	15 (2.8)	-	7 (3.2)	43 (0.5)

Prevalence of chronic/long-term disorders in pregnancy and related medication use, overall and by drug groups	REGION						
	Western Europe n=3,201 *n (%)*	Northern Europe n=2,820 *n (%)*	Eastern Europe n=2,342 *n (%)*	North America n=533 *n (%)*	South America n=346 *n (%)*	Australia n=217 *n (%)*	Total n=9,459 *n (%)*
s, benzodiazepine (N05BA)	6 (0.2)	2 (0.1)	5 (0.2)	-	-	1 (0.5)	14 (0.1)
Antipsychotics quetiapine/olanzapine (N05AH)	2 (0.1)	4 (0.1)	-	3 (0.6)	-	3 (1.4)	12 (0.1)
Total prevalence of any chronic/long-term disorder	**617 (19.3)**	**831 (29.5)**	**576 (24.6)**	**154 (28.9)**	**51 (14.7)**	**72 (33.2)**	**2,301 (24.3)**
Total medication use for any chronic/long-term disorder	**462 (14.4)**	**593 (21.0)**	**322 (13.7)**	**119 (22.3)**	**38 (11.0)**	**70 (32.3)**	**1,604 (17.0)**

*Countries are grouped into regions as shown in Figure 1.

†Sums of percentages do not add up to total medication use as only most common medication groups are presented. Rates do not include mineral supplements, vitamins, iron, and herbal or alternative medicine products.

Abbreviations: COPD: Chronic obstructive pulmonary disease; SSRI: Selective serotonin re-uptake inhibitors; SNRI: Serotonin–noradrenaline reuptake inhibitors.

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation
Title and abstract	1	✗ (*a*) Indicate the study's design with a commonly used term in the title or the abstract
		✗ (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	✗ Explain the scientific background and rationale for the investigation being reported
Objectives	3	✗ State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	✗ Present key elements of study design early in the paper
Setting	5	✗ Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	✗ (*a*) Give the eligibility criteria, and the sources and methods of selection of participants
Variables	7	✗ Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	✗ For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	✗ Describe any efforts to address potential sources of bias
Study size	10	✗ Explain how the study size was arrived at
Quantitative variables	11	✗ Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	✗ (*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		✗ (*c*) Explain how missing data were addressed
		(*d*) If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	✗ (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	✗ (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
Outcome data	15*	✗ Report numbers of outcome events or summary measures
Main results	16	✗ (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		✗ (*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a

		meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	✗ Summarise key results with reference to study objectives
Limitations	19	✗ Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	✗ Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	✗ Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	✗ Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Medication use in pregnancy: a multinational perspective

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Medication use in pregnancy: a multinational perspective

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ABSTRACT

Objectives: Inter-country comparability between studies on medication use in pregnancy is difficult due to dissimilarities in study design and methodology. This study aimed to examine patterns and factors associated with medications use in pregnancy from a multinational perspective, with emphasis on type of medication utilized and indication for use.

Design: Cross-sectional, internet-based study performed within the period from 1-Oct-2011 to 29-Feb-2012. Uniform collection of drug utilization data was performed via an anonymous online questionnaire.

Setting: Multinational study in Europe (Western, Northern, and Eastern), North and South America, and Australia.

Participants: Pregnant women and new mothers with children less than one year of age.

Primary and secondary outcome measures: Prevalence and factors associated with medication use for acute/short-term illnesses, chronic/long-term disorders and over-the-counter (OTC) medication use.

Results: The study population included 9,459 women whereof 81.2% reported use of at least one medication (prescribed or OTC) during pregnancy. Overall, OTC medication use occurred in 66.9% of the pregnancies, whereas 68.4% and 17.0% of women reported use of at least one medication for treatment of acute/short-term illnesses and chronic/long-term disorders, respectively. The extent of self-reported

medicated illnesses and types of medication used by indication varied across regions, especially in relation to urinary tract infections, depression or OTC nasal sprays. Women with higher age or lower educational level, housewives, or women with an unplanned pregnancy were those most often reporting use of medication for chronic/long-term disorders. Immigrant women in Western (aOR: 0.55, 95% CI: 0.34-0.87) and Northern Europe (aOR: 0.50, 95% CI: 0.31-0.83) were less likely to report use of medication for chronic/long-term disorders during pregnancy than non-immigrants.

Conclusions:

In this study, the majority of women in Europe, North America, South America and Australia used at least one medication during pregnancy. There was a substantial inter-region variability in the types of medication used.

ARTICLE SUMMARY

Strengths and limitations of this study

- Uniform data collection of drug utilization data across all participating countries allows for inter-country comparability of the prevalence of medication use during pregnancy, up to now impeded by differences in study design and methodology.
- The study adds a multinational perspective on OTC medication use during pregnancy to the limited number of studies quantifying the extent of self-medication during pregnancy.
- Lack of validity of the self-reported diagnoses is a limitation since all disorders and related medication use were self-reported by the study participants.
- An internet survey as a study method impedes calculation of a conventional response rate and may cause selection bias of the target population.

INTRODUCTION

Ethical reasons preclude inclusion of pregnant women in the vast majority of pre-marketing clinical trials.[1] As a consequence, most medications are placed onto the market without a directly established safety profile in human pregnancy.[2] So far, few medications have been shown to be major teratogens, yet the risk of minor teratogenicity or of more subtle effects on fetal development still have to be determined for most of them.[3] Despite this, medication use during pregnancy is common. Mitchell et al. found that use of medications, either prescribed or purchased over-the-counter (OTC), occurred in 88.8% of all pregnancies in the USA.[4] In Europe, prevalence estimates of prescribed medication use vary considerably across countries, ranging from 26% in Serbia to 93% in France.[5-10] Such inter-country variability could, at least in part, be caused by differences in study design, methodology and exposure ascertainment across studies.[11] Uniform collection of drug utilization data during pregnancy between countries may overcome such drawbacks, allowing for inter-country comparability of prevalence estimates and shedding light on differences in prenatal care in the various countries.

Prior studies have addressed research priorities in this area such as presenting results on an individual drug level according to the indication of use, quantifying the extent of OTC and prescribed medication use during pregnancy, and taking into account inter-country comparability.[4] Only a few studies have individually examined maternal factors associated with specific types of medication use during pregnancy.[11-14]

The objectives of the current study were to examine patterns of medication use in pregnancy from a multinational perspective, with special emphasis on type of medication utilized, including OTC medications, and self-reported indications for use, and to identify maternal background factors potentially associated with medication use for acute/short-term illnesses, medication use for chronic/long-term disorders and OTC medication use during pregnancy.

METHODS

Study design and data collection

This is a multinational, cross-sectional, internet-based study. Pregnant women at any gestational week and mothers with children less than one year of age were eligible to participate. Member countries of the European Network of Teratology Information Services (ENTIS), The Organization of Teratology Information Specialists (OTIS) in North America, MotherSafe in Australia and European institutions conducting public health research were invited to take part in the project. Of these, 18 countries participated (Australia, Austria, Canada, Croatia, Finland, France, Iceland, Italy, Netherlands, Norway, Poland, Russia, Serbia, Slovenia, Sweden, Switzerland, United Kingdom and USA). Data originating from some South and Central American countries were also collected through OTIS. Because of the low number of participants on the individual country level, the region of Central America was excluded and countries in South America were aggregated into one region. Data selection to achieve the final study sample was performed as depicted in Figure 1. Participants were categorized according to the reported country of residency and grouped into six regions: Western Europe, Northern Europe, Eastern Europe, North America, South America and Australia.

Data were collected through an anonymous on-line questionnaire administered by Quest Back (http://www.questback.com) and accessible for a period of two months in each participating country within the period 1-Oct-2011 to 29-Feb-2012. The complete questionnaire is presented in Appendix 1. The questionnaire was open to the public via utilization of banners (invitations to participate in the study) on national websites and/or social networks commonly visited and consulted by pregnant women and/or new mothers. Detailed information about recruitment tools utilized and internet penetration rates is summarized in Appendix 2.

The questionnaire was first developed in Norwegian and English and then translated into the other relevant languages. A pilot study was carried out in September 2011 (n=47) and elicited no major change to the questionnaire. Collected data were scrutinized for the presence of potential duplicates (based on reported country of residency, socio-demographic characteristics, date and exact time of questionnaire completion) but none were identified.

Exposure variables

Maternal socio-demographics (i.e. region of residency, age, educational level, mother tongue, working status at time of conception, previous children, marital status and unplanned pregnancy) and life-style characteristics (i.e. smoking status before and during pregnancy and alcohol consumption after awareness of pregnancy) constituted the exposure variables. To assess external validity, we compared socio-demographic and life-style characteristics of our study population on an individual country level with those of the general birthing population in the same country. Reports of National Statistics Bureaus or previous national studies were utilized for this purpose. The ratio

between the number of respondents and the estimated number of live births in the 2-months period was also examined for each country (Appendix 3).

Outcome variables

Use of any medication, medication for acute/short-term illnesses, medication for chronic/long-term disorders and OTC medication use during pregnancy constituted the outcome variables. Participants were first confronted with a list of the most common acute/short-term illnesses (i.e. nausea, heartburn, constipation, common cold, urinary tract infections (UTIs), other infections, pain in the neck/back/pelvic girdle, headache, sleeping problems) and the most prevalent chronic/long-term disorders (i.e. asthma, allergy, hypothyroidism, rheumatic disorders, diabetes, epilepsy, depression, anxiety, cardiovascular disease, other disorders) and asked whether they suffered/had suffered from these conditions during pregnancy. In case of an affirmative response, women were questioned about medication use for each individual indication as a free-text entry. Use of OTC medications was also recorded. Recall was aided with a list of five OTC medication categories: painkillers, nasal spray/drops, antinauseants, antacids and laxatives, along with examples of brand name products of relevance in each country. It was optional to report timing of exposure for each of the medication use questions (the alternatives were gestational weeks 0-12 (1st trimester), 13-24 (2nd trimester) and 25-delivery (3rd trimester)).

We defined a medicine as a single product containing one or more active ingredients. We initially identified the main active ingredient(s) and formulation of the reported medicinal products either in the relevant national medicines database or in the "Martindale" textbook.[15] All recorded medications were coded into the corresponding Anatomical Therapeutic Chemical (ATC) codes at the ATC 5th level

(i.e. the substance level) whenever possible, otherwise into the 2nd- 4th levels as appropriate, in accordance with the World Health Organization ATC index.[16] The OTC status of medications was crosschecked with the prescription policies within each country. Whenever a prescription medication was reported under the OTC question, this record was omitted from the analysis of OTC use but counted in the estimation of total medication use (including prescription and OTC). Iron, mineral supplements, vitamins, herbal remedies and any type of alternative medicine were recorded separately and excluded from the estimation of medication use.

The required sample size calculation for the outcome variables on region and individual country levels are outlined in Appendix 4. The expected prevalence estimates were set according to results of previous studies.[5-10,17,18]

Ethics

All participants gave informed consent by answering "Yes" to the question "Are you willing to participate in the study?" The study was approved by the Regional Ethics Committee, Region South-East in Norway. Ethical approval or study notification to the relevant national Ethics Boards was achieved in specific countries as required by national legislation. All data were handled and stored anonymously.

Statistical analysis

Descriptive statistics were utilized as appropriate. Univariate and multivariate logistic regression analyses were used to examine the association between maternal characteristic and three categorical outcome measures (Yes/No): Medication use for acute/short-term illnesses; medication use for chronic/long-term disorders; OTC medication use. P-values of <0.05 were considered statistically significant. Data are

presented as adjusted odds ratios (aOR) with 95% confidence intervals (CI). The analyzed explanatory variables included all maternal socio-demographics and life-style characteristics. After fitting the univariate logistic regression model for all explanatory variables, the multivariate model was built and adjusted for all remaining covariates. The Hosmer and Lemeshow test was used to assess goodness of fit of the final multivariate model.[19] Analogue sub-analyses on individual region level were performed. In these instances, region of residency was not included in the model. All statistical analyses were performed by using the Statistical Package for the Social Sciences (SPSS) version 20.0 (IBM® SPSS® Statistics).

RESULTS

Population characteristics

A total of 9,615 women accessed the on-line questionnaire whereof 98.6% completed it. The participant flow-chart to achieve final study population (n=9,459) is depicted in Figure 1. A total of 5,089 women (53.8%) were pregnant at the time of completion of the questionnaire, whereas 4,370 women (46.2%) had delivered their babies within the previous year. Of the former group, 1,095 (21.5%), 1,702 (33.4%) and 2,291 (45.0%) women were in the first, second and third trimester of pregnancy, respectively. Of the latter group, 1,320 (30.2%), 947 (21.7%) and 2,102 (48.1%) had a baby of age ≤ 16 weeks, 17-28 weeks, and ≥ 29 weeks, respectively. For two women the time of gestation/baby´s age was unknown. Overall, the birthing population in each participating country was reflected quite well by the sample with respect to age, parity and smoking habits (Appendix 3). However, there was a difference in terms of educational level; on average, the women in the study had higher education than the general birthing population in each country. In addition, participants in Sweden,

Austria, Iceland and Italy were slightly more often primiparous, whereas the responders in Australia, USA, The Netherlands, Slovenia and Croatia were somewhat older than the general birthing population.

Total medication use

After exclusion of vitamins, mineral supplements and iron, use of at least one medication either prescribed or OTC at any time during pregnancy was reported by 7,678 out of 9,459 women (81.2%). Figure 2 depicts prevalence estimates of total medication use during pregnancy by region and country of residence. The extent of OTC medication use, as well as medication use for acute/short-term illnesses and chronic/long-term disorders is also outlined. The highest prevalence of total medication use during pregnancy was observed in The Netherlands (95.1%), Iceland (93.0%) and Finland (92.3%). The overall prevalence estimates of medication use in pregnancy according to timing and drug class (ATC level 1 and 2) are presented in Appendix 5. Medications for the nervous system (ATC class N) were the most commonly used during pregnancy (57.5%), mostly due to paracetamol (acetaminophen) and its combinations.

A corollary analysis according to pregnancy status showed that pregnant women reported in a significantly lower degree than new mothers any medication use during pregnancy (78.8% vs. 84.0%, p-value<0.001), as well as OTC medication use (63.0% vs. 71.5%, p-value<0.001) and medication use for acute/short-term illnesses (66.2% vs. 70.9%, p-value<0.001). In contrast, the difference in medication use for chronic/long-term disorders was not significant (17.4% vs. 16.5%, p-value=0.271). None of the rates differed significantly when women in the third trimester of pregnancy were compared to new mothers.

Medication use according to indication

Headache, heartburn, pain, nausea and UTIs constituted the leading indications for use of medication during pregnancy among the acute/short-term illnesses analyzed. Hypothyroidism, asthma, allergy and depression were the leading indications for chronic/long-term medication use. Observed prevalence rates of these disorders, overall and by region of residency, are presented in Appendices 6 and 7, respectively, along with rates of total and specific medication use. Table 1 outlines prevalence estimates of OTC medication use during pregnancy by region and indication for use. Only the most common medication groups reported are presented. Inter-region variations in rates and types of medication used during pregnancy were observed both for acute/short-term illnesses (e.g. nausea and UTIs), chronic/long-term disorders (e.g. asthma and depression) and OTC medications (e.g. nasal spray).

Factors associated with medication use

Factors associated with medication use during pregnancy according to type of medication utilized are presented in table 2. Use of chronic/long-term medications during pregnancy was reported in a significant larger extent by women in Northern Europe (aOR:1.68, 95% CI:1.46-1.94), North America (aOR:1.80, 95% CI:1.42-2.28) and Australia (aOR:2.76, 95% CI:2.03-3.76) compared to women in Western Europe. Older women or housewives, those with low education or with an unplanned pregnancy, were the ones most often reporting use of chronic/long-term medication. Sub-analysis on individual region level revealed that women not having the official language of the country of residency as mother tongue were less likely to report chronic/long-term medication use in Western (aOR: 0.55, 95% CI: 0.34-0.87) and Northern Europe (aOR: 0.50, 95% CI: 0.31-0.83), but not in the other regions.

Table 1: Use of OTC medication at any time during pregnancy by ATC level, indication for use and region (n=9,459) [*†]

OTC medication use, overall and by drug groups	REGION						
	Western Europe n=3,201 *n (%)*	**Northern Europe n=2,820** *n (%)*	**Eastern Europe n=2,342** *n (%)*	**North America n=533** *n (%)*	**South America n=346** *n (%)*	**Australian n=217** *n (%)*	**Total n=9,459** *n (%)*
OTC painkillers, total	**1,714 (53.5)**	**1,773 (62.9)**	**734 (31.3)**	**284 (53.3)**	**127 (36.7)**	**151 (69.9)**	**4,783 (50.6)**
By drug group							
Paracetamol (incl. combinations) (N02BE)	1,655 (51.7)	1,735 (61.5)	630 (26.9)	263 (49.3)	87 (25.1)	146 (67.3)	4,516 (47.7)
Non-steroideal antiinflammatory drugs (M01A)	70 (2.2)	182 (6.5)	68 (2.9)	40 (7.5)	59 (17.1)	7 (3.2)	426 (4.5)
Acetylsalicylic acid (incl. combinations) (N02BA)	7 (0.2)	11 (0.4)	32 (1.4)	2 (0.4)	2 (0.6)	1 (0.5)	55 (0.6)
Metamizole (N02BB02)	-	6 (0.2)	31 (1.3)	1 (0.2)	12 (3.5)	-	50 (0.5)
OTC antacids, total	**1,011 (31.6)**	**883 (31.3)**	**583 (24.9)**	**129 (24.2)**	**48 (13.9)**	**76 (35.0)**	**2,730 (28.9)**
By drug group							
Antacids (aluminium, salts combinations, antiflatulents)	472 (14.7)	550 (19.5)	508 (21.7)	47 (8.8)	36 (10.4)	54 (24.9)	1,667 (17.6)
Alginic acid complex/sucralfate/bismuth (A02BX)	606 (18.9)	421 (14.9)	87 (3.7)	4 (0.8)	1 (0.3)	17 (7.8)	1,136 (12.0)
H_2 receptor antagonists (A02BA)	20 (0.6)	20 (0.7)	16 (0.7)	57 (10.1)	10 (2.9)	17 (7.8)	137 (1.4)
Antacids with calcium (A02AC)	23 (0.7)	12 (0.4)	10 (0.4)	69 (12.9)	2 (0.6)	10 (4.6)	126 (1.3)
Proton pump inhibitors (A02BC)	38 (1.2)	52 (1.8)	-	10 (1.9)	2 (0.6)	5 (0.3)	107 (1.1)
OTC nasal sprays/drops, total	**272 (8.5)**	**742 (26.3)**	**451 (19.3)**	**35 (6.6)**	**7 (2.0)**	**14 (6.5)**	**1,521 (16.1)**
By drug group							
Sympathomimetic nasal decongestants (R01AA/R01BB)	204 (6.4)	683 (24.2)	365 (15.6)	20 (3.8)	3 (0.9)	4 (1.8)	1,279 (13.5)
Nasal corticosteroids (R01AD)	31 (1.0)	49 (1.7)	12 (0.5)	5 (0.9)	2 (0.6)	10 (4.6)	109 (1.2)
Nasal immunostimulants (low dose interferon) (L03A)	-	-	28 (1.2)	-	-	-	28 (0.3)
OTC laxatives, total	**240 (7.5)**	**227 (8.0)**	**237 (10.1)**	**50 (9.4)**	**8 (2.3)**	**19 (8.8)**	**781 (8.3)**
By drug group							
Osmotically acting laxatives (A06AD)	159 (5.0)	171 (6.1)	197 (8.4)	2 (0.4)	2 (0.6)	8 (3.7)	539 (5.7)
Contact laxatives (A06AB)	28 (0.9)	44 (1.6)	18 (0.8)	7 (1.3)	6 (1.7)	2 (0.9)	105 (1.1)

OTC medication use, overall and by drug groups	REGION						
	Western Europe	**Northern Europe**	**Eastern Europe**	**North America**	**South America**	**Australian**	**Total**
	n=3,201	**n=2,820**	**n=2,342**	**n=533**	**n=346**	**n=217**	**n=9,459**
	n (%)	***n (%)***	***n (%)***	***n (%)***	***n (%)***	***n (%)***	***n (%)***
Enemas (A06AG)	3 (0.1)	25 (0.9)	34 (1.5)	4 (0.8)	-	2 (0.9)	68 (0.7)
Softeners, emollients (A06AA)	8 (0.2)	-	-	38 (7.1)	-	6 (2.8)	52 (0.5)
OTC antinauseants, total	**263 (8.2)**	**273 (9.7)**	**41 (1.8)**	**60 (11.3)**	**28 (8.1)**	**40 (18.4)**	**705 (7.5)**
By drug group							
First generation antihistamines (R06A)	141 (4.4)	256 (9.1)	7 (1.5)	55 (10.3)	5 (1.4)	5 (2.3)	469 (5.0)
Metoclopramide/domperidone/bromopride (A03FA)	113 (3.5)	5 (0.2)	18 (0.8)	2 (0.4)	19 (5.5)	27 (12.4)	184 (1.9)
Total OTC medication use	**2,163 (67.6)**	**2,155 (76.4)**	**1,347 (57.5)**	**342 (64.2)**	**156 (45.1)**	**168 (77.4)**	**6,331 (66.9)**

*Countries are grouped into regions as shown in Figure 1.

†Sums of percentages do not add up to total medication use as only most common medication groups are presented. Rates do not include mineral supplements, vitamins, iron, and herbal or alternative medicine products.

Abbreviations: OTC: Over-The-Counter medications.

Table 2: Factors associated with medication use in pregnancy (n=9,459)*

	Medication use					
	For acute/short-term illnesses (n=6,469)		For chronic/long-term disorders (n=1,604)		OTC (n=6,331)	
	n (%)	*aOR (95% CI)*	*n (%)*	*aOR (95% CI)*	*n (%)*	*aOR (95% CI)*
Region of residency†						
Western Europe	2,224 (69.5)	Reference	462 (14.4)	Reference	2,163 (67.6)	Reference
Northern Europe	1,954 (69.3)	0.96 (0.86-1.08)	593 (21.0)	**1.68 (1.46-1.94)**	2,155 (76.4)	**1.54 (1.36-1.74)**
Eastern Europe	1,474 (62.9)	**0.69 (0.61-0.78)**	322 (13.7)	1.03 (0.87-1.21)	1,347 (57.5)	**0.60 (0.53-0.67)**
North America	403 (75.6)	**1.28 (1.03-1.60)**	119 (22.3)	**1.80 (1.42-2.28)**	342 (64.2)	**0.81 (0.66-0.99)**
South America	250 (82.3)	1.03 (0.79-1.34)	38 (11.0)	0.70 (0.48-1.01)	156 (45.1)	**0.34 (0.27-0.44)**
Australia	164 (75.6)	1.29 (0.93-1.79)	70 (32.3)	**2.76 (2.03-3.76)**	168 (77.4)	**1.57 (1.12-2.20)**
Maternal age (years)						
≤20	232 (70.5)	1.22 (0.93-1.60)	761 (14.7)	**0.58 (0.39-0.87)**	205 (62.3)	1.05 (0.81-1.36)
21-30	3,531 (68.2)	Reference	33 (10.0)	Reference	3,461 (66.8)	Reference
31-40	2,576 (68.6)	0.90 (0.82-1.00)	764 (20.4)	**1.44 (1.27-1.63)**	2,531 (67.4)	**0.85 (0.77-0.94)**
≥41	130 (66.3)	0.73 (0.54-1.00)	46 (23.5)	**1.61 (1.13-2.29)**	134 (68.4)	0.86 (0.62-1.19)
Previous children						
No	3,082 (65.5)	Reference	735 (15.6)	Reference	2,949 (62.6)	Reference
Yes	3,387 (71.3)	**1.34 (1.22-1.47)**	869 (18.3)	1.08 (0.96-1.21)	3,382 (71.2)	**1.58 (1.44-1.74)**
Marital status						
Married/cohabiting	6,066 (68.5)	Reference	1,503 (17.0)	Reference	5,960 (67.3)	Reference
Single/divorced/others	403 (66.3)	0.91 (0.75-1.10)	101 (16.6)	1.06 (0.83-1.35)	371 (61.0)	0.91 (0.75-1.10)
Working status						
Employed, but not as HCP	3,737 (66.8)	Reference	905 (16.2)	Reference	3,667 (65.6)	Reference
HCP	934 (74.4)	**1.41 (1.23-1.63)**	240 (19.1)	1.13 (0.96-1.33)	944 (75.2)	**1.42 (1.23-1.64)**
Student	592 (69.1)	1.11 (0.94-1.31)	128 (14.9)	1.04 (0.84-1.30)	578 (67.4)	1.10 (0.93-1.30)
Housewife	608 (72.6)	1.14 (0.96-1.35)	170 (20.3)	**1.34 (1.10-1.63)**	577 (68.9)	1.05 (0.88-1.24)
Job seeker	281 (66.0)	0.96 (0.78-1.20)	66 (15.5)	1.03 (0.78-1.36)	258 (60.6)	0.85 (0.68-1.05)
Other than above	311 (65.2)	0.91 (0.75-1.12)	94 (19.7)	**1.29 (1.01-1.65)**	302 (63.3)	0.91 (0.74-1.12)
Educational level						

	Medication use					
	For acute/short-term illnesses (n=6,469)		For chronic/long-term disorders (n=1,604)		OTC (n=6,331)	
	n (%)	*aOR (95% CI)*	*n (%)*	*aOR (95% CI)*	*n (%)*	*aOR (95% CI)*
Less than high school	331 (72.7)	1.17 (0.93-1.49)	92 (20.2)	**1.51 (1.15-1.97)**	317 (69.7)	**1.32 (1.04-1.67)**
High school	1,864 (68.7)	Reference	428 (15.8)	Reference	1,779 (65.6)	Reference
More than high school	3,574 (68.4)	0.99 (0.89-1.11)	916 (17.5)	1.04 (0.91-1.20)	3,489 (66.8)	1.07 (0.96-1.19)
Others, unspecified	700 (65.7)	0.82 (0.70-0.96)	168 (15.8)	0.94 (0.77-1.16)	746 (70.0)	1.13 (0.97-1.33)
Alcohol use after awareness of pregnancy						
No	5,270 (67.1)	Reference	1,322 (16.8)	Reference	5,133 (65.3)	Reference
Yes	1,144 (75.7)	**1.59 (1.39-1.81)**	270 (17.9)	1.11 (0.95-1.29)	1,150 (76.1)	**1.95 (1.71-2.23)**
Smoking during pregnancy						
No	5,835 (68.5)	Reference	1,441 (16.9)	Reference	5,716 (67.0)	Reference
Yes, but less than before pregnancy	530 (69.0)	1.08 (0.91-1.27)	130 (16.9)	1.01 (0.82-1.25)	511 (66.5)	1.06 (0.90-1.26)
Yes, the same or more than before pregnancy	88 (67.7)	0.95 (0.64-1.40)	28 (21.5)	1.19 (0.74-1.90)	89 (68.5)	1.21 (0.81-1.82)
Planned pregnancy						
Yes	5,836 (68.4)	Reference	1,427 (16.7)	Reference	5,727 (67.2)	Reference
No	616 (68.4)	0.96 (0.82-1.12)	173 (19.2)	**1.29 (1.06-1.56)**	587 (65.1)	1.00 (0.85-1.17)
First language different from the official main language in the country of residency						
No	6,089 (68.5)	Reference	1,530 (17.2)	Reference	5,972 (67.1)	Reference
Yes	363 (67.2)	0.93 (0.76-1.12)	71 (13.1)	**0.66 (0.50-0.86)**	347 (64.3)	0.89 (0.74-1.08)

Abbreviation: HCP: health care provider.

*Numbers may not add up due to missing values. Missing values are less than 5% of the total. Mineral supplements, vitamins, iron, herbal or alternative medicine products are not included in the medication use estimates.

†Countries are grouped into regions as shown in Figure 1.

DISCUSSION

This is the first internet-based study examining patterns and factors associated with medication use during pregnancy on a multinational level. In all regions, approximately eight out of ten women reported use of at least one medication, either prescribed or OTC, during the course of their pregnancy. This finding is in line with previous research conducted in Europe, North America, South America and Australia,[4,20-25] though our estimates were somewhat higher in some of the Eastern European countries, e.g. Serbia, than those observed in a previous study.[5] Different recruitment strategies, i.e. internet-based in our study versus maternity care unit-/community pharmacy-based in the previous study could explain such discrepancy.

Overall, analgesics, antacids, nasal decongestants/antiallergics and systemic antibiotics were the medication groups dominating the drug utilization scenario, as also shown by previous research.[4,20-22] However, our study also provides insights into the proportion of medicated women among those suffering from a specific illness during pregnancy across the six regions. We found that approximately seven out of ten women who reported UTIs were treated with antibiotics during pregnancy. This related to all regions, except Eastern Europe where it was only four out of ten women. Since women may perceive dysuria without ascertainment of bacteriuria in the urine as UTI, an over-reporting of the illness could have occurred. Yet, a sub-optimal treatment of UTIs during pregnancy in Eastern Europe cannot be ruled out. The inter-country variability in the types of antibiotics used for UTIs could simply be explained by differences in prescribing practice,[26] presence of screening for bacteriuria in early pregnancy, or specific antibiotic resistance patterns.

Even though nausea was the condition affecting most women in all six regions, the corresponding proportions of medicated nausea were generally low. This scenario is probably due to two main factors: a) the predominantly mild character of nausea and the possibility of non-pharmacological management (e.g. dietary advices); b) the reluctance of general practitioners to prescribe antinauseants even though safety profile assessments are in place.[27,28] As also shown in previous studies,[4,29] use of serotonin antagonists in North America and Australia is increasing also in pregnancy compared to the other regions, eliciting the need of sound studies assessing the safety profile of this drug group in pregnancy.

In most regions, the self-reported prevalence of hypothyroidism was somewhat higher than the reported hormone substitution rate. Because of its known association with adverse pregnancy outcomes,[30] the unexpected finding of potential sub-optimal treatment of hypothyroidism during pregnancy deserves attention. It could probably be due to a lack of information about hypothyroidism typology and its diagnostic ascertainment in our study.

In our study, depression was self-reported and not based on any psychometric assessment, thus the observed substantial inter-regional variability in the extent of this disorder and related medication use could have certainly been affected by women's attitudes in reporting. Our estimate of medication use for depression in Australia was higher than that observed in a recent study (10.6% versus 2.1%).[31] However, the similarity in self-reported depression itself (11.5% versus 15.6%) suggests that our population might mostly comprise women who did not discontinue their pharmacological therapy once they became pregnant. Our estimates for North America and Western Europe were in line with recent literature showing an increase in antidepressant use in pregnancy during the last years.[4,32]

In most regions approximately 60-70% of women reported use of at least one OTC medication during the course of their pregnancy, mostly for pain conditions, heartburn and

upper airways disorders, indicating a substantially high rate of self-medication during pregnancy. This estimate aligns with previous research carried out in North America.[17] Of note, self-medication with OTC sympathomimetic nasal decongestants was more extensive in Northern and Eastern Europe than in the remaining regions; this could be explained by the time of the year when the data collection was performed.

Region of residency was an important factor associated with medication use during pregnancy. As also shown by Cleary et al.,[33] we found that rates of medication use among women originally from Eastern Europe and South America were significantly lower than those observed in Western Europe, North America and Australia. Such geographical differences could be due to culture, variations in prenatal care assistance or access to medications in the various regions and the related costs.

Women working as health care providers, those consuming alcohol during pregnancy and those with previous children were those more likely to use short-term and OTC medications, possibly reflecting higher confidence in self-treatment and use of medications in general in the former instance, and less anxiety for the pregnancy outcome in the latter two instances. Contrary to previous studies indicating an association between higher maternal education and more prevalent use of medication during pregnancy,[14,17,23] we found that lower education was associated with a higher use of OTC medications as well as medication for chronic/long-term disorders (30-50% increased risk). Results of similar magnitude (30% increased risk) were also observed by Olesen et al.[34], whereas Stokholm et al. [35] identified a stronger association (2.3-fold increased risk) between low maternal education and use of antibiotic for respiratory tract infections during pregnancy. One factor negatively associated with chronic/long-term medication use was not having the official language of the country of residency as mother tongue. This tendency was detected in Western and Northern Europe,

rising concerns about the potential health risks for immigrant women in these two regions. As shown by Hameen-Anttila et al., 57% of pregnant women have perceived information needs about medications during pregnancy.[36] Thus, identification of potential users or non-users of medication during pregnancy might be of clinical relevance, allowing tailored evidence-based information about medication safety or outcome of sub-optimal medication of severe medical conditions in pregnancy.

Strengths and limitations

The main strength is that data collection was performed uniformly across all participating countries, allowing for inter-country comparison of the prevalence of medication use during pregnancy. By quantifying the extent of self-medication with OTC drugs and medication use according to self-reported indication, it was possible to determine the leading causes for medication use among pregnant women. Categorization of maternal characteristics positively associated with the various types of medications used during pregnancy enabled us to identify which groups of women are more likely to need information about medication use during pregnancy. The utilization of an anonymous web-based questionnaire enabled us to reach a large proportion of the birthing population in several countries worldwide. However, we cannot exclude the possibility that the women who decided to participate in the study differed from the general birthing population in other ways that our analysis could not control for. In most participating countries the study sample was large enough to warrant calculation of prevalence estimates with a precision of 5%. However, less precise estimates were permitted by the study sample in Austria, Iceland and The Netherlands (precision of 9-11%), as well as in Australia, Canada, Croatia, Serbia, Slovenia, and USA (precision of 6-7%).

One main limitation of the study is the lack of validity of the self-reported diagnoses. All disorders were self-reported by the participants and hence dependent on the women's

perception of the medical condition. Similarly, information about medication use during pregnancy was dependent on the accuracy of the women's reporting and recall. For new mothers, data were registered retrospectively; hence a risk of recall bias cannot be ruled out. In specific countries (Australia, Canada, France, Russia, The Netherlands, and the USA) the study sample was a small proportion of the general birthing population; hence the generalizability of our findings for these specific countries should be interpreted with caution.

The questionnaire was only available through internet websites; by using this kind of approach a conventional response rate cannot be calculated and a selection bias of the target population cannot be ruled out. However, recent epidemiological studies indicate reasonable validity of web-based recruitment methods.[37,38] Also, the penetration rate of the internet either in households or at work is relatively high among women in childbearing age.[39-43] Hence, the degree to which our findings can be extrapolated to the target population is based on the representativeness of the respondents to the general birthing populations in each country. The sample in each country had a somewhat higher educational level than the general birthing populations. Such a limitation might have led to biased estimates of the association between maternal education and medication use during pregnancy. Since many ailments requiring pharmacotherapy occur in mid or late pregnancy, inclusion of pregnant women at early gestation in the total material has somewhat inflated the prevalence of non-users of medications during pregnancy. Also, women with specific disorders or in need of information about medication use during pregnancy might have been more likely to consult internet websites and therefore participate in this study.

CONCLUSIONS

Use of medications for acute/short-term illnesses and chronic/long-term disorders as well as use of OTC medications, were common during pregnancy. The extent of medicated illnesses

and types of medications used for the different indications varied across the six regions. This was especially relevant for acute/short-term illnesses such as nausea and UTIs, but also for chronic/long-term disorders such as hypothyroidism or depression. Women with higher age or lower educational level, housewives, or women with an unplanned pregnancy were those most often reporting chronic/long-term medication use, as opposed to immigrants residing in Western and Northern Europe who reported the least use of this medication category. Future research should definitely focus on this specific group of women, but also address more insights into the outcome of sub-optimal medication of severe conditions in pregnancy.

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AUTHOR'S CONTRIBUTION: AL, OS and HN conceived the idea for the study and participated in its design and coordination. AL drafted the manuscript and analyzed the data. MJT, KZ, ACM, MEM, MD, AP, KHA, AR, RGJ, MO, DK, GR, HJ, AP and IB contributed to the data collection. All authors contributed to the interpretation of the results and revised the manuscript critically for important intellectual content. All the authors read and approved the final manuscript.

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Medication use in pregnancy: a multinational perspective

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ABSTRACT

Objectives: Inter-country comparability between studies on medication use in pregnancy is difficult due to dissimilarities in study design and methodology. This study aimed to examine patterns and factors associated with medications use in pregnancy from a multinational perspective, with emphasis on type of medication utilized and indication for use.

Design: Cross-sectional, internet-based study performed within the period from 1-Oct-2011 to 29-Feb-2012. Uniform collection of drug utilization data was performed via an anonymous online questionnaire.

Setting: Multinational study in Europe (Western, Northern, and Eastern), North and South America, and Australia.

Participants: Pregnant women and new mothers with children less than one year of age.

Primary and secondary outcome measures: Prevalence and factors associated with medication use for acute/short-term illnesses, chronic/long-term disorders and over-the-counter (OTC) medication use.

Results: The study population included 9,459 women whereof 81.2% reported use of at least one medication (prescribed or OTC) during pregnancy. Overall, OTC medication use occurred in 66.9% of the pregnancies, whereas 68.4% and 17.0% of women reported use of at least one medication for treatment of acute/short-term illnesses and chronic/long-term disorders, respectively. The extent of self-reported

medicated illnesses and types of medication used by indication varied across regions, especially in relation to urinary tract infections, depression or OTC nasal sprays. Women with higher age or lower educational level, housewives, or women with an unplanned pregnancy were those most often reporting use of medication for chronic/long-term ~~chronic medication~~disorders. Immigrant women in Western (aOR: 0.55, 95% CI: 0.34-0.87) and Northern Europe (aOR: 0.50, 95% CI: 0.31-0.83) were less likely to report use of medication for chronic/long-term disorders ~~chronic medication use~~ during pregnancy than non-immigrants.

Conclusions:

In this study, the majority of women in Europe, North America, South America and Australia used at least one medication during pregnancy. There was a substantial inter-region variability in the types of medication used.

ARTICLE SUMMARY

Strengths and limitations of this study

- Uniform data collection of drug utilization data across all participating countries allows for inter-country comparability of the prevalence of medication use during pregnancy, up to now impeded by differences in study design and methodology.
- The study adds a multinational perspective on OTC medication use during pregnancy to the limited number of studies quantifying the extent of self-medication during pregnancy.
- Lack of validity of the self-reported diagnoses is a limitation since all disorders and related medication use were self-reported by the study participants.
- An internet survey as a study method impedes calculation of a conventional response rate and may cause selection bias of the target population.

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INTRODUCTION

Ethical reasons preclude inclusion of pregnant women in the vast majority of pre-marketing clinical trials.[1] As a consequence, most medications are placed onto the market without a directly established safety profile in human pregnancy.[2] So far, few medications have been shown to be major teratogens, yet the risk of minor teratogenicity or of more subtle effects on fetal development still have to be determined for most of them.[3] Despite this, medication use during pregnancy is common. Mitchell et al. found that use of medications, either prescribed or purchased over-the-counter (OTC), occurred in 88.8% of all pregnancies in the USA.[4] In Europe, prevalence estimates of prescribed medication use vary considerably across countries, ranging from 26% in Serbia to 93% in France.[5-10] Such inter-country variability could, at least in part, be caused by differences in study design, methodology and exposure ascertainment across studies.[11] Uniform collection of drug utilization data during pregnancy between countries may overcome such drawbacks, allowing for inter-country comparability of prevalence estimates and shedding light on differences in prenatal care in the various countries.

Prior studies have addressed research priorities in this area such as presenting results on an individual drug level according to the indication of use, quantifying the extent of OTC and prescribed medication use during pregnancy, and taking into account inter-country comparability.[4] Only a few studies have individually examined maternal factors associated with specific types of medication use during pregnancy.[11-14]

The objectives of the current study were to examine patterns of medication use in pregnancy from a multinational perspective, with special emphasis on type of medication utilized, including OTC medications, and self-reported indications for use, and to identify maternal background factors potentially associated with medication use for acute/short-term illnesses, medication use for chronic/long-term disorders and OTC medication use during pregnancy.

METHODS

Study design and data collection

This is a multinational, cross-sectional, internet-based study. Pregnant women at any gestational week and mothers with children less than one year of age were eligible to participate. Member countries of the European Network of Teratology Information Services (ENTIS), The Organization of Teratology Information Specialists (OTIS) in North America, MotherSafe in Australia and European institutions conducting public health research were invited to take part in the project. Of these, 18 countries participated (Australia, Austria, Canada, Croatia, Finland, France, Iceland, Italy, Netherlands, Norway, Poland, Russia, Serbia, Slovenia, Sweden, Switzerland, United Kingdom and USA). Data originating from some South and Central American countries were also collected through OTIS. Because of the low number of participants on the individual country level, the region of Central America was excluded and countries in South America were aggregated into one region. Data selection to achieve the final study sample was performed as depicted in Figure 1. Participants were categorized according to the reported country of residency and grouped into six regions: Western Europe, Northern Europe, Eastern Europe, North America, South America and Australia.

Data were collected through an anonymous on-line questionnaire administered by Quest Back (http://www.questback.com) and accessible for a period of two months in each participating country within the period 1-Oct-2011 to 29-Feb-2012. The complete questionnaire is presented in Appendix 1. The questionnaire was open to the public via utilization of banners (invitations to participate in the study) on national websites and/or social networks commonly visited and consulted by pregnant women and/or new mothers. Detailed information about recruitment tools utilized and internet penetration rates is summarized in Appendix 2.

The questionnaire was first developed in Norwegian and English and then translated into the other relevant languages. A pilot study was carried out in September 2011 (n=47) and elicited no major change to the questionnaire. Collected data were scrutinized for the presence of potential duplicates (based on reported country of residency, socio-demographic characteristics, date and exact time of questionnaire completion) but none were identified.

Exposure variables

Maternal socio-demographics (i.e. region of residency, age, educational level, mother tongue, working status at time of conception, previous children, marital status and unplanned pregnancy) and life-style characteristics (i.e. smoking status before and during pregnancy and alcohol consumption after awareness of pregnancy) constituted the exposure variables. To assess external validity, we compared socio-demographic and life-style characteristics of our study population on an individual country level with those of the general birthing population in the same country. Reports of National Statistics Bureaus or previous national studies were utilized for this purpose. The ratio

between the number of respondents and the estimated number of live births in the 2-months period was also examined for each country (Appendix 3).

Outcome variables

Use of any medication, ~~prescribed~~ medication for acute/short-term illnesses, medication for chronic/long-term disorders and OTC medication use during pregnancy constituted the outcome variables. Participants were first confronted with a list of the most common acute/short-term illnesses (i.e. nausea, heartburn, constipation, common cold, urinary tract infections (UTIs), other infections, pain in the neck/back/pelvic girdle, headache, sleeping problems) and the most prevalent chronic/long-term disorders (i.e. asthma, allergy, hypothyroidism, rheumatic disorders, diabetes, epilepsy, depression, anxiety, cardiovascular disease, other disorders) and asked whether they suffered/had suffered from these conditions during pregnancy. In case of an affirmative response, women were questioned about medication use for each individual indication as a free-text entry. Use of OTC medications was also recorded. Recall was aided with a list of five OTC medication categories: painkillers, nasal spray/drops, antinauseants, antacids and laxatives, along with examples of brand name products of relevance in each country. It was optional to report timing of exposure for each of the medication use questions (the alternatives were gestational weeks 0-12 (1st trimester), 13-24 (2nd trimester) and 25-delivery (3rd trimester)).

We defined a medicine as a single product containing one or more active ingredients. We initially identified the main active ingredient(s) and formulation of the reported medicinal products either in the relevant national medicines database or in the "Martindale" textbook.[15] All recorded medications were coded into the corresponding Anatomical Therapeutic Chemical (ATC) codes at the ATC 5th level

(i.e. the substance level) whenever possible, otherwise into the 2nd- 4th levels as appropriate, in accordance with the World Health Organization ATC index.[16] The OTC status of medications was crosschecked with the prescription policies within each country. Whenever a prescription medication was reported under the OTC question, this record was omitted from the analysis of OTC use but counted in the estimation of total medication use (including prescription and OTC). Iron, mineral supplements, vitamins, herbal remedies and any type of alternative medicine were recorded separately and excluded from the estimation of medication use.

The required sample size calculation for the outcome variables on region and individual country levels are outlined in Appendix 4. The expected prevalence estimates were set according to results of previous studies.[5-10,17,18]

Ethics

All participants gave informed consent by answering "Yes" to the question "Are you willing to participate in the study?" The study was approved by the Regional Ethics Committee, Region South-East in Norway. Ethical approval or study notification to the relevant national Ethics Boards was achieved in specific countries as required by national legislation. All data were handled and stored anonymously.

Statistical analysis

Descriptive statistics were utilized as appropriate. Univariate and multivariate logistic regression analyses were used to examine the association between maternal characteristic and three categorical outcome measures (Yes/No): Medication use for acute/short-term illnesses; medication use for chronic/long-term disorders; OTC medication use. P-values of <0.05 were considered statistically significant. Data are

presented as adjusted odds ratios (aOR) with 95% confidence intervals (CI). The analyzed explanatory variables included all maternal socio-demographics and life-style characteristics. After fitting the univariate logistic regression model for all explanatory variables, the multivariate model was built and adjusted for all remaining covariates. The Hosmer and Lemeshow test was used to assess goodness of fit of the final multivariate model.[19] Analogue sub-analyses on individual region level were performed. In these instances, region of residency was not included in the model. All statistical analyses were performed by using the Statistical Package for the Social Sciences (SPSS) version 20.0 (IBM® SPSS® Statistics).

RESULTS

Population characteristics

A total of 9,615 women accessed the on-line questionnaire whereof 98.6% completed it. The participant flow-chart to achieve final study population (n=9,459) is depicted in Figure 1. A total of 5,089 women (53.8%) were pregnant at the time of completion of the questionnaire, whereas 4,370 women (46.2%) had delivered their babies within the previous year. Of the former group, 1,095 (21.5%), 1,702 (33.4%) and 2,291 (45.0%) women were in the first, second and third trimester of pregnancy, respectively. Of the latter group, 1,320 (30.2%), 947 (21.7%) and 2,102 (48.1%) had a baby of age ≤ 16 weeks, 17-28 weeks, and ≥ 29 weeks, respectively. For two women the time of gestation/baby´s age was unknown. Overall, the birthing population in each participating country was reflected quite well by the sample with respect to age, parity and smoking habits (Appendix 3). However, there was a difference in terms of educational level; on average, the women in the study had higher education than the general birthing population in each country. In addition, participants in Sweden,

Austria, Iceland and Italy were slightly more often primiparous, whereas the responders in Australia, USA, The Netherlands, Slovenia and Croatia were somewhat older than the general birthing population.

Total medication use

After exclusion of vitamins, mineral supplements and iron, use of at least one medication either prescribed or OTC at any time during pregnancy was reported by 7,678 out of 9,459 women (81.2%). Figure 2 depicts prevalence estimates of total medication use during pregnancy by region and country of residence~~, with specific rates according to inclusion or exclusion of vitamins, mineral supplements and iron~~. The extent of OTC ~~-~~medication use, as well as medication use for acute/short-term illnesses and chronic/long-term disorders ~~use~~ is also outlined. The highest prevalence of total medication use during pregnancy was observed in The Netherlands (95.1%), Iceland (93.0%) and Finland (92.3%). The overall prevalence estimates of medication use in pregnancy according to timing and drug class (ATC level 1 and 2) are presented in Appendix 5. Medications for the nervous system (ATC class N) were the most commonly used during pregnancy (57.5%), mostly due to paracetamol (acetaminophen) and its combinations.

A corollary analysis according to pregnancy status showed that pregnant women reported in a significantly lower degree than new mothers any medication use during pregnancy (78.8% vs. 84.0%, p-value<0.001), as well as OTC medication use (63.0% vs. 71.5%, p-value<0.001) and medication use for acute/short-term illnesses (66.2% vs. 70.9%, p-value<0.001). In contrast, the difference in medication use for chronic/long-term disorders was not significant (17.4% vs. 16.5%, p-value=0.271).

None of the rates differed significantly when women in the third trimester of pregnancy were compared to new mothers.

Medication use according to indication

Headache, heartburn, pain, nausea and UTIs constituted the leading indications for use of medication during pregnancy among the acute/short-term illnesses analyzed. Hypothyroidism, asthma, allergy and depression were the leading indications for chronic/long-term medication use. Observed prevalence rates of these disorders, overall and by region of residency, are presented in Appendices 6 and 7, respectively, along with rates of total and specific medication use. Table 1 outlines prevalence estimates of OTC medication use during pregnancy by region and indication for use. Only the most common medication groups reported are presented. Inter-region variations in rates and types of medication used during pregnancy were observed both for acute/short-term illnesses (e.g. nausea and UTIs), chronic/long-term disorders (e.g. asthma and depression) and OTC medications (e.g. nasal spray).

Factors associated with medication use

Factors associated with medication use during pregnancy according to type of medication utilized are presented in table 2. Use of chronic/long-term medications during pregnancy was reported in a significant larger extent by women in Northern Europe (aOR:1.68, 95% CI:1.46-1.94), North America (aOR:1.80, 95% CI:1.42-2.28) and Australia (aOR:2.76, 95% CI:2.03-3.76) compared to women in Western Europe. Older women or housewives, those with low education or with an unplanned pregnancy, were the ones most often reporting use of chronic/long-term medication. Sub-analysis on individual region level revealed that women not having the official

language of the country of residency as mother tongue were less likely to report chronic/long-term medication use in Western (aOR: 0.55, 95% CI: 0.34-0.87) and Northern Europe (aOR: 0.50, 95% CI: 0.31-0.83), but not in the other regions.

Table 1: Use of OTC medication at any time during pregnancy by ATC level, indication for use and region (n=9,459) [*†]

OTC medication use, overall and by drug groups	REGION						
	Western Europe n=3,201 *n (%)*	**Northern Europe n=2,820** *n (%)*	**Eastern Europe n=2,342** *n (%)*	**North America n=533** *n (%)*	**South America n=346** *n (%)*	**Australian n=217** *n (%)*	**Total n=9,459** *n (%)*
OTC painkillers, total	**1,714 (53.5)**	**1,773 (62.9)**	**734 (31.3)**	**284 (53.3)**	**127 (36.7)**	**151 (69.9)**	**4,783 (50.6)**
By drug group							
Paracetamol (incl. combinations) (N02BE)	1,655 (51.7)	1,735 (61.5)	630 (26.9)	263 (49.3)	87 (25.1)	146 (67.3)	4,516 (47.7)
Non-steroideal antiinflammatory drugs (M01A)	70 (2.2)	182 (6.5)	68 (2.9)	40 (7.5)	59 (17.1)	7 (3.2)	426 (4.5)
Acetylsalicylic acid (incl. combinations) (N02BA)	7 (0.2)	11 (0.4)	32 (1.4)	2 (0.4)	2 (0.6)	1 (0.5)	55 (0.6)
Metamizole (N02BB02)	-	6 (0.2)	31 (1.3)	1 (0.2)	12 (3.5)	-	50 (0.5)
OTC antacids, total	**1,011 (31.6)**	**883 (31.3)**	**583 (24.9)**	**129 (24.2)**	**48 (13.9)**	**76 (35.0)**	**2,730 (28.9)**
By drug group							
Antacids (aluminium, salts combinations, antiflatulents)	472 (14.7)	550 (19.5)	508 (21.7)	47 (8.8)	36 (10.4)	54 (24.9)	1,667 (17.6)
Alginic acid complex/sucralfate/bismuth (A02BX)	606 (18.9)	421 (14.9)	87 (3.7)	4 (0.8)	1 (0.3)	17 (7.8)	1,136 (12.0)
H_2 receptor antagonists (A02BA)	20 (0.6)	20 (0.7)	16 (0.7)	57 (10.1)	10 (2.9)	17 (7.8)	137 (1.4)
Antacids with calcium (A02AC)	23 (0.7)	12 (0.4)	10 (0.4)	69 (12.9)	2 (0.6)	10 (4.6)	126 (1.3)
Proton pump inhibitors (A02BC)	38 (1.2)	52 (1.8)	-	10 (1.9)	2 (0.6)	5 (0.3)	107 (1.1)
OTC nasal sprays/drops, total	**272 (8.5)**	**742 (26.3)**	**451 (19.3)**	**35 (6.6)**	**7 (2.0)**	**14 (6.5)**	**1,521 (16.1)**
By drug group							
Sympathomimetic nasal decongestants (R01AA/R01BB)	204 (6.4)	683 (24.2)	365 (15.6)	20 (3.8)	3 (0.9)	4 (1.8)	1,279 (13.5)
Nasal corticosteroids (R01AD)	31 (1.0)	49 (1.7)	12 (0.5)	5 (0.9)	2 (0.6)	10 (4.6)	109 (1.2)
Nasal immunostimulants (low dose interferon) (L03A)	-	-	28 (1.2)	-	-	-	28 (0.3)
OTC laxatives, total	**240 (7.5)**	**227 (8.0)**	**237 (10.1)**	**50 (9.4)**	**8 (2.3)**	**19 (8.8)**	**781 (8.3)**
By drug group							
Osmotically acting laxatives (A06AD)	159 (5.0)	171 (6.1)	197 (8.4)	2 (0.4)	2 (0.6)	8 (3.7)	539 (5.7)
Contact laxatives (A06AB)	28 (0.9)	44 (1.6)	18 (0.8)	7 (1.3)	6 (1.7)	2 (0.9)	105 (1.1)

OTC medication use, overall and by drug groups	REGION						
	Western Europe	**Northern Europe**	**Eastern Europe**	**North America**	**South America**	**Australian**	**Total**
	n=3,201	**n=2,820**	**n=2,342**	**n=533**	**n=346**	**n=217**	**n=9,459**
	n (%)	***n (%)***	***n (%)***	***n (%)***	***n (%)***	***n (%)***	***n (%)***
Enemas (A06AG)	3 (0.1)	25 (0.9)	34 (1.5)	4 (0.8)	-	2 (0.9)	68 (0.7)
Softeners, emollients (A06AA)	8 (0.2)	-	-	38 (7.1)	-	6 (2.8)	52 (0.5)
OTC antinauseants, total	**263 (8.2)**	**273 (9.7)**	**41 (1.8)**	**60 (11.3)**	**28 (8.1)**	**40 (18.4)**	**705 (7.5)**
By drug group							
First generation antihistamines (R06A)	141 (4.4)	256 (9.1)	7 (1.5)	55 (10.3)	5 (1.4)	5 (2.3)	469 (5.0)
Metoclopramide/domperidone/bromopride (A03FA)	113 (3.5)	5 (0.2)	18 (0.8)	2 (0.4)	19 (5.5)	27 (12.4)	184 (1.9)
Total OTC medication use	**2,163 (67.6)**	**2,155 (76.4)**	**1,347 (57.5)**	**342 (64.2)**	**156 (45.1)**	**168 (77.4)**	**6,331 (66.9)**

*Countries are grouped into regions as shown in Figure 1.

†Sums of percentages do not add up to total medication use as only most common medication groups are presented. Rates do not include mineral supplements, vitamins, iron, and herbal or alternative medicine products.

Abbreviations: OTC: Over-The-Counter medications.

Table 2: Factors associated with medication use in pregnancy (n=9,459)*

	Medication use					
	For acute/short-term illnesses (n=6,469)		For chronic/long-term disorders (n=1,604)		OTC (n=6,331)	
	n (%)	*aOR (95% CI)*	*n (%)*	*aOR (95% CI)*	*n (%)*	*aOR (95% CI)*
Region of residency†						
Western Europe	2,224 (69.5)	Reference	462 (14.4)	Reference	2,163 (67.6)	Reference
Northern Europe	1,954 (69.3)	0.96 (0.86-1.08)	593 (21.0)	**1.68 (1.46-1.94)**	2,155 (76.4)	**1.54 (1.36-1.74)**
Eastern Europe	1,474 (62.9)	**0.69 (0.61-0.78)**	322 (13.7)	1.03 (0.87-1.21)	1,347 (57.5)	**0.60 (0.53-0.67)**
North America	403 (75.6)	**1.28 (1.03-1.60)**	119 (22.3)	**1.80 (1.42-2.28)**	342 (64.2)	**0.81 (0.66-0.99)**
South America	250 (82.3)	1.03 (0.79-1.34)	38 (11.0)	0.70 (0.48-1.01)	156 (45.1)	**0.34 (0.27-0.44)**
Australia	164 (75.6)	1.29 (0.93-1.79)	70 (32.3)	**2.76 (2.03-3.76)**	168 (77.4)	**1.57 (1.12-2.20)**
Maternal age (years)						
≤20	232 (70.5)	1.22 (0.93-1.60)	761 (14.7)	**0.58 (0.39-0.87)**	205 (62.3)	1.05 (0.81-1.36)
21-30	3,531 (68.2)	Reference	33 (10.0)	Reference	3,461 (66.8)	Reference
31-40	2,576 (68.6)	0.90 (0.82-1.00)	764 (20.4)	**1.44 (1.27-1.63)**	2,531 (67.4)	**0.85 (0.77-0.94)**
≥41	130 (66.3)	0.73 (0.54-1.00)	46 (23.5)	**1.61 (1.13-2.29)**	134 (68.4)	0.86 (0.62-1.19)
Previous children						
No	3,082 (65.5)	Reference	735 (15.6)	Reference	2,949 (62.6)	Reference
Yes	3,387 (71.3)	**1.34 (1.22-1.47)**	869 (18.3)	1.08 (0.96-1.21)	3,382 (71.2)	**1.58 (1.44-1.74)**
Marital status						
Married/cohabiting	6,066 (68.5)	Reference	1,503 (17.0)	Reference	5,960 (67.3)	Reference
Single/divorced/others	403 (66.3)	0.91 (0.75-1.10)	101 (16.6)	1.06 (0.83-1.35)	371 (61.0)	0.91 (0.75-1.10)
Working status						
Employed, but not as HCP	3,737 (66.8)	Reference	905 (16.2)	Reference	3,667 (65.6)	Reference
HCP	934 (74.4)	**1.41 (1.23-1.63)**	240 (19.1)	1.13 (0.96-1.33)	944 (75.2)	**1.42 (1.23-1.64)**
Student	592 (69.1)	1.11 (0.94-1.31)	128 (14.9)	1.04 (0.84-1.30)	578 (67.4)	1.10 (0.93-1.30)
Housewife	608 (72.6)	1.14 (0.96-1.35)	170 (20.3)	**1.34 (1.10-1.63)**	577 (68.9)	1.05 (0.88-1.24)
Job seeker	281 (66.0)	0.96 (0.78-1.20)	66 (15.5)	1.03 (0.78-1.36)	258 (60.6)	0.85 (0.68-1.05)
Other than above	311 (65.2)	0.91 (0.75-1.12)	94 (19.7)	**1.29 (1.01-1.65)**	302 (63.3)	0.91 (0.74-1.12)
Educational level						

	Medication use					
	For acute/short-term illnesses (n=6,469)		For chronic/long-term disorders (n=1,604)		OTC (n=6,331)	
	n (%)	*aOR (95% CI)*	*n (%)*	*aOR (95% CI)*	*n (%)*	*aOR (95% CI)*
Less than high school	331 (72.7)	1.17 (0.93-1.49)	92 (20.2)	**1.51 (1.15-1.97)**	317 (69.7)	**1.32 (1.04-1.67)**
High school	1,864 (68.7)	Reference	428 (15.8)	Reference	1,779 (65.6)	Reference
More than high school	3,574 (68.4)	0.99 (0.89-1.11)	916 (17.5)	1.04 (0.91-1.20)	3,489 (66.8)	1.07 (0.96-1.19)
Others, unspecified	700 (65.7)	0.82 (0.70-0.96)	168 (15.8)	0.94 (0.77-1.16)	746 (70.0)	1.13 (0.97-1.33)
Alcohol use after awareness of pregnancy						
No	5,270 (67.1)	Reference	1,322 (16.8)	Reference	5,133 (65.3)	Reference
Yes	1,144 (75.7)	**1.59 (1.39-1.81)**	270 (17.9)	1.11 (0.95-1.29)	1,150 (76.1)	**1.95 (1.71-2.23)**
Smoking during pregnancy						
No	5,835 (68.5)	Reference	1,441 (16.9)	Reference	5,716 (67.0)	Reference
Yes, but less than before pregnancy	530 (69.0)	1.08 (0.91-1.27)	130 (16.9)	1.01 (0.82-1.25)	511 (66.5)	1.06 (0.90-1.26)
Yes, the same or more than before pregnancy	88 (67.7)	0.95 (0.64-1.40)	28 (21.5)	1.19 (0.74-1.90)	89 (68.5)	1.21 (0.81-1.82)
Planned pregnancy						
Yes	5,836 (68.4)	Reference	1,427 (16.7)	Reference	5,727 (67.2)	Reference
No	616 (68.4)	0.96 (0.82-1.12)	173 (19.2)	**1.29 (1.06-1.56)**	587 (65.1)	1.00 (0.85-1.17)
First language different from the official main language in the country of residency						
No	6,089 (68.5)	Reference	1,530 (17.2)	Reference	5,972 (67.1)	Reference
Yes	363 (67.2)	0.93 (0.76-1.12)	71 (13.1)	**0.66 (0.50-0.86)**	347 (64.3)	0.89 (0.74-1.08)

Abbreviation: HCP: health care provider.

*Numbers may not add up due to missing values. Missing values are less than 5% of the total. Mineral supplements, vitamins, iron, herbal or alternative medicine products are not included in the medication use estimates.

†Countries are grouped into regions as shown in Figure 1.

DISCUSSION

This is the first internet-based study examining patterns and factors associated with medication use during pregnancy on a multinational level. ~~In specific countries (Australia, Canada, France, Russia, The Netherlands, and the USA) the study sample was a small proportion of the general birthing population; hence the generalizability of our findings for these specific countries should be interpreted with caution.~~ In all regions, approximately eight out of ten women reported use of at least one medication, either prescribed or OTC, during the course of their pregnancy. This finding is in line with previous research conducted in Europe, North America, South America and Australia,[4,20-25] though our estimates were somewhat higher in some of the Eastern European countries, e.g. Serbia, than those observed in a previous study.[5] Different recruitment strategies, i.e. internet-based in our study versus maternity care unit-/community pharmacy-based in the previous study could explain such discrepancy.

Overall, analgesics, antacids, nasal decongestants/antiallergics and systemic antibiotics were the medication groups dominating the drug utilization scenario, as also shown by previous research.[4,20-22] However, our study also provides insights into the proportion of medicated women among those suffering from a specific illness during pregnancy across the six regions. We found that approximately seven out of ten women who reported UTIs were treated with antibiotics during pregnancy. This related to all regions, except Eastern Europe where it was only four out of ten women. Since women may perceive dysuria without ascertainment of bacteriuria in the urine as UTI, an over-reporting of the illness could have occurred. Yet, a sub-optimal treatment of UTIs during pregnancy in Eastern Europe cannot be ruled out. The inter-country variability in the types of antibiotics used for UTIs could simply be explained by

differences in prescribing practice,[26] presence of screening for bacteriuria in early pregnancy, or specific antibiotic resistance patterns.

Even though nausea was the condition affecting most women in all six regions, the corresponding proportions of medicated nausea were generally low. This scenario is probably due to two main factors: a) the predominantly mild character of nausea and the possibility of non-pharmacological management (e.g. dietary advices); b) the reluctance of general practitioners to prescribe antinauseants even though safety profile assessments are in place.[27,28] As also shown in previous studies,[4,29] use of serotonin antagonists in North America and Australia is increasing also in pregnancy compared to the other regions, eliciting the need of sound studies assessing the safety profile of this drug group in pregnancy.

In most regions, the self-reported prevalence of hypothyroidism was somewhat higher than the reported hormone substitution rate. Because of its known association with adverse pregnancy outcomes,[30] the unexpected finding of potential sub-optimal treatment of hypothyroidism during pregnancy deserves attention. It could probably be due to a lack of information about hypothyroidism typology and its diagnostic ascertainment in our study.

In our study, depression was self-reported and not based on any psychometric assessment, thus the observed substantial inter-regional variability in the extent of this disorder and related medication use could have certainly been affected by women's attitudes in reporting. Our estimate of medication use for depression in Australia was higher than that observed in a recent study (10.6% versus 2.1%).[31] However, the similarity in self-reported depression itself (11.5% versus 15.6%) suggests that our population might mostly comprise women who did not discontinue their pharmacological therapy once they became pregnant. Our estimates for North America and Western Europe were in line with recent literature showing an increase in antidepressant use in pregnancy during the last years.[4,32]

In most regions approximately 60-70% of women reported use of at least one OTC medication during the course of their pregnancy, mostly for pain conditions, heartburn and upper airways disorders, indicating a substantially high rate of self-medication during pregnancy. This estimate aligns with previous research carried out in North America.[17] Of note, self-medication with OTC sympathomimetic nasal decongestants was more extensive in Northern and Eastern Europe than in the remaining regions; this could be explained by the time of the year when the data collection was performed.

Region of residency was an important factor associated with medication use during pregnancy. As also shown by Cleary et al.,[33] we found that rates of medication use among women originally from Eastern Europe and South America were significantly lower than those observed in Western Europe, North America and Australia. Such geographical differences could be due to culture, variations in prenatal care assistance or access to medications in the various regions and the related costs.

Women working as health care providers, those consuming alcohol during pregnancy and those with previous children were those more likely to use short-term and OTC medications, possibly reflecting higher confidence in self-treatment and use of medications in general in the former instance, and less anxiety for the pregnancy outcome in the latter two instances. Contrary to previous studies indicating an association between higher maternal education and more prevalent use of medication during pregnancy,[14,17,23] we found that lower education was associated with a higher use of OTC medications as well as medication for chronic/long-term disorders (30-50% increased risk). Results of similar magnitude (30% increased risk) were also observed by Olesen et al.[34], whereas Stokholm et al. [35] identified a stronger association (2.3-fold increased risk) between low maternal education and use of antibiotic for respiratory tract infections during pregnancy. One factor negatively associated with

chronic/long-term medication use was not having the official language of the country of residency as mother tongue. This tendency was detected in Western and Northern Europe, rising concerns about the potential health risks for immigrant women in these two regions. As shown by Hameen-Anttila et al., 57% of pregnant women have perceived information needs about medications during pregnancy.[36] Thus, identification of potential users or non-users of medication during pregnancy might be of clinical relevance, allowing tailored evidence-based information about medication safety or outcome of sub-optimal medication of severe medical conditions in pregnancy.

Strengths and limitations

The main strength is that data collection was performed uniformly across all participating countries, allowing for inter-country comparison of the prevalence of medication use during pregnancy. By quantifying the extent of self-medication with OTC drugs and medication use according to self-reported indication, it was possible to determine the leading causes for medication use among pregnant women. Categorization of maternal characteristics positively associated with the various types of medications used during pregnancy enabled us to identify which groups of women are more likely to need information about medication use during pregnancy. The utilization of an anonymous web-based questionnaire enabled us to reach a large proportion of the birthing population in several countries worldwide. However, we cannot exclude the possibility that the women who decided to participate in the study differed from the general birthing population in other ways that our analysis could not control for. In most participating countries the study sample was large enough to warrant calculation of prevalence estimates with a precision of 5%. However, less precise estimates were permitted by the study sample in Austria, Iceland and The Netherlands (precision of 9-11%), as well as in Australia, Canada, Croatia, Serbia, Slovenia, and USA (precision of 6-7%).

One main limitation of the study is the lack of validity of the self-reported diagnoses. All disorders were self-reported by the participants and hence dependent on the women's perception of the medical condition. Similarly, information about medication use during pregnancy was dependent on the accuracy of the women's reporting and recall. For new mothers, data were registered retrospectively; hence a risk of recall bias cannot be ruled out. In specific countries (Australia, Canada, France, Russia, The Netherlands, and the USA) the study sample was a small proportion of the general birthing population; hence the generalizability of our findings for these specific countries should be interpreted with caution.

The questionnaire was only available through internet websites; by using this kind of approach a conventional response rate cannot be calculated and a selection bias of the target population cannot be ruled out. However, recent epidemiological studies indicate reasonable validity of web-based recruitment methods.[37,38] Also, the penetration rate of the internet either in households or at work is relatively high among women in childbearing age.[39-43] Hence, the degree to which our findings can be extrapolated to the target population is based on the representativeness of the respondents to the general birthing populations in each country. The sample in each country had a somewhat higher educational level than the general birthing populations. Such a limitation might have led to biased estimates of the association between maternal education and medication use during pregnancy. Since many ailments requiring pharmacotherapy occur in mid or late pregnancy, inclusion of pregnant women at early gestation in the total material has somewhat inflated the prevalence of non-users of medications during pregnancy. Also, women with specific disorders or in need of information about medication use during pregnancy might have been more likely to consult internet websites and therefore participate in this study.

CONCLUSIONS

Use of medications for acute/short-term illnesses and chronic/long-term disorders as well as use of OTC medications, were common during pregnancy. The extent of medicated illnesses and types of medications used for the different indications varied across the six regions. This was especially relevant for acute/short-term illnesses such as nausea and UTIs, but also for chronic/long-term disorders such as hypothyroidism or depression. Women with higher age or lower educational level, housewives, or women with an unplanned pregnancy were those most often reporting ~~use of~~ chronic/long-term medication use, as opposed to i~~- and may therefore be more in need of information about medication during pregnancy. Moreover, maternal-fetal health among~~ immigrants residing in Western and Northern Europe who reported the least use of this medication category. ~~might be jeopardized.~~ Future research should definitely focus on this specific group of women, but also address more insights into the outcome of sub-optimal medication of severe conditions in pregnancy.

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DATA SHARING STATEMENT: No additional data are available. Researchers can apply for data access for subprojects within the overall aims of the main study 'The Multinational Medication Use in Pregnancy Study'.

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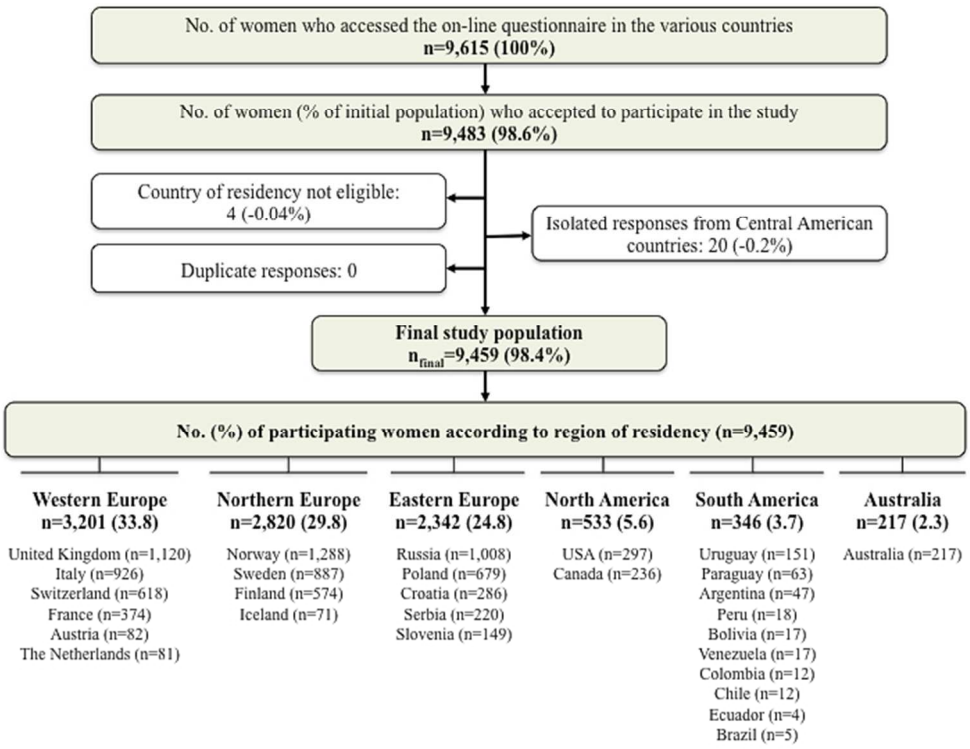

Figure 1 shows the participant flow-chart to achieve the final sample analyzed
60x45mm (300 x 300 DPI)

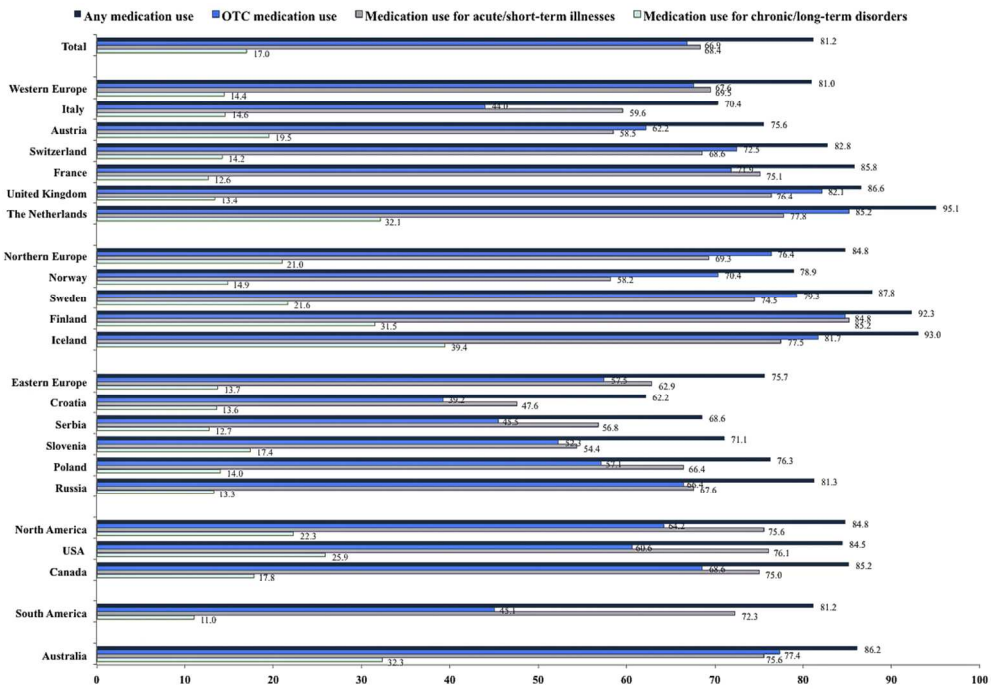

Figure 2 shows the proportion of respondents (%) reporting use of any medication, over-the-counter (OTC) medication, medication for acute/short-term illnesses and medication for chronic/long-term disorders during pregnancy according to region and country of residency. The observed estimates do not include vitamins, mineral supplements, iron, and herbal or alternative medicine products.
100x69mm (300 x 300 DPI)

Appendix 1: Survey questionnaire

Internet questionnaire

Medication use in pregnancy with focus on attitudes, perception of risk and mental health

The Multinational Medication Use in Pregnancy Study

INFORMATION ABOUT YOURSELF

1. In which country do you live? **Country:**_____	**In which region/province do you live?** **Region:** _____
2. Are you pregnant right now? □ Yes	□ No
(If yes in Q2) In which pregnancy week are you? **From 1 to 44** **(If yes in Q2) Is it a multiple pregnancy?** □ No □ Yes (e.g. twins, triplets, etc)	**(If No in Q2) How old is your newborn child (in weeks)?** **0-4 / 5-8 / 9-12 / 13-16 / 17-20 / 21-24 / 25-28 / > 29** **(If No in Q2) Do you breast feed your child?** □ Yes □ No
3. How many children do you already have from before? □ None □ One □ Two □ More than two	
4. What is your marital status? □ Married □ Cohabitant □ Single □ Divorced/Separated □ Other	
5. What is the highest education you have completed? □ Primary school (8-9 years of education) □ High-school (11-13 years of education) □ University □ Other education	
6. What was your work situation when you became pregnant? □ Student □ Housewife □ Health care personnel, i.e., physician, nurse, or pharmacist □ Employed in another sector □ Job seeker □ None of the above	
7. Is English your mother tongue? □ Yes □ No **(If No in Q7 above) What is your mother tongue**? _____	
8. Your age: Years, from 15 to 55	

INFORMATION ABOUT YOUR PREGNANCY

9. (If pregnant) Are you attending any pregnancy/birth preparation course or similar?

□ Yes
□ No, but I am planning to attend
□ No, I am not going to attend it

10. (If pregnant) What are your thoughts about how the experience of giving birth is going to be?

Please indicate your thoughts in a scale from 1 to 6, where **1 corresponds to absolutely terrible and 6 to absolutely fantastic**

Absolutely terrible	1 □	2 □	3 □	4 □	5 □	6 □	Absolutely fantastic

11. Was your pregnancy planned?

□ Yes
□ No, but it was not completely unexpected
□ No, it was not planned

12. Did you contact any healthcare provider due to infertility?

□ Yes
□ No

(If Yes in Q12 above) Did you, in this pregnancy, become pregnant secondarily to infertility treatment?

□ Yes
□ No

13. Have you taken folic acid? (alone or as part of multivitamins)

□ Yes, before pregnancy
□ Yes, before and during pregnancy
□ Yes, only during pregnancy
□ No
□ cannot remember

14. Did you smoke cigarettes before becoming pregnant?

□ Yes, regularly
□ Yes, occasionally
□ No, never

(If yes in Q14 as regularly/occasionally) Do you/did you smoke during pregnancy?

□ Yes, more than before
□ Yes, approximately the same
□ Yes, but less
□ No

(If yes) How many cigarettes (on average) do you/did you smoke per day?

□ < 1
□ 1-5
□ 6-10
□ > 11

15. Did you drink any alcohol after finding out that you were pregnant?

□ Yes
□ No
□ Cannot remember

(If yes) How much did you drink (in units)?
1 alcohol unit is equivalent to:
one 25ml single measure of whisky (ABV 40%),
or a third of a pint of beer (ABV 5-6%)
or half a standard (175ml) glass of red wine (ABV 12%).

□ More than 1-2 units per week
□ 1-2 units per week
□ 1-4 units per month
□ 1-2 units during the pregnancy
□ Can not remember

HEALTH DISORDERS AND MEDICATIONS DURING PREGNANCY

16. Have you experienced any of the disorders listed below during this pregnancy? If you use or have used any medicines in relation to [each health disorder listed] please enter the names of the medicines. In which weeks of pregnancy have you used them?

Health disorder		Medicine	Period of use (pregnancy weeks)
Nausea	□ Yes □ No	(If Nausea ticked) If you use or have used any medicines in relation to nausea, please enter the names of the medicines	□ week 0-12 □ week 13-24 □ week 25- delivery
Heartburn or reflux problems	□ Yes □ No	(If Heartburn ticked) If you use or have used any medicines in relation to heartburn or reflux problem, please enter the names of the medicines	□ week 0-12 □ week 13-24 □ week 25- delivery
Constipation	□ Yes □ No	(If Constipation ticked) If you use or have used any medicines in relation to constipation, please enter the names of the medicines	□ week 0-12 □ week 13-24 □ week 25- delivery
Common cold	□ Yes □ No	(If common cold ticked If you use or have used any medicines in relation to common cold, please enter the names of the medicines	□ week 0-12 □ week 13-24 □ week 25- delivery
Urinary tract infections	□ Yes □ No	(If UTI ticked) If you use or have used any medicines in relation to urinary tract infections, please enter the names of the medicines	□ week 0-12 □ week 13-24 □ week 25- delivery
Other infections	□ Yes □ No	(If other infections ticked) If you use or have used any medicines in relation to other infections, please enter the names of the medicines	□ week 0-12 □ week 13-24 □ week 25- delivery
Pain in neck or back or pelvic girdle	□ Yes □ No	(If pain ticked) If you use or have used any medicines in relation to pain in neck or back or pelvic girdle, please enter the names of the medicines	□ week 0-12 □ week 13-24 □ week 25- delivery
Headache	□ Yes □ No	(If headache ticked) If you use or have used any medicines in relation to headache, please enter the names of the medicines	□ week 0-12 □ week 13-24 □ week 25- delivery
Sleeping problems	□ Yes □ No	(If sleeping problems ticked) If you use or have used any medicines in relation to sleeping problems, please enter the names of the medicines	□ week 0-12 □ week 13-24 □ week 25- delivery

17. Have you been on sick leave during this pregnancy?	
□ Yes	□ No

18. (If yes in Q17) What was the reason for it? In which pregnancy weeks have you been on sick leave?

Reason of the sick leave	**Sick leave period (pregnancy week)**
_____ _____	□ week 0-12 □ week 13-24 □ week 25-delivery

19. Below, some common over-the-counter (OTC) medicines are mentioned. Please indicate whether you have used any of them during pregnancy.

Please enter the name of all *X* medicines you have used.
In which pregnancy weeks have you used them?

		Name of the medicine(s) you have used	**Period of use (pregnancy week)**
Pain killers (*e.g. paracetamol*)	□ Yes □ No	(If painkillers ticked) Please enter the name of all pain killers you have used during pregnancy.	□ week 0-12 □ week 13-24 □ week 25- delivery
Nasal spray/drops (excluding salt water solution) (*e.g. Otrivine, Vicks Sinex decongestant Nasal spray*)	□ Yes □ No	(If nasal spray ticked) Please enter the name of all nasal sprays/drops you have used during pregnancy.	□ week 0-12 □ week 13-24 □ week 25- delivery
Medication against heartburn (*e.g. Gaviscon or Rennie*)	□ Yes □ No	(If OTC for heartburn ticked) Please enter the name of all medications you have used against heartburn during pregnancy.	□ week 0-12 □ week 13-24 □ week 25- delivery
Medication against nausea/travel sickness (*e.g. Cetirizine, Sea-Legs)*	□ Yes □ No	(If OTC for nausea ticked) Please enter the name of all medications you have used against nausea during pregnancy.	□ week 0-12 □ week 13-24 □ week 25- delivery
Medication against constipation (*e.g.Lactulose, Dulcolax)*	□ Yes □ No	(If OTC for constipation ticked) Please enter the name of all medications you have used against constipation during pregnancy.	□ week 0-12 □ week 13-24 □ week 25- delivery

20. Did you take any herbal preparations during pregnancy (e.g. ginger, echinacea, valerian, cranberries)**?**

□ Yes □ No □ Cannot remember

(If yes) Please provide the name of all herbal preparations you have taken during pregnancy**.**
(If yes) What was the reason for taking herbal preparations (health disorder, illness)?
(If yes) In which pregnancy weeks did you take herbal preparations?

Name of herbal preparation used	**Reason for use (health disorder, illness)**	**Period of use (pregnancy week**
_____ _____ _____	_____ _____ _____	□ week 0-12 □ week 13-24 □ week 25- delivery
_____ _____ _____	_____ _____ _____	□ week 0-12 □ week 13-24 □ week 25- delivery

21. (If you used herbal preparations during pregnancy) Who recommended to you to take herbal preparations during pregnancy? (You may tick more than one answer)

□ My own initiative
□ Family/friends
□ Physician
□ Midwife/Nurse
□ Pharmacy personnel
□ Herbal shop personnel
□ Internet
□ Magazines, media, etc.
□ Other (please specify:_____)

22. Did you use homeopathic products during pregnancy?

□ Yes □ No □ Cannot remember

(If yes in Q22 above) What was the reason for use?

_____

A BIT MORE ABOUT MEDICATION USE DURING PREGNANCY

23. Have you deliberately avoided taking an over-the-counter medicine during your pregnancy?

□ Yes □ No □ Cannot remember

(If yes in Q23 above) Which medicine was it?

_____

(If yes in Q23 above) What was the reason for doing so?

_____

_____

24. Have you deliberately chosen not to use a medicine prescribed by a doctor because you were pregnant?

□ Yes □ No □ Can not remember

(If yes in Q24 above) Which medicine was it?

_____

(If yes in Q24 above) What was the reason for doing so?

_____

_____

YOUR NEEDS FOR INFORMATION

25. Did you need information about medicines during the course of your pregnancy?
□ Yes □ No □ Cannot remember

26. (If yes in Q25) Whom did you turn to for information? (*You may tick more than one answer*)
□ Family/friends
□ Physician
□ Midwife/Nurse
□ Pharmacy personnel
□ Herbal shop personnel
□ Drug formulary/information leaflet
□ Poison information centre
□ Teratology information service
□ National center of information on medicines
□ Internet
□ Magazines, media, etc
□ Other (please specify:_____)

27. (if yes in Q25) If you have obtained information from various sources, was such information similar?
□ Yes, completely similar
□ Yes, as a whole (only the wording or detail level was somewhat different)
□ No, part of the information was different
□ No, the information was completely contradictory

28. (If No – last 2 options in Q27) If there were discrepancies among the sources, what did it mean to you? (*You may tick more than one answer*)
□ Nothing
□ I became anxious
□ I decided not to use the medication
□ I sought for a new information source (Which new source have you consulted? _____)
□ I chose to rely on one source and ignore the conflicting one (On which source have you relied? _____Which source have you ignored? _____)

29. How often do you have someone help you read hospital materials?
□ Always
□ Often
□ Sometimes
□ Occasionally
□ Never

30. How confident are you filling out medical forms by yourself?
□ Extremely
□ Quite a bit
□ Somewhat
□ A little bit
□ Not at all

31. How often do you have problems learning about your medical condition because of difficulty understanding written information?
□ Always
□ Often
□ Sometimes
□ Occasionally
□ Never

The following section will pop-up only if the subject has reported to be suffering from a chronic disease

I. MEDICATIONS FOR CHRONIC DISEASES DURING PREGNANCY

If you use or have used medicines for a chronic disease during your pregnancy fill out this part of the questionnaire (I, II, III) and provide some information about those medicines you use daily.

Some chronic diseases are asthma, allergy, hypothyroidism (low thyroid hormone), rheumatic diseases (incl. rheumatoid arthritis, psoriatic arthritis), diabetes (type I or II), epilepsy, depression, anxiety, cardiovascular diseases (incl. hypertension, high cholesterol, and heart diseases)

Do you suffer of any chronic disease? □ Yes □ No

(If Yes above) Please indicate whether you suffer of any of the following chronic diseases.

		If you use or have used medicines for *X* during your pregnancy, please enter the name of the medicines.	**In which weeks of pregnancy did you use them?**
Asthma	□ Yes □ No	(If Asthma ticked) If you use or have used medicines for asthma during pregnancy, please enter the names of the medicines.	□ week 0-12 □ week 13-24 □ week 25-delivery
Allergy	□ Yes □ No	(If Allergy ticked) If you use or have used medicines for allergy during pregnancy, please enter the names of the medicines.	□ week 0-12 □ week 13-24 □ week 25-delivery
Hypothyroidism (low thyroid hormone)	□ Yes □ No	(If Hypothyroidism ticked) If you use or have used medicines for hypothyroidism during pregnancy, please enter the names of the medicines.	□ week 0-12 □ week 13-24 □ week 25-delivery
Rheumatic disorders (incl. rheumatoid arthritis, psoriatic arthritis)	□ Yes □ No	(If Rheumatic disorders ticked) If you use or have used medicines for rheumatic disorder during pregnancy, please enter the names of the medicines.	□ week 0-12 □ week 13-24 □ week 25-delivery
Diabetes (type I or II)	□ Yes □ No	(If Diabetes ticked) If you use or have used medicines for diabetes during pregnancy, please enter the names of the medicines.	□ week 0-12 □ week 13-24 □ week 25-delivery
Epilepsy	□ Yes □ No	(If Epilepsy ticked) If you use or have used medicines for epilepsy during pregnancy, please enter the names of the medicines.	□ week 0-12 □ week 13-24 □ week 25-delivery
Depression	□ Yes □ No	(If Depression ticked) If you use or have used medicines for depression, please enter the names of the medicines.	□ week 0-12 □ week 13-24 □ week 25-delivery
Anxiety	□ Yes □ No	(If Anxiety ticked) If you use or have used medicines for anxiety during pregnancy, please enter the names of the medicines.	□ week 0-12 □ week 13-24 □ week 25-delivery

		If you use or have used medicines for *X* during your pregnancy, please enter the name of the medicines.	In which weeks of pregnancy did you use them?
Cardiovascular diseases (incl. hypertension, high cholesterol, heart diseases)	□ Yes □ No	(If Cardio disease ticked) If you use or have used medicines for cardiovascular diseases during pregnancy, please enter the names of the medicines.	□ week 0-12 □ week 13-24 □ week 25-delivery
Others (If Others ticked) (Please specify which other disease(s): _____)	□ Yes □ No	(If Other disease ticked) If you use or have used medicines for your chronic disease during pregnancy, please enter the names of the medicines.	□ week 0-12 □ week 13-24 □ week 25-delivery

Section II will pop-up only if the subject has reported to be suffering of a chronic disease

II. YOUR VIEWS ABOUT PRESCRIBED MEDICINES

In this section of the survey questionnaire, the **Belief About Prescribed Medicine Questionnaire (BMQ-Specific)** was presented (Horne R, Weinman J, Hankins M. The beliefs about medicines questionnaire: The development and evaluation of a new method for assessing the cognitive representation of medication. Psychol Health. 1999;14(1):1-24).

Section III will pop-up only if the subject has reported to be suffering of a chronic disease. There will be one single scale for each chronic condition reported

III. QUESTION ABOUT YOUR USE OF MEDICATIONS FOR X DURING PREGNANCY AND/OR POSTPARTUM

In this section of the survey questionnaire, the **8-item Morisky Medication Adherence Questionnaire (MMAS-8)** was presented (*Morisky DE, Green LW, Levine DM. Concurrent and predictive validity of a self-reported measure of medication adherence. Medical care. 1986;24(1):67-74*).

Do you have any other comments about your medication use during pregnancy?

_____

_____

_____

_____

_____

YOUR VIEWS ABOUT MEDICATIONS

In this section of the survey questionnaire, the **Belief About Medicine Questionnaire (BMQ-General)** was presented (*Horne R, Weinman J, Hankins M. The beliefs about medicines questionnaire: The development and evaluation of a new method for assessing the cognitive representation of medication. Psychol Health. 1999;14(1):1-24*).

32. Below are some statements about use of medicines in pregnancy. Please specify how much you agree or disagree with these statements by ticking where appropriate. (*You may only tick once per line*)					
	Strongly agree	**Agree**	**Uncertain**	**Disagree**	**Strongly disagree**
I have a higher threshold for using medicines when I am pregnant than when I'm not pregnant	○	○	○	○	○
Even though I am ill and could have taken medicines, it is better for the foetus that I refrain from using them	○	○	○	○	○
Pregnant women should preferably use herbal remedies than conventional medicines	○	○	○	○	○

YOUR ASSESSMENT OF PREGNANCY RISKS

33. Among 100 healthy women in a healthy environment, how many do you think will give birth to a child with a birth defect?

_____

34. Here below is a list with various medicines, food and other substances.
Please indicate how harmful you think they are for the foetus in a scale from 0 to 10, where 0 corresponds to 'not harmful' and 10 to 'very harmful'.

If you have not heard before about such substance, tick 'unknown substance'.

	Unknown substance	0	1	2	3	4	5	6	7	8	9	10
Paracetamol/acetaminophen	o	o	o	o	o	o	o	o	o	o	o	o
Antibiotics (*e.g. Penicillins*)	o	o	o	o	o	o	o	o	o	o	o	o
Antidepressants	o	o	o	o	o	o	o	o	o	o	o	o
Thalidomide	o	o	o	o	o	o	o	o	o	o	o	o
Swine influenza vaccine	o	o	o	o	o	o	o	o	o	o	o	o
OTC medicines against nausea/travel sickness	o	o	o	o	o	o	o	o	o	o	o	o
Ginger	o	o	o	o	o	o	o	o	o	o	o	o
Cranberries	o	o	o	o	o	o	o	o	o	o	o	o
Blue veined cheese *(e.g. Gorgonzola)*	o	o	o	o	o	o	o	o	o	o	o	o
Eggs	o	o	o	o	o	o	o	o	o	o	o	o
Alcohol during the 1. trimester (*e.g. wine, beer, spirits*)	o	o	o	o	o	o	o	o	o	o	o	o
Smoking (*e.g. cigarettes*)	o	o	o	o	o	o	o	o	o	o	o	o
Dental X-ray	o	o	o	o	o	o	o	o	o	o	o	o

HOW YOU ARE FEELING NOW

In this section of the survey questionnaire, the **Edinburgh Postnatal Depression Scale (EPDS)** was presented (*Cox J, Holden J, Sagovsky R. Detection of postnatal depression. Development of the 10-item edinburgh postnatal depression scale. The British Journal of Psychiatry. 1987 June 1, 1987;150(6):782-6*).

HOW YOU SEE YOURSELF

In this section of the survey questionnaire, the **Big Five Inventory (BFI)** was presented (*John OP, Srivastava S, editors. The big five trait taxonomy: History, measurement, and theoretical perspectives: New York: Guilford; 1999; John OP, Robins RW, Pervin LA. Handbook of personality: Theory and research: The Guilford Press; 2008*).

Appendix 2: Websites used for recruitment and internet penetration rates in each country where data were collected

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Country	*Website used for recruitment*	*Internet penetration rates (%)*
EUROPE		
	Western Europe	
Austria	www.schwangerschaft.at; www.schwangerschafts-blog.at; www.fratz.at; www.netdoctor.at; www.babycenter.at; www.baby-boom.at; www.ekiz-dachverband.at; www.babyguide.at	93* [1]
France	www.aufeminin.com (*Including ipad application to website subscribers*)	91* [1]
Italy	*Pregnancy Forums*: www.gravidanzaonline.it; www.forumsalute.it; www.mammole.it; www.pianetamamma.it; www.miobambino.it *Targeted email to pregnancy forum subscribers*: www.gravidanzaonline.it	70* [1]
Switzerland	www.bebe-bebe.com; www.swissmom.ch	84* [2]
The Netherlands	www.lareb.nl; www.gezondzwangerzijn.nl; www.babybytes.nl	98* [1]
United Kingdom	*Targeted email to pregnancy forum subscribers*: www.bounty.com *Pregnancy Forums*: www.pregnancyforum.co.uk; www.pregnancyforum.org.uk	93* [1]
	Northern Europe	
Finland	www.vauva.fi; www.meidanperhe.fi; www.kaksplus.fi	99* [1]
Iceland	*Pregnancy Forums*: www.bland.is	100* [1]
Norway	www.barnimagen.com; www.klikk.no; www.jormorsiri.no; www.tryggmamamedisin.no	99* [1]
Sweden	www.barntotal.se; www.minbebis.com; www.se.babycenter.com; www.socmed.gu.se	99* [1]
	Eastern Europe	
Croatia	www.cybermed.hr	80* [1] (data from 2010)
Poland	www.zzief.umlub.pl *Pregnancy Forums*: www.ebrzuszek.pl; www.babyboom.pl; www.zapytajpolozna.pl; www.planujemydziecko.pl; www.twoja-ciaza.com.pl	84* [1]

Country	*Website used for recruitment*	*Internet penetration rates (%)*
Russia	www.babyblog.ru; www.littleone.ru *Pregnancy Forums*: www.woman.ru; www.9months.ru; www.bemam; www.280dney.ru; www.iampregnant.ru www.pregnancy.org.ua; www.baby.ru; www.mama66.ru; www.spuzom.ru	48* [2]
Serbia	www.ringeraja.rs	52* [1] (data from 2009)
Slovenia	*Pregnancy Forums*: www.med.over.net	92* [1]
AMERICAS		
	North America	
Canada	www.otispregnancy.org; Facebook page of OTIS; www.babyontheway.com.ca *Pregnancy Forums*: www.babycentre.com.ca; www.thecradle.com; www.talk.sheknows.com; www.parenting.com	94† [3]
USA	www.otispregnancy.org; Facebook page of OTIS; www.justmommies.com *Pregnancy Forums*: www.babyandbump.com www.thecradle.com; www.talk.sheknows.com; www.parenting.com	80§ [4]
	Central America	
Belize	www.otispregnancy.org; Facebook page of OTIS	23[2]
Costa Rica		43[2]
El Salvador		25[2]
Guatemala		16[2]
Honduras		16[2]
Nicaragua		14[2]
Panama		43[2]
	South America	
Argentina	www.otispregnancy.org; Facebook page of OTIS	67[2]
Bolivia		30[2]
Brazil	*Pregnancy Forums*: www.semanaasemana.com; www.univision.com; www.elembarazo.net	46[2]
Chile		59[2]
Colombia		59[2]
Ecuador		44[2]
Paraguay		24[2]
Peru		37[2]

Country	*Website used for recruitment*	*Internet penetration rates (%)*
Uruguay		56[2]
Venezuela		41[2]
	AUSTRALIA	
Australia	www.mothersafe.org.au; www.bubhub.com.au *Pregnancy Forums*: www.abds.org.au; www.birth.com.au	83ζ [5]

*Indicates the frequency of internet access - at least once a week, including every day - among individuals aged 25- 34 years. Differences between men and women were relatively small. Slightly more than two thirds of men (70%) and 65% of women used the Internet regularly.
†Indicates individuals aged 16-45 years who used the internet for personal use.
§Indicates individuals > 18 years old, access from anywhere; household internet for women is equal to 68.1%; higher percentages are observed for people aged 25-54 years.
ζ Indicates households with access to the internet at home.

Sources of internet penetration rates:

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Appendix 3: Socio-demographic characteristics of the study population and general birthing population on individual country

Appendix 3a: Socio-demographic characteristics in Western European countries (Switzerland, Italy and United Kingdom (UK))

	Study sample in Switzerland n=618	General birthing population in Switzerland LB=80,808[1]	Study sample in Italy n=926	General birthing population in Italy LB=546,606[1]	Study sample in the UK n=1,120	General birthing population in UK* LB=723,165[2]
	(%)	(%)	(%)	(%)	(%)	(%)
No. of respondents/No. live births ¶	4.6%		1.0%		0.9%	
Mean Age +/- sd	31.6 +/- 4.3	31.4[3]	32.3 +/- 5.0	31.3[4]	30.5 +/- 5.2	29.6[2]
Marital status						
In marriage	80.0	80.7[3]	68.8	75.1[1]	63.3	53.2[2]
Outside marriage	20.0	19.3[3]	31.2	31.5[1]	36.7	46.8[2]
Parity						
No previous children	53.2	-	59.7	48.7[5]	48.0†	41.9[2] †
Educational level						
Less than high school	11.0	11.7[6]	7.0	25.2[6]	0.6	16.5[2]
High school	13.6	49.2[6]	47.2	49.2[6]	27.9	37.2[2]
More than high school	47.2	39.1[6]	44.3	25.6[6]	52.1	46.3[2]
Other	28.2	-	1.5	-	19.3	-
Women smoking before pregnancy	25.1	25.4[7]	34.2	33.3[4]	25.2	25.7[7]
Women smoking during pregnancy	5.5	6.6[8]	10.5	22.7[9]	7.1‡	13.2[10] ‡
Use of alcohol during pregnancy	20.7	29.9[8]	17.9	17.7[9]	28.3	24.0[11] §

Abbreviations: LB: Number of live births per year.

*The figures shown here are statistic estimates for England and Wales. Scotland and Northern Ireland have separate statistical reports. Since more than 85% of the study population in UK were resident in England and about 8% in Wales, we are only showing national statistic data for these two parts of the UK.

¶The ratio "No. of respondents/No. live births" is calculated as the proportion (%) of pregnancies included in the study among live births in the country in two months (period of data collection).
†Among married women only – as provided by the Statistics Bureau in the UK.
‡Among women resident in England only (as provided by the Statistics Bureau in the UK, data on 4th Quarter of 2011).
§Women reporting at least one occasion during pregnancy of consuming more than four drinks in a day.

Appendix 3b: Socio-demographic characteristics in Western European countries (Austria, France and The Netherlands)

	Study sample in Austria n=82 (%)	General birthing population in Austria LB=78,109[1] (%)	Study sample in France n=374 (%)	General birthing population in France LB=824,263[1] (%)	Study sample in The Netherlands n=81 (%)	General birthing population in The Netherlands LB=180,060[1] (%)
No. of respondents/No. live births *	0.6%		0.3%		0.3%	
Mean Age +/- sd	30.6 +/- 4.6	30.0[12]	29.6 +/- 4.9	30.1[13]	32.0 +/- 6.4	31.0[14]
Marital status						
In marriage	48.8	59.6[15]	48.9	45.0[1]	69.1	58.2[14]
Outside marriage	51.2	40.4[15]	51.1	55.0[1]	30.8	41.8[14]
Parity						
No previous children	63.4	47.96[15]	52.9	44.2[16]	38.3	46.4[14]
Educational level						
Less than high school	9.8	13.3[6]	1.6	15.4[6]	9.9	15.9[6]
High-school	32.9	64.1[6]	25.1	37.4[6]	66.7	40.2[6]
More than high school	40.2	22.7[6]	57.0	47.2[6]	23.5	43.9[6]
Other	17.1	-	16.3	-	-	-
Women smoking before pregnancy	31.7	32.1[17]	39.3	39.0[16]	34.6	29.5[7]
Women smoking during pregnancy	4.9	-	14.2	28.0[16]	14.8	17.1[18]
Use of alcohol during pregnancy	13.4	-	11.5	52.0[19]	11.1	16-35[14]

Abbreviations: LB: Number of live births per year.

*The ratio "No. of respondents/No. live births" is calculated as the proportion (%) of pregnancies included in the study among live births in the country in two months (period of data collection).

Appendix 3c: Socio-demographic characteristics in Northern European countries (Norway, Finland and Sweden)

	Study sample in Norway n=1,228	General birthing population in Norway LB=60,220[1]	Study sample in Finland n=574	General birthing population in Finland LB=59,961[1]	Study sample in Sweden n=887	General birthing population in Sweden LB=111,770[1]
	(%)	**(%)**	**(%)**	**(%)**	**(%)**	**(%)**
No. of respondents/No. live births *	12.2%		5.7%		4.8%	
Mean Age +/- sd	29.0 +/- 4.6	29.8 +/- 5.3[20]	29.0+/-5.1	30.1[21]	29.8 +/- 5.3	30.3[22]
Marital status						
In marriage	39.1	46.0[20]	59.4	57.8[21]	40.7	45.8[1]
Outside marriage	60.9	53.4[20]	40.6	42.0[21]	59.3	54.2[1]
Unknown	-	0.6[20]	-	0.2[21]		
Parity						
No previous children	41.4	42.4[20]	35.5	42.2[21]	63.1	44.9[22]
Educational level						
Less than high school	4.5	14.7[6]	8.2	7.1[6]	5.2	11.1[6]
High-school	28.0	31.4[6]	36.4	44.5[6]	30.0	38.2[6]
More than high school	46.9	53.9[6]	52.6	48.4[6]	60.6	50.6[6]
Other	20.7	-	2.8	-	4.2	-
Women smoking before pregnancy	33.5	36.5[7]	36.7	19.7[7]	25.0	27.2[7]
Women smoking during pregnancy	6.8	7.0[20]	11.7	15.2[21]	5.4	6.5[22]
Use of alcohol during pregnancy	4.1	7.4[23]	13.9	-	7.2	5.9[24]

Abbreviations: LB: Number of live births per year.

*The ratio "No. of respondents/No. live births" is calculated as the proportion (%) of pregnancies included in the study among live births in the country in two months (period of data collection).

Appendix 3d: Socio-demographic characteristics in Northern European countries (Iceland)

	Study sample in Iceland n=71	General birthing population in Iceland LB=4,492[1]
	(%)	**(%)**
No. of respondents/No. live births *	9.3%	
Age range (in years)		
15-20	11.3	5.1[25]
21-25	16.9	19.3[25]
26-30	42.3	34.2[25]
31-35	15.5	27.3[25]
36-40	12.7	11.7[25]
≥41	1.4	2.4[25]
Marital status		
In marriage	31.0	35.0[25]
Outside marriage	69.0	65.0[25]
Parity		
No previous children	47.9	38.1[25]
Educational level		
Less than high school	25.4	21.4[6]
High-school	18.3	30.5[6]
More than high school	43.7	48.1[6]
Other	12.7	-
Women smoking before pregnancy	40.8	35.5[7]

Abbreviations: LB: Number of live births per year.

*The ratio "No. of respondents/No. live births" is calculated as the proportion (%) of pregnancies included in the study among live births in the country in two months (period of data collection).

Appendix 3e: Socio-demographic characteristics in Eastern European countries (Croatia, Slovenia and Serbia)

	Study sample in Croatia n=286	General birthing population in Croatia LB=41,197[1]	Study sample in Slovenia n=149	General birthing population in Slovenia LB=21,947[1]	Study sample in Serbia n=220	General birthing population in Serbia LB=65,598[1]
	n (%)	**(%)**	**n (%)**	**(%)**	**n (%)**	**(%)**
*No. of respondents/No. live births**	4.2%		4.1%		2.0%	
Mean Age +/- sd	29.1 +/- 4.5†	27.7[26]	31.7 +/- 4.5	30.4[27]	29.2 +/- 3.9*	28.7[1,28]
Marital status						
In marriage	83.9	86.7[26]	47.0	43.2[27]	90.1	76.1[28]
Outside marriage	16.1	13.3[26]	53.0	56.8[27]	9.9	23.9[28]
Parity						
No previous children	50.7	46.9[26]	45.6	48.5[27]	46.8	51.1[28,29]
Educational level						
Less than high school	1.0	3.1[26]	2.0	8.5[27]	0.9	15.9[29]
High-school	36.7	52.5[26]	24.8	48.5[27]	33.6	54.9[29]
More than high school	61.2	44.4[26]	69.1	43.0[27]	61.8	29.2[29]
Other	1.0	-	4.0	-	3.6	-
Women smoking before pregnancy	50.0	34.4[26]	32.9	34.4[7]	49.1	29.9[30,31]
Women smoking during pregnancy	18.8	23.1[32]	6.7	9.6-11.2[33]	18.2	18.4[31]
Use of alcohol during pregnancy	12.6	15.5[34]	32.2	-	15.0	-

Abbreviations: LB: Number of live births per year.

* The ratio "No. of respondents/No. live births" is calculated as the proportion (%) of pregnancies included in the study among live births in the country in two months (period of data collection).

†Mean age for first child (as it is available from the Statistics Bureau reports in Croatia and Serbia).

Appendix 3f: Socio-demographic characteristics in Eastern European countries (Poland and Russia)

	Study sample in Poland n=679	General birthing population in Poland LB=388,416[1]	Study sample in Russia n=1,008	General birthing population in Russia LB=1,796,629[1]
	(%)	**(%)**	**(%)**	**(%)**
No. of respondents/No. live births[*]	1.0%		0.3%	
Mean Age +/- sd	27.1 +/- 4.1	28.6[35] †	27.7 +/- 4.8	27.4[36]
Marital status				
In marriage	85.0	79.4[35]	85.3	73.9[36]
Outside marriage	15.0	20.6[35]	14.7	26.1[36]
Parity				
No previous children	40.6	50.1[35]	57.9	-
Educational level				
Less than high school	1.9	8.7[35]	1.6	-
High-school	31.1	49.6[35]	9.3	-
More than high school	65.1	41.6[35]	75.1	-
Other	1.9	-	14.0	-
Women smoking before pregnancy	49.2	25.0[37]	46.1	30.8[38]
Women smoking during pregnancy	12.8	22-30[37]	9.6	4.3-6.5[39,40]
Use of alcohol during pregnancy	9.6	15.3[41]	26.0	60.0[42]

Abbreviations: LB: Number of live births per year.

[*] The ratio "No. of respondents/No. live births" is calculated as the proportion (%) of pregnancies included in the study among live births in the country in two months (period of data collection).

[†]Median age of women at birth, not mean age.

Appendix 3g: Socio-demographic characteristics in North American countries (Canada and USA)

	Study sample in Canada n=236 n (%)	General birthing population in Canada[43] LB=377,636 (%)	Study sample in The USA n=297 n (%)	General birthing population in USA[44] LB=3,999,386 (%)
*No. of respondents/No. live births**	0.4%		0.04%	
Age range (in years)				
15-19	2.1	3.9[43]	4.7	9.3[44]
20-24	25.0	14.6[43]	18.2	23.8[44]
25-29	30.1	30.2[43]	28.3	28.3[44]
30-34	30.5	32.2[43]	29.3	24.1[44]
35-39	11.0	15.6[43]	15.2	11.6[44]
40-44	1.3	3.1[43]	4.0	2.7[44]
≥45	-	0.2[43]	0.3	0.2[44]
Mean Age +/- sd	28.3 +/- 5.2	29.6[43]	29.3 +/- 6.1	-
Marital status				
In marriage	42.4	60.4[43]	67.0	59.2[45]
Outside marriage	57.6	28.8[43]	33.0	39.9[45]
Unknown	-	10.8[43]	-	0.9[45]
Parity				
No previous children	48.3	43.3[43]	41.1	40.1[44]
Educational level				
Less than high school	1.3	8.4[46]	2.7	17.4[47]
High-school	24.6	-	25.3	24.4[47]
More than high school	67.8	69.6[46]	62.0	58.2[47]
Other	6.4	-	10.1	-
Women smoking before pregnancy	29.2	22.0[48]	28.3	21.5[49]

	Study sample in Canada n=236 n (%)	General birthing population in Canada[43] LB=377,636 (%)	Study sample in The USA n=297 n (%)	General birthing population in USA[44] LB=3,999,386 (%)
Women smoking during pregnancy	16.1	13.4[46]	8.1	10.2[50]
Use of alcohol during pregnancy	16.1	10.5[46]	17.5	15.5[49]

Abbreviations: LB: Number of live births per year.

*The ratio "No. of respondents/No. live births" is calculated as the proportion (%) of pregnancies included in the study among live births in the country in two months (period of data collection).

Appendix 3h: Socio-demographic characteristics in Australia

	Study sample in Australia n=217	General birthing population in Australia[51] LB=301,617
	n (%)	**(%)**
*No. of respondents/No. live births**	0.4%	
Mean Age +/- sd	31.1 +/- 5.7	30.7[51]
Marital status		
In marriage	70.5	65.8[51]
Outside marriage	29.5	34.2[51]
Parity		
No previous children	47.9	43.8[51]
Educational level		
Less than high school	0.5	20.6†[52]
High-school	29.0	
More than high school	63.1	56.0[53]
Other	7.4	-
Women smoking before pregnancy	29.1	29.9[54]
Women smoking during pregnancy	14.3	14.5[55]
Use of alcohol during pregnancy	27.2	29.0[56]

Abbreviations: LB: Number of live births per year.

*The ratio "No. of respondents/No. live births" is calculated as the proportion (%) of pregnancies included in the study among live births in the country in two months (period of data collection).

†Refers to the educational levels "high school" and "less than high school" grouped together.

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Appendix 4: Sample size calculation (using 5% precision with 95% confidence interval) for the population survey on region and individual country levels.

	Study sample	Population size*	Expected prevalence				
			Any medication use=80%	*Any medication use=70%*	*OTC medication use=60%*	*Chronic medication use=30%*	*Chronic medication use=15%*
			Required sample size				
Western Europe	3,201	Not known	246	323	369	323	196
United Kingdom	1,120	120,528	245	322	368	322	196
Italy	926	91,101	245	322	367	322	195
Switzerland	618	13,468	241	315	359	315	193
France	374	137,377	245	322	368	322	196
Austria†	82	13,018	241	315	359	315	193
The Netherlands†	81	30,010	244	319	364	319	195
Northern Europe	2,820	Not known	246	323	369	323	196
Norway	1,228	10,037	240	313	356	313	192
Sweden	887	18,628	243	317	362	317	194
Finland	574	9,994	240	313	356	313	192
Iceland†	71	749	185	225	247	225	155
Eastern Europe	2,342	Not known	246	323	369	323	196
Russia	1,008	299,438	246	322	368	322	196
Poland	679	64,736	245	321	367	321	195
Croatia§	286	6,866	237	308	350	308	190
Serbia¶	220	10,933	240	313	357	313	192
Slovenia**	149	3,658	230	297	335	297	186
North America	533	Not known	246	323	369	323	196
USA§	297	666,564	246	323	369	323	196
Canada††	236	62,939	245	321	367	321	195
South America¶¶	346	Not known	246	323	369	323	196
Australia§§	217	50,270	245	321	366	321	195

Sample size calculations were performed in Epi Info ™ 7 available at: Center for DiseaseControl and Prevention (CDC), Epi Info. URL: http://wwwn.cdc.gov/epiinfo/. Accessed 2013 Dec 31.

[*]The population size indicates the number of live births in the country in two months (corresponds to the period of data collection) (cf. Appendix 3 for annual estimates of live births in each country). For the all regions except Australia, the population size is very large but not known exactly (i.e. infinite population). Infinite population size is therefore assumed in the calculation of the required sample size.

[†]The sample size allows for prevalence estimates with a precision of 9% (expected prevalence=80%), 10% (expected prevalence=70% and 30%), 11% (expected prevalence=60%) and 8% (expected prevalence=15%).

[§]The sample size allows for prevalence estimates with a precision of 6% (expected prevalence=70%, 60% and 30%).

[¶]The sample size allows for prevalence estimates with a precision of 6% (expected prevalence=80%) and 7% (expected prevalence=70%, 60% and 30%).

[**]The sample size allows for prevalence estimates with a precision of 7% (expected prevalence=80%), 8% (expected prevalence=70%, 60% and 30%) and 6% (expected prevalence=15%).

[††]The sample size allows for prevalence estimates with a precision of 6% (expected prevalence=80%, 70% and 30%) and 7% (expected prevalence=60%).

[¶¶]The sample size allows for prevalence estimates with a precision of 6% (expected prevalence=60%).

[§§]The sample size allows for prevalence estimates with a precision of 6% (expected prevalence=80%) and 7% (expected prevalence=70%, 60% and 30%).

Appendix 5: Overall medication use on 1st and 2nd ATC level according to timing of use in pregnancy (n=9,459)*

Anatomical Therapeutic Chemical (ATC) classification index 1st and 2nd levels		Anytime during pregnancy n (%)	1st trimester n (%)	2nd trimester n (%)	3rd trimester n (%)
A	**Alimentary tract and metabolism**	**4,275 (45.2)**	**2,786 (29.5)**	**3,390 (35.8)**	**3,160 (33.4)**
A01	Stomatological preparations	62 (0.7)	42 (0.4)	52 (0.5)	46 (0.5)
A02	*Drugs for acid related disorders*	3,242 (34.3)	2,034 (21.5)	2,634 (27.8)	2,615 (27.6)
A03	Drugs for functional gastrointestinal disorders	650 (6.9)	543 (5.7)	512 (5.4)	381 (4.0)
A04	Antiemetics and antinauseants	136 (1.4)	124 (1.3)	114 (1.2)	81 (0.9)
A05	Bile and liver therapy	24 (0.3)	15 (0.2)	17 (0.2)	16 (0.2)
A06	*Laxatives*	978 (10.3)	696 (7.4)	835 (8.8)	735 (7.8)
A07	Antidiarrheals, intestinal antiinflammatory/antiinfective agents	89 (0.9)	61 (0.6)	69 (0.7)	57 (0.6)
A09	Digestives, incl. enzymes	9 (0.1)	7 (0.1)	8 (0.1)	3 (0.0)
A10	Drugs used in diabetes	85 (0.9)	57 (0.6)	58 (0.6)	45 (0.5)
-	Unspecified medications for nausea	6 (0.1)	5 (0.1)	4 (0.0)	3 (0.0)
B	**Blood and blood forming organs**	**148 (1.6)**	**89 (0.9)**	**102 (1.1)**	**79 (0.8)**
B01	*Antithrombotic agents*	135 (1.4)	78 (0.8)	95 (1.0)	72 (0.8)
B02	Antihemorrhagics	5 (0.1)	4 (0.0)	2 (0.0)	3 (0.0)
B05	Blood substitutes and perfusion solutions	7 (0.1)	5 (0.1)	5 (0.1)	2 (0.0)
B06	Other hematological agents	3 (0.0)	2 (0.0)	2 (0.0)	3 (0.0)
C	**Cardiovascular system**	**202 (2.1)**	**132 (1.4)**	**161 (1.7)**	**133 (1.4)**
C01	Cardiac therapy	7 (0.1)	4 (0.0)	5 (0.1)	4 (0.1)
C02	*Antihypertensives*	56 (0.6)	34 (0.4)	42 (0.4)	31 (0.3)
C03	Diuretics	6 (0.1)	5 (0.1)	3 (0.0)	2 (0.0)
C04	Peripheral vasodilators	3 (0.0)	3 (0.0)	3 (0.0)	3 (0.0)
C05	Vasoprotectives	44 (0.5)	24 (0.3)	35 (0.4)	31 (0.3)
C07	*Beta blocking agents*	74 (0.8)	51 (0.5)	59 (0.6)	51 (0.5)
C08	Calcium channel blockers	21 (0.2)	16 (0.2)	18 (0.2)	13 (0.1)
C09	Agents acting on the renin-angiotensin system	4 (0.0)	2 (0.0)	2 (0.0)	2 (0.0)
C10	Lipid modifying agents	5 (0.1)	3 (0.0)	4 (0.0)	4 (0.0)
-	Unspecified medications for hypertension	4 (0.0)	3 (0.0)	3 (0.0)	2 (0.0)

Anatomical Therapeutic Chemical (ATC) classification index 1st and 2nd levels		Anytime during pregnancy n (%)	1st trimester n (%)	2nd trimester n (%)	3rd trimester n (%)
D	**Dermatologicals**	**162 (1.7)**	**116 (1.2)**	**127 (1.3)**	**103 (1.1)**
D01	*Antifungals for dermatological use*	38 (0.4)	28 (0.3)	33 (0.3)	27 (0.3)
D02	Emollients and protectives	14 (0.1)	11 (0.1)	12 (0.1)	10 (0.1)
D03	Preparations for treatment of wounds and ulcers	4 (0.0)	3 (0.0)	3 (0.0)	3 (0.0)
D04	Antipruritics, incl. antihistamines, anaesthetics, etc.	6 (0.1)	3 (0.0)	5 (0.1)	4 (0.0)
D05	Antipsoriatics	3 (0.0)	1 (0.0)	1 (0.0)	1 (0.0)
D06	Antibiotics and chemotherapeutics for dermatological use	21 (0.2)	15 (0.2)	16 (0.2)	13 (0.1)
D07	*Corticosteroids, dermatological preparations*	56 (0.6)	40 (0.4)	39 (0.4)	31 (0.3)
D08	Antiseptics and disinfectants	14 (0.1)	9 (0.1)	10 (0.1)	9 (0.1)
D09	Medicated dressings	5 (0.1)	5 (0.1)	5 (0.1)	3 (0.0)
D10	Anti-acne preparations	4 (0.0)	4 (0.0)	4 (0.0)	2 (0.0)
D11	Other dermatological preparations	1 (0.0)	-	1 (0.0)	1 (0.0)
-	Unspecified medications for skin disorders	5 (0.1)	4 (0.0)	4 (0.0)	3 (0.0)
G	**Genitourinary system and sex hormones**	**488 (5.2)**	**318 (3.4)**	**394 (4.2)**	**303 (3.2)**
G01	*Gynaecological antiinfective and antiseptics*	406 (4.3)	255 (2.7)	337 (3.6)	258 (2.7)
G02	Other gynecologicals	13 (0.1)	10 (0.1)	10 (0.1)	8 (0.1)
G03	Sex hormones and modulators of the genital system	68 (0.7)	55 (0.6)	50 (0.5)	36 (0.4)
G04	Urologicals	12 (0.1)	8 (0.1)	7 (0.1)	8 (0.1)
H	**Systemic hormonal preparations, excl. sex hormones and insulins**	**486 (5.1)**	**304 (3.2)**	**346 (3.7)**	**262 (2.8)**
H01	Pituitary and hypothalamic hormones and analogues	4 (0.0)	4 (0.0)	3 (0.0)	4 (0.0)
H02	Corticosteroids for systemic use	93 (1.0)	64 (0.7)	78 (0.8)	63 (0.7)
H03	*Thyroid therapy*	397 (4.2)	242 (2.6)	273 (2.9)	201 (2.1)
J	**Anti-infective for systemic use**	**1,381 (14.6)**	**874 (9.2)**	**1,107 (11.7)**	**943 (10.0)**
J01	*Antibacterials for systemic use*	1,325 (14.0)	840 (8.9)	1,061 (11.2)	908 (9.6)
J02	Antimycotics for systemic use	23 (0.2)	16 (0.2)	21 (0.2)	17 (0.2)
J05	Antivirals for systemic use	39 (0.4)	27 (0.3)	30 (0.3)	26 (0.3)
J06	Immune sera and immunoglobulins	4 (0.0)	2 (0.0)	3 (0.0)	4 (0.0)
J07	Vaccines	10 (0.1)	5 (0.1)	8 (0.1)	5 (0.1)

Anatomical Therapeutic Chemical (ATC) classification index 1st and 2nd levels		Anytime during pregnancy n (%)	1st trimester n (%)	2nd trimester n (%)	3rd trimester n (%)
L	**Antineoplastic and immunomodulating agents**	**134 (1.4)**	**83 (0.9)**	**117 (1.2)**	**97 (1.0)**
L01	Antineoplastic agents	4 (0.0)	3 (0.0)	4 (0.0)	1 (0.0)
L03	*Immunostimulants*	96 (1.0)	58 (0.6)	86 (0.9)	78 (0.8)
L04	Immunosuppressants	34 (0.4)	22 (0.2)	27 (0.3)	18 (0.2)
M	**Musculo-skeletal system**	**571 (6.0)**	**416 (4.4)**	**437 (4.6)**	**380 (4.0)**
M01	*Antiinflammatory and antirheumatic products*	515 (5.4)	378 (4.0)	396 (4.2)	342 (3.6)
M02	Topical products for joint and muscular pain	54 (0.6)	37 (0.4)	41 (0.4)	41 (0.4)
M03	Muscle relaxants	8 (0.1)	8 (0.1)	4 (0.0)	1 (0.0)
M05	Drugs for treatment of bone diseases	1 (0.0)	-	1 (0.0)	-
M09	Other drugs for disorders of the musculo-skeletal system	2 (0.0)	2 (0.0)	2 (0.0)	2 (0.0)
-	Unspecified medications for headache	2 (0.0)	1 (0.0)	1 (0.0)	1 (0.0)
N	**Nervous system**	**5,441 (57.5)**	**3,638 (38.5)**	**4,247 (44.9)**	**3,449 (36.5)**
N01	Anaesthetics	13 (0.1)	10 (0.1)	7 (0.1)	8 (0.1)
N02	*Analgesics*	5,297 (56.0)	3,562 (37.7)	4,171 (44.1)	3,387 (35.8)
N03	Antiepileptics	76 (0.8)	46 (0.5)	49 (0.5)	42 (0.4)
N05	*Psycholeptics*	210 (2.2)	173 (1.8)	164 (1.7)	138 (1.5)
N06	*Psychoanaleptics*	275 (2.9)	211 (2.2)	213 (2.3)	179 (1.9)
N07	Other nervous system drugs	6 (0.1)	4 (0.0)	5 (0.1)	3 (0.0)
-	Unspecified analgesics/medications for the nervous system	52 (0.5)	38 (0.4)	43 (0.5)	35 (0.4)
P	**Antiparasitic products, insecticides and repellents**	**26 (0.3)**	**20 (0.2)**	**22 (0.2)**	**16 (0.2)**
P01	*Antiprotozoals*	25 (0.3)	20 (0.2)	22 (0.2)	16 (0.2)
P02	Anthelmintics	1 (0.0)	-	-	-
R	**Respiratory system**	**2,609 (27.6)**	**1,878 (19.9)**	**2,047 (21.6)**	**1,702 (18.0)**
R01	*Nasal preparations*	1,547 (16.4)	1,079 (11.4)	1,229 (13.0)	1,046 (11.1)
R02	Throat preparations	167 (1.8)	110 (1.2)	131 (1.4)	122 (1.3)
R03	*Drugs for obstructive airway diseases*	396 (4.2)	269 (2.8)	304 (3.2)	242 (2.6)
R05	Cough and cold preparations	152 (1.6)	103 (1.1)	125 (1.3)	101 (1.1)
R06	*Antihistamines for systemic use*	912 (9.6)	777 (8.2)	740 (7.8)	580 (6.1)

Anatomical Therapeutic Chemical (ATC) classification index 1st and 2nd levels		Anytime during pregnancy n (%)	1st trimester n (%)	2nd trimester n (%)	3rd trimester n (%)
R07	Other respiratory system products	3 (0.0)	2 (0.0)	3 (0.0)	3 (0.0)
-	Unspecified medications of the respiratory system	142 (1.5)	101 (1.1)	118 (1.2)	99 (1.0)
S	**Sensory organs**	**45 (0.5)**	**33 (0.3)**	**38 (0.4)**	**28 (0.3)**
S01	*Ophthalmologicals*	33 (0.3)	24 (0.3)	28 (0.3)	23 (0.2)
S02	Otologicals	5 (0.1)	3 (0.0)	4 (0.0)	2 (0.0)
S03	Ophthalmological and otological preparations	3 (0.0)	2 (0.0)	2 (0.0)	2 (0.0)
-	Unspecified medications for eye disorders	5 (0.1)	4 (0.0)	5 (0.1)	2 (0.0)
V	**Various**	15 (0.2)	10 (0.1)	11 (0.1)	9 (0.1)
Total medication use (any ATC)		**7,678 (81.2)**	**4,710 (49.8)**	**5,538 (58.5)**	**4,663 (49.3)**

*The most common medication groups within each ATC class are in italics. Exposure timing is defined as follows: 1st trimester (gestational weeks 0-12), 2nd trimester (gestational week 13-24), 3rd trimester (gestational week 25 and up to childbirth).

Appendix 6: Prevalence of acute/short-term illnesses and most common medications used at any time during pregnancy by ATC level, indication for use and region (n=9,459) [*†]

	REGION						
Prevalence of acute/short-term illnesses in pregnancy and related medication use, overall and by drug groups	**Western Europe n=3,201** *n (%)*	**Northern Europe n=2,820** *n (%)*	**Eastern Europe n=2,342** *n (%)*	**North America n=533** *n (%)*	**South America n=346** *n (%)*	**Australia n=217** *n (%)*	**Total n=9,459** *n (%)*
Prevalence of headache	1,699 (53.1)	1,657 (58.8)	1,138 (48.6)	373 (70.0)	197 (56.9)	147 (67.7)	5,211 (55.1)
Medication use for headache, total	**1,027 (32.1)**	**1,057 (37.5)**	**522 (22.3)**	**226 (42.4)**	**121 (35.0)**	**109 (50.2)**	**3,062 (32.4)**
By drug group							
Paracetamol (incl. combinations) (N02BE)	994 (31.1)	1,009 (35.8)	372 (15.9)	206 (38.6)	92 (26.6)	101 (46.5)	2,774 (29.3)
Non-steroidal antiinflammatory drugs (M01A)	28 (0.9)	78 (2.8)	37 (1.6)	18 (3.0)	18 (5.2)	2 (0.9)	179 (1.9)
Acetylsalicylic acid (incl. combinations) (N02BA)	7 (0.2)	4 (0.1)	81 (3.5)	1 (0.2)	4 (1.2)	2 (0.9)	99 (1.0)
Opioid analgesics (N02A)	14 (0.4)	46 (1.6)	3 (0.1)	3 (0.6)	-	13 (6.0)	79 (0.8)
Selective serotonin (5-HT_1) agonists (N02CC)	6 (0.2)	22 (0.8)	2 (0.1)	3 (0.6)	-	1 (0.5)	34 (0.4)
Prevalence of heartburn	2,196 (68.6)	1,875 (66.5)	1,425 (60.8)	374 (70.2)	248 (71.7)	141 (65.0)	6,259 (66.2)
Medication use for heartburn, total	**984 (30.7)**	**885 (31.4)**	**525 (22.4)**	**202 (37.9)**	**88 (25.4)**	**72 (33.2)**	**2,756 (29.1)**
By drug group							
Antacids (aluminium, salts combinations, antiflatulents)	384 (12.0)	503 (17.8)	440 (18.8)	51 (9.6)	63 (18.2)	20 (9.2)	1,461 (15.4)
Alginic acid complex/sucralfate/bismuth (A02BX)	569 (17.8)	332 (11.8)	86 (3.7)	4 (0.8)	3 (0.9)	14 (6.5)	1,008 (10.7)
Proton pump inhibitors (A02BC)	77 (2.4)	86 (3.0)	4 (0.2)	13 (2.4)	3 (0.9)	7 (3.2)	190 (2.0)
Antacid with calcium (A02AC)	20 (0.6)	13 (0.5)	10 (0.4)	123 (23.1)	2 (0.6)	9 (4.1)	177 (1.9)
H_2 receptor antagonists (A02BA)	27 (0.8)	27 (1.0)	7 (0.3)	45 (8.4)	5 (1.4)	38 (17.5)	149 (1.6)
Prevalence of pain	2,150 (67.2)	2,067 (73.3)	1,484 (63.4)	369 (69.2)	248 (71.7)	157 (72.4)	6,475 (68.5)
Medication use for pain, total	**533 (16.7)**	**426 (15.1)**	**147 (6.3)**	**110 (20.6)**	**80 (23.1)**	**59 (27.2)**	**1,355 (14.3)**
By drug group							
Paracetamol (incl. combinations) (N02BE)	444 (13.9)	374 (13.3)	65 (2.8)	99 (18.6)	44 (12.7)	55 (25.3)	1,081 (11.4)
Non-steroidal antiinflammatory drugs (M01A)	19 (0.6)	36 (1.3)	21 (0.9)	11 (2.1)	24 (6.9)	3 (1.4)	114 (1.2)
Opioid analgesics (N02A)	39 (1.2)	51 (1.8)	2 (0.1)	4 (0.8)	-	12 (5.5)	108 (1.1)

Prevalence of acute/short-term illnesses in pregnancy and related medication use, overall and by drug groups	REGION						
	Western Europe	**Northern Europe**	**Eastern Europe**	**North America**	**South America**	**Australia**	**Total**
	n=3,201	**n=2,820**	**n=2,342**	**n=533**	**n=346**	**n=217**	**n=9,459**
	n (%)	***n (%)***	***n (%)***	***n (%)***	***n (%)***	***n (%)***	***n (%)***
Prevalence of nausea	2,324 (72.6)	2,244 (79.6)	1,503 (64.2)	409 (76.7)	238 (68.8)	173 (79.7)	6,891 (72.9)
Medication use for nausea, total	**413 (12.9)**	**380 (13.5)**	**140 (6.0)**	**128 (24.0)**	**71 (20.5)**	**39 (18.0)**	**1,171 (12.4)**
By drug group							
First generation antihistamines (R06A)	150 (4.7)	259 (9.2)	21 (0.9)	84 (15.9)	9 (2.6)	4 (1.8)	527 (5.6)
Metoclopramide/domperidone/bromopride (A03FA)	134 (4.2)	69 (2.4)	27 (1.2)	10 (1.9)	45 (13.0)	25 (11.5)	310 (3.3)
Serotonin antagonists (A04AA)	4 (0.1)	8 (0.3)	1 (0.0)	28 (5.3)	1 (0.3)	11 (5.1)	53 (0.6)
Prevalence of UTI	513 (16.0)	327 (11.6)	452 (19.3)	93 (17.4)	92 (26.6)	25 (11.5)	1,502 (15.9)
Medication use for UTI, total	**315 (9.8)**	**221 (7.8)**	**192 (8.2)**	**56 (10.5)**	**63 (18.2)**	**17 (7.8)**	**864 (9.1)**
By drug group							
Unspecified penicillins (J01C-)	94 (2.9)	99 (3.5)	46 (2.0)	16 (3.0)	17 (4.9)	1 (0.5)	273 (2.9)
NOS Antibacterials for systemic use (J01-)	116 (3.6)	85 (3.0)	25 (1.1)	20 (3.8)	14 (4.0)	6 (2.8)	266 (2.8)
Penicillins with extended spectrum +/- beta-lactamase inhibitors (J01CA/J01CR)	85 (2.7)	78 (2.8)	44 (1.9)	14 (2.6)	17 (4.9)	1 (0.5)	239 (2.5)
Nitrofurantoin (J01XE)	7 (0.2)	25 (0.9)	54 (2.3)	10 (1.9)	3 (0.9)	1 (0.5)	100 (1.1)
Cephalosporins (J01D)	20 (0.6)	10 (0.4)	36 (1.5)	2 (0.4)	11 (3.2)	6 (2.8)	85 (0.9)
Total prevalence of any acute/short-term illness	**3,159 (98.7)**	**2,803 (99.4)**	**2,299 (98.2)**	**523 (98.1)**	**341 (98.6)**	**214 (98.6)**	**9,339 (98.7)**
Total medication use for any acute/short-term illness	**2,224 (69.5)**	**1,954 (69.3)**	**1,474 (62.9)**	**403 (75.6)**	**250 (72.3)**	**164 (75.6)**	**6,469 (68.4)**

*Countries are grouped into regions as shown in Figure 1.

†Sums of percentages do not add up to total medication use as only most common medication groups are presented. Rates do not include mineral supplements, vitamins, iron, and herbal or alternative medicine products.

Abbreviations: UTI: Urinary tract infection; NOS: Not otherwise specified.

Appendix 7: Prevalence of chronic/long-term disorders and most common medications used at any time during pregnancy by ATC level, indication for use and region (n=9,459) [*†]

	REGION						
Prevalence of chronic/long-term disorders in pregnancy and related medication use, overall and by drug groups	**Western Europe n=3,201** *n (%)*	**Northern Europe n=2,820** *n (%)*	**Eastern Europe n=2,342** *n (%)*	**North America n=533** *n (%)*	**South America n=346** *n (%)*	**Australia n=217** *n (%)*	**Total n=9,459** *n (%)*
Prevalence of hypothyroidism	130 (4.1)	118 (4.2)	105 (4.5)	22 (4.1)	11 (3.2)	6 (2.8)	392 (4.1)
Medication use for hypothyroidism, total	**118 (3.7)**	**113 (4.0)**	**96 (4.1)**	**21 (3.9)**	**9 (2.6)**	**6 (2.8)**	**363 (3.8)**
By drug group							
Thyroid hormone, levothyroxine (H03AA01)	117 (3.7)	112 (4.0)	89 (3.8)	21 (3.9)	9 (2.6)	6 (2.8)	354 (3.7)
Prevalence of asthma	163 (5.1)	193 (6.8)	58 (2.5)	43 (8.1)	12 (3.5)	24 (11.1)	493 (5.2)
Medication use for asthma, total	**122 (3.8)**	**133 (4.7)**	**38 (1.6)**	**35 (6.6)**	**8 (2.3)**	**24 (11.1)**	**360 (3.8)**
By drug group							
Inhalant selective beta-2 agonists (R03AC)	94 (2.9)	66 (2.3)	26 (1.1)	32 (6.0)	7 (2.0)	24 (11.1)	249 (2.6)
Adrenergics and other drugs for COPD (R03AK)	33 (1.0)	46 (1.6)	10 (0.4)	3 (0.6)	2 (0.6)	7 (3.2)	101 (1.1)
Inhalant glucocorticoids (R03BA)	28 (0.9)	40 (1.4)	13 (0.6)	12 (2.3)	-	4 (1.8)	97 (1.0)
Systemic selective beta-2 agonists (R03CC)	-	30 (1.1)	-	2 (0.4)	-	-	32 (0.3)
Prevalence of allergy	205 (6.4)	372 (13.2)	163 (7.0)	51 (9.6)	20 (5.8)	23 (10.6)	834 (8.8)
Medication use for allergy, total	**66 (2.1)**	**171 (6.1)**	**65 (2.8)**	**24 (4.5)**	**13 (3.8)**	**17 (7.8)**	**356 (3.8)**
By drug group							
Second generation antihistamines (R06A)	29 (0.9)	104 (3.7)	27 (1.2)	17 (3.2)	4 (1.2)	5 (2.3)	186 (2.0)
Nasal corticosteroids (R01AD)	11 (0.3)	32 (1.1)	17 (0.7)	-	-	7 (3.2)	67 (0.7)
First generation antihistamines (R06A)	13 (0.4)	29 (1.0)	10 (0.4)	9 (1.7)	6 (1.7)	4 (1.8)	71 (0.8)
Prevalence of depression	95 (3.0)	144 (5.1)	29 (1.2)	52 (9.8)	4 (1.2)	25 (11.5)	349 (3.7)
Medication use for depression, total	**61 (1.9)**	**100 (3.5)**	**11 (0.5)**	**29 (5.4)**	**1 (0.3)**	**23 (10.6)**	**225 (2.4)**
By drug group							
SSRI antidepressants (N06AB)	44 (1.4)	82 (2.9)	6 (0.3)	14 (2.6)	-	14 (6.5)	160 (1.7)
SNRIs/mianserin/trazodone/mirtazapine/bupropion	9 (0.3)	11 (0.4)	1 (0.0)	15 (2.8)	-	7 (3.2)	43 (0.5)

Prevalence of chronic/long-term disorders in pregnancy and related medication use, overall and by drug groups	REGION						
	Western Europe n=3,201 *n (%)*	Northern Europe n=2,820 *n (%)*	Eastern Europe n=2,342 *n (%)*	North America n=533 *n (%)*	South America n=346 *n (%)*	Australia n=217 *n (%)*	Total n=9,459 *n (%)*
Anxiolytics, benzodiazepine (N05BA)	6 (0.2)	2 (0.1)	5 (0.2)	-	-	1 (0.5)	14 (0.1)
Antipsychotics quetiapine/olanzapine (N05AH)	2 (0.1)	4 (0.1)	-	3 (0.6)	-	3 (1.4)	12 (0.1)
Total prevalence of any chronic/long-term disorder	**617 (19.3)**	**831 (29.5)**	**576 (24.6)**	**154 (28.9)**	**51 (14.7)**	**72 (33.2)**	**2,301 (24.3)**
Total medication use for any chronic/long-term disorder	**462 (14.4)**	**593 (21.0)**	**322 (13.7)**	**119 (22.3)**	**38 (11.0)**	**70 (32.3)**	**1,604 (17.0)**

*Countries are grouped into regions as shown in Figure 1.

†Sums of percentages do not add up to total medication use as only most common medication groups are presented. Rates do not include mineral supplements, vitamins, iron, and herbal or alternative medicine products.

Abbreviations: COPD: Chronic obstructive pulmonary disease; SSRI: Selective serotonin re-uptake inhibitors; SNRI: Serotonin–noradrenaline reuptake inhibitors.

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation
Title and abstract	1	✗ (*a*) Indicate the study's design with a commonly used term in the title or the abstract
		✗ (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	✗ Explain the scientific background and rationale for the investigation being reported
Objectives	3	✗ State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	✗ Present key elements of study design early in the paper
Setting	5	✗ Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	✗ (*a*) Give the eligibility criteria, and the sources and methods of selection of participants
Variables	7	✗ Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	✗ For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	✗ Describe any efforts to address potential sources of bias
Study size	10	✗ Explain how the study size was arrived at
Quantitative variables	11	✗ Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	✗ (*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		✗ (*c*) Explain how missing data were addressed
		(*d*) If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	✗ (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	✗ (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
Outcome data	15*	✗ Report numbers of outcome events or summary measures
Main results	16	✗ (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		✗ (*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a

		meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	✗ Summarise key results with reference to study objectives
Limitations	19	✗ Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	✗ Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	✗ Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	✗ Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Medication use in pregnancy: a cross-sectional, multinational web-based study

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Medication use in pregnancy: a cross-sectional, multinational web-based study

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ABSTRACT

Objectives: Inter-country comparability between studies on medication use in pregnancy is difficult due to dissimilarities in study design and methodology. This study aimed to examine patterns and factors associated with medications use in pregnancy from a multinational perspective, with emphasis on type of medication utilized and indication for use.

Design: Cross-sectional, web-based study performed within the period from 1-Oct-2011 to 29-Feb-2012. Uniform collection of drug utilization data was performed via an anonymous online questionnaire.

Setting: Multinational study in Europe (Western, Northern, and Eastern), North and South America, and Australia.

Participants: Pregnant women and new mothers with children less than one year of age.

Primary and secondary outcome measures: Prevalence of and factors associated with medication use for acute/short-term illnesses, chronic/long-term disorders and over-the-counter (OTC) medication use.

Results: The study population included 9,459 women whereof 81.2% reported use of at least one medication (prescribed or OTC) during pregnancy. Overall, OTC medication use occurred in 66.9% of the pregnancies, whereas 68.4% and 17.0% of women reported use of at least one medication for treatment of acute/short-term illnesses and chronic/long-term disorders, respectively. The extent of self-reported

medicated illnesses and types of medication used by indication varied across regions, especially in relation to urinary tract infections, depression or OTC nasal sprays. Women with higher age or lower educational level, housewives, or women with an unplanned pregnancy were those most often reporting use of medication for chronic/long-term disorders. Immigrant women in Western (aOR: 0.55, 95% CI: 0.34-0.87) and Northern Europe (aOR: 0.50, 95% CI: 0.31-0.83) were less likely to report use of medication for chronic/long-term disorders during pregnancy than non-immigrants.

Conclusions:

In this study, the majority of women in Europe, North America, South America and Australia used at least one medication during pregnancy. There was a substantial inter-region variability in the types of medication used.

ARTICLE SUMMARY

Strengths and limitations of this study

- Uniform data collection of drug utilization data across all participating countries allows for inter-country comparability of the prevalence of medication use during pregnancy, up to now impeded by differences in study design and methodology.
- The study adds a multinational perspective on OTC medication use during pregnancy to the limited number of studies quantifying the extent of self-medication during pregnancy.
- Lack of validity of the self-reported diagnoses is a limitation since all disorders and related medication use were self-reported by the study participants.
- A web-based survey as a study method impedes calculation of a conventional response rate and may cause selection bias of the target population.

INTRODUCTION

Ethical reasons preclude inclusion of pregnant women in the vast majority of pre-marketing clinical trials.[1] As a consequence, most medications are placed onto the market without a directly established safety profile in human pregnancy.[2] So far, few medications have been shown to be major teratogens, yet the risk of minor teratogenicity or of more subtle effects on fetal development still have to be determined for most of them.[3] Despite this, medication use during pregnancy is common. Mitchell et al. found that use of medications, either prescribed or purchased over-the-counter (OTC), occurred in 88.8% of all pregnancies in the USA.[4] In Europe, prevalence estimates of prescribed medication use vary considerably across countries, ranging from 26% in Serbia to 93% in France.[5-10] Such inter-country variability could, at least in part, be caused by differences in study design, methodology and exposure ascertainment across studies.[11] Uniform collection of drug utilization data during pregnancy between countries may overcome such drawbacks, allowing for inter-country comparability of prevalence estimates and shedding light on differences in prenatal care in the various countries.

Prior studies have addressed research priorities in this area such as presenting results on an individual drug level according to the indication of use, quantifying the extent of OTC and prescribed medication use during pregnancy, and taking into account inter-country comparability.[4] Only a few studies have individually examined maternal factors associated with specific types of medication use during pregnancy.[11-14]

The objectives of the current study were to examine patterns of medication use in pregnancy from a multinational perspective, with special emphasis on type of medication utilized, including OTC medications, and self-reported indications for use, and to identify maternal background factors potentially associated with medication use for acute/short-term illnesses, medication use for chronic/long-term disorders and OTC medication use during pregnancy.

METHODS

Study design and data collection

This is a multinational, cross-sectional, web-based study. Pregnant women at any gestational week and mothers with children less than one year of age were eligible to participate. Member countries of the European Network of Teratology Information Services (ENTIS), The Organization of Teratology Information Specialists (OTIS) in North America, MotherSafe in Australia and European institutions conducting public health research were invited to take part in the project. Of these, 18 countries participated (Australia, Austria, Canada, Croatia, Finland, France, Iceland, Italy, Netherlands, Norway, Poland, Russia, Serbia, Slovenia, Sweden, Switzerland, United Kingdom and USA). Data originating from some South and Central American countries were also collected through OTIS. Because of the low number of participants on the individual country level, the region of Central America was excluded and countries in South America were aggregated into one region. Data selection to achieve the final study sample was performed as depicted in Figure 1. Participants were categorized according to the reported country of residency and grouped into six regions: Western Europe, Northern Europe, Eastern Europe, North America, South America and Australia.

Data were collected through an anonymous on-line questionnaire administered by Quest Back (http://www.questback.com) and accessible for a period of two months in each participating country within the period 1-Oct-2011 to 29-Feb-2012. The questionnaire was open to the public via utilization of banners (invitations to participate in the study) on national websites and/or social networks commonly visited and consulted by pregnant women and/or new mothers. The complete questionnaire is presented in Appendix 1. Detailed information about recruitment tools utilized and internet penetration rates is summarized in Appendix 2.

The questionnaire was first developed in Norwegian and English and then translated into the other relevant languages. A pilot study was carried out in September 2011 (n=47) and elicited no major change to the questionnaire. Collected data were scrutinized for the presence of potential duplicates (based on reported country of residency, socio-demographic characteristics, date and exact time of questionnaire completion) but none were identified.

Exposure variables

Maternal socio-demographics (i.e. region of residency, age, educational level, mother tongue, working status at time of conception, previous children, marital status and unplanned pregnancy) and life-style characteristics (i.e. smoking status before and during pregnancy and alcohol consumption after awareness of pregnancy) constituted the exposure variables. To assess external validity, we compared socio-demographic and life-style characteristics of our study population on an individual country level with those of the general birthing population in the same country. Reports of National Statistics Bureaus or previous national studies were utilized for this purpose. The ratio

between the number of respondents and the estimated number of live births in the 2-months period was also examined for each country (Appendix 3).

Outcome variables

Use of any medication, medication for acute/short-term illnesses, medication for chronic/long-term disorders and OTC medication use during pregnancy constituted the outcome variables. Participants were first confronted with a list of the most common acute/short-term illnesses (i.e. nausea, heartburn, constipation, common cold, urinary tract infections (UTIs), other infections, pain in the neck/back/pelvic girdle, headache, sleeping problems) and the most prevalent chronic/long-term disorders (i.e. asthma, allergy, hypothyroidism, rheumatic disorders, diabetes, epilepsy, depression, anxiety, cardiovascular disease, other disorders) and asked whether they suffered/had suffered from these conditions during pregnancy. In case of an affirmative response, women were questioned about medication use for each individual indication as a free-text entry. Use of OTC medications was also recorded. Recall was aided with a list of five OTC medication categories: painkillers, nasal spray/drops, antinauseants, antacids and laxatives, along with examples of brand name products of relevance in each country. It was optional to report timing of exposure for each of the medication use questions (the alternatives were gestational weeks 0-12 (1st trimester), 13-24 (2nd trimester) and 25-delivery (3rd trimester)).

We defined a medicine as a single product containing one or more active ingredients. We initially identified the main active ingredient(s) and formulation of the reported medicinal products either in the relevant national medicines database or in the "Martindale" textbook.[15] All recorded medications were coded into the corresponding Anatomical Therapeutic Chemical (ATC) codes at the ATC 5th level

(i.e. the substance level) whenever possible, otherwise into the 2nd- 4th levels as appropriate, in accordance with the World Health Organization ATC index.[16] The OTC status of medications was crosschecked with the prescription policies within each country. Whenever a prescription medication was reported under the OTC question, this record was omitted from the analysis of OTC use but counted in the estimation of total medication use (including prescription and OTC). Iron, mineral supplements, vitamins, herbal remedies and any type of alternative medicine were recorded separately and excluded from the estimation of medication use.

The required sample size calculation for the outcome variables on region and individual country levels are outlined in Appendix 4. The expected prevalence estimates were set according to results of previous studies.[5-10,17,18]

Ethics

All participants gave informed consent by answering "Yes" to the question "Are you willing to participate in the study?" The study was approved by the Regional Ethics Committee, Region South-East in Norway. Ethical approval or study notification to the relevant national Ethics Boards was achieved in specific countries as required by national legislation. All data were handled and stored anonymously.

Statistical analysis

Descriptive statistics were utilized as appropriate. Univariate and multivariate logistic regression analyses were used to examine the association between maternal characteristic and three categorical outcome measures (Yes/No): Medication use for acute/short-term illnesses; medication use for chronic/long-term disorders; OTC medication use. P-values of <0.05 were considered statistically significant. Data are

presented as adjusted odds ratios (aOR) with 95% confidence intervals (CI). The analyzed explanatory variables included all maternal socio-demographics and life-style characteristics. After fitting the univariate logistic regression model for all explanatory variables, the multivariate model was built and adjusted for all remaining covariates. The Hosmer and Lemeshow test was used to assess goodness of fit of the final multivariate model.[19] Analogue sub-analyses on individual region level were performed. In these instances, region of residency was not included in the model. All statistical analyses were performed by using the Statistical Package for the Social Sciences (SPSS) version 20.0 (IBM® SPSS® Statistics).

RESULTS

Population characteristics

A total of 9,615 women accessed the on-line questionnaire whereof 98.6% completed it. The participant flow-chart to achieve final study population (n=9,459) is depicted in Figure 1. A total of 5,089 women (53.8%) were pregnant at the time of completion of the questionnaire, whereas 4,370 women (46.2%) had delivered their babies within the previous year. Of the former group, 1,095 (21.5%), 1,702 (33.4%) and 2,291 (45.0%) women were in the first, second and third trimester of pregnancy, respectively. Of the latter group, 1,320 (30.2%), 947 (21.7%) and 2,102 (48.1%) had a baby of age ≤ 16 weeks, 17-28 weeks, and ≥ 29 weeks, respectively. For two women the time of gestation/baby´s age was unknown. Overall, the birthing population in each participating country was reflected quite well by the sample with respect to age, parity and smoking habits (Appendix 3). However, there was a difference in terms of educational level; on average, the women in the study had higher education than the general birthing population in each country. In addition, participants in Sweden,

Austria, Iceland and Italy were slightly more often primiparous, whereas the responders in Australia, USA, The Netherlands, Slovenia and Croatia were somewhat older than the general birthing population.

Total medication use

After exclusion of vitamins, mineral supplements and iron, use of at least one medication either prescribed or OTC at any time during pregnancy was reported by 7,678 out of 9,459 women (81.2%). Figure 2 depicts prevalence estimates of total medication use during pregnancy by region and country of residence. The extent of OTC medication use, as well as medication use for acute/short-term illnesses and chronic/long-term disorders is also outlined. The highest prevalence of total medication use during pregnancy was observed in The Netherlands (95.1%), Iceland (93.0%) and Finland (92.3%). The overall prevalence estimates of medication use in pregnancy according to timing and drug class (ATC level 1 and 2) are presented in Appendix 5. Medications for the nervous system (ATC class N) were the most commonly used during pregnancy (57.5%), mostly due to paracetamol (acetaminophen) and its combinations.

A corollary analysis according to pregnancy status showed that pregnant women reported in a significantly lower degree than new mothers any medication use during pregnancy (78.8% vs. 84.0%, p-value<0.001), as well as OTC medication use (63.0% vs. 71.5%, p-value<0.001) and medication use for acute/short-term illnesses (66.2% vs. 70.9%, p-value<0.001). In contrast, the difference in medication use for chronic/long-term disorders was not significant (17.4% vs. 16.5%, p-value=0.271). None of the rates differed significantly when women in the third trimester of pregnancy were compared to new mothers.

Medication use according to indication

Headache, heartburn, pain, nausea and UTIs constituted the leading indications for use of medication during pregnancy among the acute/short-term illnesses analyzed. Hypothyroidism, asthma, allergy and depression were the leading indications for chronic/long-term medication use. Observed prevalence rates of these disorders, overall and by region of residency, are presented in Appendices 6 and 7, respectively, along with rates of total and specific medication use. Table 1 outlines prevalence estimates of OTC medication use during pregnancy by region and indication for use. Only the most common medication groups reported are presented. Inter-region variations in rates and types of medication used during pregnancy were observed both for acute/short-term illnesses (e.g. nausea and UTIs), chronic/long-term disorders (e.g. asthma and depression) and OTC medications (e.g. nasal spray).

Factors associated with medication use

Factors associated with medication use during pregnancy according to type of medication utilized are presented in table 2. Use of chronic/long-term medications during pregnancy was reported in a significant larger extent by women in Northern Europe (aOR: 1.68, 95% CI: 1.46-1.94), North America (aOR: 1.80, 95% CI: 1.42-2.28) and Australia (aOR: 2.76, 95% CI: 2.03-3.76) compared to women in Western Europe. Older women or housewives, those with low education or with an unplanned pregnancy, were the ones most often reporting use of chronic/long-term medication. Sub-analysis on individual region level revealed that women not having the official language of the country of residency as mother tongue were less likely to report chronic/long-term medication use in Western (aOR: 0.55, 95% CI: 0.34-0.87) and Northern Europe (aOR: 0.50, 95% CI: 0.31-0.83), but not in the other regions.

Table 1: Use of OTC medication at any time during pregnancy by ATC level, indication for use and region (n=9,459) [*†]

	REGION						
OTC medication use, overall and by drug groups	**Western Europe n=3,201** *n (%)*	**Northern Europe n=2,820** *n (%)*	**Eastern Europe n=2,342** *n (%)*	**North America n=533** *n (%)*	**South America n=346** *n (%)*	**Australian n=217** *n (%)*	**Total n=9,459** *n (%)*
OTC painkillers, total	**1,714 (53.5)**	**1,773 (62.9)**	**734 (31.3)**	**284 (53.3)**	**127 (36.7)**	**151 (69.9)**	**4,783 (50.6)**
By drug group							
Paracetamol (incl. combinations) (N02BE)	1,655 (51.7)	1,735 (61.5)	630 (26.9)	263 (49.3)	87 (25.1)	146 (67.3)	4,516 (47.7)
Non-steroideal antiinflammatory drugs (M01A)	70 (2.2)	182 (6.5)	68 (2.9)	40 (7.5)	59 (17.1)	7 (3.2)	426 (4.5)
Acetylsalicylic acid (incl. combinations) (N02BA)	7 (0.2)	11 (0.4)	32 (1.4)	2 (0.4)	2 (0.6)	1 (0.5)	55 (0.6)
Metamizole (N02BB02)	-	6 (0.2)	31 (1.3)	1 (0.2)	12 (3.5)	-	50 (0.5)
OTC antacids, total	**1,011 (31.6)**	**883 (31.3)**	**583 (24.9)**	**129 (24.2)**	**48 (13.9)**	**76 (35.0)**	**2,730 (28.9)**
By drug group							
Antacids (aluminium, salts combinations, antiflatulents)	472 (14.7)	550 (19.5)	508 (21.7)	47 (8.8)	36 (10.4)	54 (24.9)	1,667 (17.6)
Alginic acid complex/sucralfate/bismuth (A02BX)	606 (18.9)	421 (14.9)	87 (3.7)	4 (0.8)	1 (0.3)	17 (7.8)	1,136 (12.0)
H_2 receptor antagonists (A02BA)	20 (0.6)	20 (0.7)	16 (0.7)	57 (10.1)	10 (2.9)	17 (7.8)	137 (1.4)
Antacids with calcium (A02AC)	23 (0.7)	12 (0.4)	10 (0.4)	69 (12.9)	2 (0.6)	10 (4.6)	126 (1.3)
Proton pump inhibitors (A02BC)	38 (1.2)	52 (1.8)	-	10 (1.9)	2 (0.6)	5 (0.3)	107 (1.1)
OTC nasal sprays/drops, total	**272 (8.5)**	**742 (26.3)**	**451 (19.3)**	**35 (6.6)**	**7 (2.0)**	**14 (6.5)**	**1,521 (16.1)**
By drug group							
Sympathomimetic nasal decongestants (R01AA/R01BB)	204 (6.4)	683 (24.2)	365 (15.6)	20 (3.8)	3 (0.9)	4 (1.8)	1,279 (13.5)
Nasal corticosteroids (R01AD)	31 (1.0)	49 (1.7)	12 (0.5)	5 (0.9)	2 (0.6)	10 (4.6)	109 (1.2)
Nasal immunostimulants (low dose interferon) (L03A)	-	-	28 (1.2)	-	-	-	28 (0.3)
OTC laxatives, total	**240 (7.5)**	**227 (8.0)**	**237 (10.1)**	**50 (9.4)**	**8 (2.3)**	**19 (8.8)**	**781 (8.3)**
By drug group							
Osmotically acting laxatives (A06AD)	159 (5.0)	171 (6.1)	197 (8.4)	2 (0.4)	2 (0.6)	8 (3.7)	539 (5.7)
Contact laxatives (A06AB)	28 (0.9)	44 (1.6)	18 (0.8)	7 (1.3)	6 (1.7)	2 (0.9)	105 (1.1)

OTC medication use, overall and by drug groups	REGION						
	Western Europe	**Northern Europe**	**Eastern Europe**	**North America**	**South America**	**Australian**	**Total**
	n=3,201	**n=2,820**	**n=2,342**	**n=533**	**n=346**	**n=217**	**n=9,459**
	n (%)	***n (%)***	***n (%)***	***n (%)***	***n (%)***	***n (%)***	***n (%)***
Enemas (A06AG)	3 (0.1)	25 (0.9)	34 (1.5)	4 (0.8)	-	2 (0.9)	68 (0.7)
Softeners, emollients (A06AA)	8 (0.2)	-	-	38 (7.1)	-	6 (2.8)	52 (0.5)
OTC antinauseants, total	**263 (8.2)**	**273 (9.7)**	**41 (1.8)**	**60 (11.3)**	**28 (8.1)**	**40 (18.4)**	**705 (7.5)**
By drug group							
First generation antihistamines (R06A)	141 (4.4)	256 (9.1)	7 (1.5)	55 (10.3)	5 (1.4)	5 (2.3)	469 (5.0)
Metoclopramide/domperidone/bromopride (A03FA)	113 (3.5)	5 (0.2)	18 (0.8)	2 (0.4)	19 (5.5)	27 (12.4)	184 (1.9)
Total OTC medication use	**2,163 (67.6)**	**2,155 (76.4)**	**1,347 (57.5)**	**342 (64.2)**	**156 (45.1)**	**168 (77.4)**	**6,331 (66.9)**

Abbreviations: OTC: Over-The-Counter medications.

*Countries are grouped into regions as shown in Figure 1.

†Sums of percentages do not add up to total medication use as only most common medication groups are presented. Rates do not include mineral supplements, vitamins, iron, and herbal or alternative medicine products.

Table 2: Factors associated with medication use in pregnancy (n=9,459)*

	Medication use					
	For acute/short-term illnesses (n=6,469)		For chronic/long-term disorders (n=1,604)		OTC (n=6,331)	
	n (%)	*aOR (95% CI)*	*n (%)*	*aOR (95% CI)*	*n (%)*	*aOR (95% CI)*
Region of residency†						
Western Europe	2,224 (69.5)	Reference	462 (14.4)	Reference	2,163 (67.6)	Reference
Northern Europe	1,954 (69.3)	0.96 (0.86-1.08)	593 (21.0)	**1.68 (1.46-1.94)**	2,155 (76.4)	**1.54 (1.36-1.74)**
Eastern Europe	1,474 (62.9)	**0.69 (0.61-0.78)**	322 (13.7)	1.03 (0.87-1.21)	1,347 (57.5)	**0.60 (0.53-0.67)**
North America	403 (75.6)	**1.28 (1.03-1.60)**	119 (22.3)	**1.80 (1.42-2.28)**	342 (64.2)	**0.81 (0.66-0.99)**
South America	250 (82.3)	1.03 (0.79-1.34)	38 (11.0)	0.70 (0.48-1.01)	156 (45.1)	**0.34 (0.27-0.44)**
Australia	164 (75.6)	1.29 (0.93-1.79)	70 (32.3)	**2.76 (2.03-3.76)**	168 (77.4)	**1.57 (1.12-2.20)**
Maternal age (years)						
≤20	232 (70.5)	1.22 (0.93-1.60)	761 (14.7)	**0.58 (0.39-0.87)**	205 (62.3)	1.05 (0.81-1.36)
21-30	3,531 (68.2)	Reference	33 (10.0)	Reference	3,461 (66.8)	Reference
31-40	2,576 (68.6)	0.90 (0.82-1.00)	764 (20.4)	**1.44 (1.27-1.63)**	2,531 (67.4)	**0.85 (0.77-0.94)**
≥41	130 (66.3)	0.73 (0.54-1.00)	46 (23.5)	**1.61 (1.13-2.29)**	134 (68.4)	0.86 (0.62-1.19)
Previous children						
No	3,082 (65.5)	Reference	735 (15.6)	Reference	2,949 (62.6)	Reference
Yes	3,387 (71.3)	**1.34 (1.22-1.47)**	869 (18.3)	1.08 (0.96-1.21)	3,382 (71.2)	**1.58 (1.44-1.74)**
Marital status						
Married/cohabiting	6,066 (68.5)	Reference	1,503 (17.0)	Reference	5,960 (67.3)	Reference
Single/divorced/others	403 (66.3)	0.91 (0.75-1.10)	101 (16.6)	1.06 (0.83-1.35)	371 (61.0)	0.91 (0.75-1.10)
Working status						
Employed, but not as HCP	3,737 (66.8)	Reference	905 (16.2)	Reference	3,667 (65.6)	Reference
HCP	934 (74.4)	**1.41 (1.23-1.63)**	240 (19.1)	1.13 (0.96-1.33)	944 (75.2)	**1.42 (1.23-1.64)**
Student	592 (69.1)	1.11 (0.94-1.31)	128 (14.9)	1.04 (0.84-1.30)	578 (67.4)	1.10 (0.93-1.30)
Housewife	608 (72.6)	1.14 (0.96-1.35)	170 (20.3)	**1.34 (1.10-1.63)**	577 (68.9)	1.05 (0.88-1.24)
Job seeker	281 (66.0)	0.96 (0.78-1.20)	66 (15.5)	1.03 (0.78-1.36)	258 (60.6)	0.85 (0.68-1.05)
Other than above	311 (65.2)	0.91 (0.75-1.12)	94 (19.7)	**1.29 (1.01-1.65)**	302 (63.3)	0.91 (0.74-1.12)
Educational level						

	Medication use					
	For acute/short-term illnesses (n=6,469)		For chronic/long-term disorders (n=1,604)		OTC (n=6,331)	
	n (%)	*aOR (95% CI)*	*n (%)*	*aOR (95% CI)*	*n (%)*	*aOR (95% CI)*
Less than high school	331 (72.7)	1.17 (0.93-1.49)	92 (20.2)	**1.51 (1.15-1.97)**	317 (69.7)	**1.32 (1.04-1.67)**
High school	1,864 (68.7)	Reference	428 (15.8)	Reference	1,779 (65.6)	Reference
More than high school	3,574 (68.4)	0.99 (0.89-1.11)	916 (17.5)	1.04 (0.91-1.20)	3,489 (66.8)	1.07 (0.96-1.19)
Others, unspecified	700 (65.7)	0.82 (0.70-0.96)	168 (15.8)	0.94 (0.77-1.16)	746 (70.0)	1.13 (0.97-1.33)
Alcohol use after awareness of pregnancy						
No	5,270 (67.1)	Reference	1,322 (16.8)	Reference	5,133 (65.3)	Reference
Yes	1,144 (75.7)	**1.59 (1.39-1.81)**	270 (17.9)	1.11 (0.95-1.29)	1,150 (76.1)	**1.95 (1.71-2.23)**
Smoking during pregnancy						
No	5,835 (68.5)	Reference	1,441 (16.9)	Reference	5,716 (67.0)	Reference
Yes, but less than before pregnancy	530 (69.0)	1.08 (0.91-1.27)	130 (16.9)	1.01 (0.82-1.25)	511 (66.5)	1.06 (0.90-1.26)
Yes, the same or more than before pregnancy	88 (67.7)	0.95 (0.64-1.40)	28 (21.5)	1.19 (0.74-1.90)	89 (68.5)	1.21 (0.81-1.82)
Planned pregnancy						
Yes	5,836 (68.4)	Reference	1,427 (16.7)	Reference	5,727 (67.2)	Reference
No	616 (68.4)	0.96 (0.82-1.12)	173 (19.2)	**1.29 (1.06-1.56)**	587 (65.1)	1.00 (0.85-1.17)
First language different from the official main language in the country of residency						
No	6,089 (68.5)	Reference	1,530 (17.2)	Reference	5,972 (67.1)	Reference
Yes	363 (67.2)	0.93 (0.76-1.12)	71 (13.1)	**0.66 (0.50-0.86)**	347 (64.3)	0.89 (0.74-1.08)

Abbreviation: HCP: health care provider.

[*]Numbers may not add up due to missing values. Missing values are less than 5% of the total. Mineral supplements, vitamins, iron, herbal or alternative medicine products are not included in the medication use estimates.

[†]Countries are grouped into regions as shown in Figure 1.

DISCUSSION

This is the first web-based study examining patterns and factors associated with medication use during pregnancy on a multinational level. In all regions, approximately eight out of ten women reported use of at least one medication, either prescribed or OTC, during the course of their pregnancy. This finding is in line with previous research conducted in Europe, North America, South America and Australia,[4,20-25] though our estimates were somewhat higher in some of the Eastern European countries, e.g. Serbia, than those observed in a previous study.[5] Different recruitment strategies, i.e. web-based in our study versus maternity care unit-/community pharmacy-based in the previous study could explain such discrepancy.

Overall, analgesics, antacids, nasal decongestants/antiallergics and systemic antibiotics were the medication groups dominating the drug utilization scenario, as also shown by previous research.[4,20-22] However, our study also provides insights into the proportion of medicated women among those suffering from a specific illness during pregnancy across the six regions. We found that approximately seven out of ten women who reported UTIs were treated with antibiotics during pregnancy. This related to all regions, except Eastern Europe where it was only four out of ten women. Since women may perceive dysuria without ascertainment of bacteriuria in the urine as UTI, an over-reporting of the illness could have occurred. Yet, a sub-optimal treatment of UTIs during pregnancy in Eastern Europe cannot be ruled out. The inter-country variability in the types of antibiotics used for UTIs could simply be explained by differences in prescribing practice,[26] presence of screening for bacteriuria in early pregnancy, or specific antibiotic resistance patterns.

Even though nausea was the condition affecting most women in all six regions, the corresponding proportions of medicated nausea were generally low. This scenario is probably

due to two main factors: a) the predominantly mild character of nausea and the possibility of non-pharmacological management (e.g. dietary advices); b) the reluctance of general practitioners to prescribe antinauseants even though safety profile assessments are in place.[27,28] As also shown in previous studies,[4,29] use of serotonin antagonists in North America and Australia is increasing also in pregnancy compared to the other regions, eliciting the need of sound studies assessing the safety profile of this drug group in pregnancy.

In most regions, the self-reported prevalence of hypothyroidism was somewhat higher than the reported hormone substitution rate. Because of its known association with adverse pregnancy outcomes,[30] the unexpected finding of potential sub-optimal treatment of hypothyroidism during pregnancy deserves attention. It could probably be due to a lack of information about hypothyroidism typology and its diagnostic ascertainment in our study.

In our study, depression was self-reported and not based on any psychometric assessment, thus the observed substantial inter-regional variability in the extent of this disorder and related medication use could have certainly been affected by women's attitudes in reporting. Our estimate of medication use for depression in Australia was higher than that observed in a recent study (10.6% versus 2.1%).[31] However, the similarity in self-reported depression itself (11.5% versus 15.6%) suggests that our population might mostly comprise women who did not discontinue their pharmacological therapy once they became pregnant. Our estimates for North America and Western Europe were in line with recent literature showing an increase in antidepressant use in pregnancy during the last years.[4,32] Selective serotonin reuptake inhibitors (SSRIs) were the most widely used antidepressant class. Recent meta-analyses have shown that antidepressants, including SSRIs, do increase the risk of poor neonatal adaptation syndrome, specific cardiovascular malformations and persistent pulmonary hypertension of the newborn.[33-35] However, the clinical impact of the latter two outcomes, in absolute

terms, is small and the risk of pharmacotherapy should always be weighted versus the risk of undertreated depression in pregnancy.

In most regions approximately 60-70% of women reported use of at least one OTC medication during the course of their pregnancies, mostly for pain conditions, heartburn and upper airways disorders, indicating a substantially high rate of self-medication during pregnancy. This estimate aligns with previous research carried out in North America.[17] Of note, self-medication with OTC sympathomimetic nasal decongestants was more extensive in Northern and Eastern Europe than in the remaining regions; this could be explained by the time of the year when the data collection was performed.

Region of residency was an important factor associated with medication use during pregnancy. As also shown by Cleary et al.,[36] we found that rates of medication use among women originally from Eastern Europe and South America were significantly lower than those observed in Western Europe, North America and Australia. Such geographical differences could be due to culture, variations in prenatal care assistance or access to medications in the various regions and the related costs.

Women working as health care providers, consuming alcohol during pregnancy, or with previous children were those more likely to use short-term and OTC medications, possibly reflecting higher confidence in self-treatment and use of medications in general in the former instance, and less anxiety for the pregnancy outcome in the latter two instances.
Contrary to previous studies indicating an association between higher maternal education and more prevalent use of medication during pregnancy,[14,17,23] we found that lower education was associated with a higher use of OTC medications as well as medication for chronic/long-term disorders (30-50% increased risk). Results of similar magnitude (30% increased risk)

were also observed by Olesen et al.[37], whereas Stokholm et al. [38] identified a stronger association (2.3-fold increased risk) between low maternal education and use of antibiotic for respiratory tract infections during pregnancy. One factor negatively associated with chronic/long-term medication use was not having the official language of the country of residency as mother tongue. This tendency was detected in Western and Northern Europe, rising concerns about the potential health risks for immigrant women in these two regions. As shown by Hämeen-Anttila et al., 57% of pregnant women have perceived information needs about medications during pregnancy.[39] Thus, identification of potential users or non-users of medication during pregnancy might be of clinical relevance. Indeed, this may allow tailored evidence-based information about medication safety or outcome of sub-optimal medication of severe medical conditions in pregnancy.

Strengths and limitations

The main strength is that data collection was performed uniformly across all participating countries, allowing for inter-country comparison of the prevalence of medication use during pregnancy. By quantifying the extent of self-medication with OTC drugs and medication use according to self-reported indication, it was possible to determine the leading causes for medication use among pregnant women. Categorization of maternal characteristics positively associated with the various types of medications used during pregnancy enabled us to identify which groups of women are more likely to need information about medication use during pregnancy. The utilization of an anonymous web-based questionnaire enabled us to reach a large proportion of the birthing population in several countries worldwide. However, we cannot exclude the possibility that the women who decided to participate in the study differed from the general birthing population in other ways that our analysis could not control for. In most participating countries the study sample was large enough to warrant calculation of

prevalence estimates with a precision of 5%. However, less precise estimates were permitted by the study sample in Austria, Iceland and The Netherlands (precision of 9-11%), as well as in Australia, Canada, Croatia, Serbia, Slovenia, and USA (precision of 6-7%).

One main limitation of the study is the lack of validity of the self-reported diagnoses. All disorders were self-reported by the participants and hence dependent on the women's perception of the medical condition. Similarly, information about medication use during pregnancy was dependent on the accuracy of the women's reporting and recall. For new mothers, data were registered retrospectively; hence a risk of recall bias cannot be ruled out. In specific countries (Australia, Canada, France, Russia, The Netherlands, and USA) the study sample was a small proportion of the general birthing population; hence the generalizability of our findings for these specific countries should be interpreted with caution.

The questionnaire was only available through internet websites; by using this kind of approach a conventional response rate cannot be calculated and a selection bias of the target population cannot be ruled out. However, recent epidemiological studies indicate reasonable validity of web-based recruitment methods.[40,41] Also, the penetration rate of the internet either in households or at work is relatively high among women in childbearing age.[42-46] Hence, the degree to which our findings can be extrapolated to the target population is based on the representativeness of the respondents to the general birthing populations in each country. The sample in each country had a somewhat higher educational level than the general birthing populations. Such a limitation might have led to an underestimation of the prevalence of medication during pregnancy. Since many ailments requiring pharmacotherapy occur in mid or late pregnancy, inclusion of pregnant women at early gestation in the total material has somewhat inflated the prevalence of non-users of medications during pregnancy. Also, women with specific disorders or in need of information about medication use during

pregnancy might have been more likely to consult internet websites and therefore participate in this study.

CONCLUSIONS

Use of medications for acute/short-term illnesses and chronic/long-term disorders as well as use of OTC medications, were common during pregnancy. The extent of medicated illnesses and types of medications used for the different indications varied across the six regions. This was especially relevant for acute/short-term illnesses such as nausea and UTIs, but also for chronic/long-term disorders such as hypothyroidism or depression. Women with higher age or lower educational level, housewives, or women with an unplanned pregnancy were those most often reporting chronic/long-term medication use, as opposed to immigrants residing in Western and Northern Europe who reported the least use of this medication category. Future research should definitely focus on this specific group of women, but also address more insights into the outcome of sub-optimal medication of severe conditions in pregnancy.

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DATA SHARING STATEMENT: No additional data are available. Researchers can apply for data access for subprojects within the overall aims of the main study 'The Multinational Medication Use in Pregnancy Study'.

COMPETING INTERESTS: None declared

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Medication use in pregnancy: a cross-sectional, multinational web-based study~~a multinational perspective~~

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ABSTRACT

Objectives: Inter-country comparability between studies on medication use in pregnancy is difficult due to dissimilarities in study design and methodology. This study aimed to examine patterns and factors associated with medications use in pregnancy from a multinational perspective, with emphasis on type of medication utilized and indication for use.

Design: Cross-sectional, web~~internet~~-based study performed within the period from 1-Oct-2011 to 29-Feb-2012. Uniform collection of drug utilization data was performed via an anonymous online questionnaire.

Setting: Multinational study in Europe (Western, Northern, and Eastern), North and South America, and Australia.

Participants: Pregnant women and new mothers with children less than one year of age.

Primary and secondary outcome measures: Prevalence of and factors associated with medication use for acute/short-term illnesses, chronic/long-term disorders and over-the-counter (OTC) medication use.

Results: The study population included 9,459 women whereof 81.2% reported use of at least one medication (prescribed or OTC) during pregnancy. Overall, OTC medication use occurred in 66.9% of the pregnancies, whereas 68.4% and 17.0% of women reported use of at least one medication for treatment of acute/short-term illnesses and chronic/long-term disorders, respectively. The extent of self-reported

medicated illnesses and types of medication used by indication varied across regions, especially in relation to urinary tract infections, depression or OTC nasal sprays. Women with higher age or lower educational level, housewives, or women with an unplanned pregnancy were those most often reporting use of medication for chronic/long-term disorders. Immigrant women in Western (aOR: 0.55, 95% CI: 0.34-0.87) and Northern Europe (aOR: 0.50, 95% CI: 0.31-0.83) were less likely to report use of medication for chronic/long-term disorders during pregnancy than non-immigrants.

Conclusions:

In this study, the majority of women in Europe, North America, South America and Australia used at least one medication during pregnancy. There was a substantial inter-region variability in the types of medication used.

ARTICLE SUMMARY

Strengths and limitations of this study

- Uniform data collection of drug utilization data across all participating countries allows for inter-country comparability of the prevalence of medication use during pregnancy, up to now impeded by differences in study design and methodology.
- The study adds a multinational perspective on OTC medication use during pregnancy to the limited number of studies quantifying the extent of self-medication during pregnancy.
- Lack of validity of the self-reported diagnoses is a limitation since all disorders and related medication use were self-reported by the study participants.
- A~~n internet~~ web-based survey as a study method impedes calculation of a conventional response rate and may cause selection bias of the target population.

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INTRODUCTION

Ethical reasons preclude inclusion of pregnant women in the vast majority of pre-marketing clinical trials.[1] As a consequence, most medications are placed onto the market without a directly established safety profile in human pregnancy.[2] So far, few medications have been shown to be major teratogens, yet the risk of minor teratogenicity or of more subtle effects on fetal development still have to be determined for most of them.[3] Despite this, medication use during pregnancy is common. Mitchell et al. found that use of medications, either prescribed or purchased over-the-counter (OTC), occurred in 88.8% of all pregnancies in the USA.[4] In Europe, prevalence estimates of prescribed medication use vary considerably across countries, ranging from 26% in Serbia to 93% in France.[5-10] Such inter-country variability could, at least in part, be caused by differences in study design, methodology and exposure ascertainment across studies.[11] Uniform collection of drug utilization data during pregnancy between countries may overcome such drawbacks, allowing for inter-country comparability of prevalence estimates and shedding light on differences in prenatal care in the various countries.

Prior studies have addressed research priorities in this area such as presenting results on an individual drug level according to the indication of use, quantifying the extent of OTC and prescribed medication use during pregnancy, and taking into account inter-country comparability.[4] Only a few studies have individually examined maternal factors associated with specific types of medication use during pregnancy.[11-14]

The objectives of the current study were to examine patterns of medication use in pregnancy from a multinational perspective, with special emphasis on type of medication utilized, including OTC medications, and self-reported indications for use, and to identify maternal background factors potentially associated with medication use for acute/short-term illnesses, medication use for chronic/long-term disorders and OTC medication use during pregnancy.

METHODS

Study design and data collection

This is a multinational, cross-sectional, ~~internet~~web-based study. Pregnant women at any gestational week and mothers with children less than one year of age were eligible to participate. Member countries of the European Network of Teratology Information Services (ENTIS), The Organization of Teratology Information Specialists (OTIS) in North America, MotherSafe in Australia and European institutions conducting public health research were invited to take part in the project. Of these, 18 countries participated (Australia, Austria, Canada, Croatia, Finland, France, Iceland, Italy, Netherlands, Norway, Poland, Russia, Serbia, Slovenia, Sweden, Switzerland, United Kingdom and USA). Data originating from some South and Central American countries were also collected through OTIS. Because of the low number of participants on the individual country level, the region of Central America was excluded and countries in South America were aggregated into one region. Data selection to achieve the final study sample was performed as depicted in Figure 1. Participants were categorized according to the reported country of residency and grouped into six regions: Western Europe, Northern Europe, Eastern Europe, North America, South America and Australia.

Data were collected through an anonymous on-line questionnaire administered by Quest Back (http://www.questback.com) and accessible for a period of two months in each participating country within the period 1-Oct-2011 to 29-Feb-2012. The questionnaire was open to the public via utilization of banners (invitations to participate in the study) on national websites and/or social networks commonly visited and consulted by pregnant women and/or new mothers. The complete questionnaire is presented in Appendix 1. Detailed information about recruitment tools utilized and internet penetration rates is summarized in Appendix 2.

The questionnaire was first developed in Norwegian and English and then translated into the other relevant languages. A pilot study was carried out in September 2011 (n=47) and elicited no major change to the questionnaire. Collected data were scrutinized for the presence of potential duplicates (based on reported country of residency, socio-demographic characteristics, date and exact time of questionnaire completion) but none were identified.

Exposure variables

Maternal socio-demographics (i.e. region of residency, age, educational level, mother tongue, working status at time of conception, previous children, marital status and unplanned pregnancy) and life-style characteristics (i.e. smoking status before and during pregnancy and alcohol consumption after awareness of pregnancy) constituted the exposure variables. To assess external validity, we compared socio-demographic and life-style characteristics of our study population on an individual country level with those of the general birthing population in the same country. Reports of National Statistics Bureaus or previous national studies were utilized for this purpose. The ratio

between the number of respondents and the estimated number of live births in the 2-months period was also examined for each country (Appendix 3).

Outcome variables

Use of any medication, medication for acute/short-term illnesses, medication for chronic/long-term disorders and OTC medication use during pregnancy constituted the outcome variables. Participants were first confronted with a list of the most common acute/short-term illnesses (i.e. nausea, heartburn, constipation, common cold, urinary tract infections (UTIs), other infections, pain in the neck/back/pelvic girdle, headache, sleeping problems) and the most prevalent chronic/long-term disorders (i.e. asthma, allergy, hypothyroidism, rheumatic disorders, diabetes, epilepsy, depression, anxiety, cardiovascular disease, other disorders) and asked whether they suffered/had suffered from these conditions during pregnancy. In case of an affirmative response, women were questioned about medication use for each individual indication as a free-text entry. Use of OTC medications was also recorded. Recall was aided with a list of five OTC medication categories: painkillers, nasal spray/drops, antinauseants, antacids and laxatives, along with examples of brand name products of relevance in each country. It was optional to report timing of exposure for each of the medication use questions (the alternatives were gestational weeks 0-12 (1st trimester), 13-24 (2nd trimester) and 25-delivery (3rd trimester)).

We defined a medicine as a single product containing one or more active ingredients. We initially identified the main active ingredient(s) and formulation of the reported medicinal products either in the relevant national medicines database or in the "Martindale" textbook.[15] All recorded medications were coded into the corresponding Anatomical Therapeutic Chemical (ATC) codes at the ATC 5th level

(i.e. the substance level) whenever possible, otherwise into the 2nd- 4th levels as appropriate, in accordance with the World Health Organization ATC index.[16] The OTC status of medications was crosschecked with the prescription policies within each country. Whenever a prescription medication was reported under the OTC question, this record was omitted from the analysis of OTC use but counted in the estimation of total medication use (including prescription and OTC). Iron, mineral supplements, vitamins, herbal remedies and any type of alternative medicine were recorded separately and excluded from the estimation of medication use.

The required sample size calculation for the outcome variables on region and individual country levels are outlined in Appendix 4. The expected prevalence estimates were set according to results of previous studies.[5-10,17,18]

Ethics

All participants gave informed consent by answering "Yes" to the question "Are you willing to participate in the study?" The study was approved by the Regional Ethics Committee, Region South-East in Norway. Ethical approval or study notification to the relevant national Ethics Boards was achieved in specific countries as required by national legislation. All data were handled and stored anonymously.

Statistical analysis

Descriptive statistics were utilized as appropriate. Univariate and multivariate logistic regression analyses were used to examine the association between maternal characteristic and three categorical outcome measures (Yes/No): Medication use for acute/short-term illnesses; medication use for chronic/long-term disorders; OTC medication use. P-values of <0.05 were considered statistically significant. Data are

presented as adjusted odds ratios (aOR) with 95% confidence intervals (CI). The analyzed explanatory variables included all maternal socio-demographics and life-style characteristics. After fitting the univariate logistic regression model for all explanatory variables, the multivariate model was built and adjusted for all remaining covariates. The Hosmer and Lemeshow test was used to assess goodness of fit of the final multivariate model.[19] Analogue sub-analyses on individual region level were performed. In these instances, region of residency was not included in the model. All statistical analyses were performed by using the Statistical Package for the Social Sciences (SPSS) version 20.0 (IBM® SPSS® Statistics).

RESULTS

Population characteristics

A total of 9,615 women accessed the on-line questionnaire whereof 98.6% completed it. The participant flow-chart to achieve final study population (n=9,459) is depicted in Figure 1. A total of 5,089 women (53.8%) were pregnant at the time of completion of the questionnaire, whereas 4,370 women (46.2%) had delivered their babies within the previous year. Of the former group, 1,095 (21.5%), 1,702 (33.4%) and 2,291 (45.0%) women were in the first, second and third trimester of pregnancy, respectively. Of the latter group, 1,320 (30.2%), 947 (21.7%) and 2,102 (48.1%) had a baby of age ≤ 16 weeks, 17-28 weeks, and ≥ 29 weeks, respectively. For two women the time of gestation/baby´s age was unknown. Overall, the birthing population in each participating country was reflected quite well by the sample with respect to age, parity and smoking habits (Appendix 3). However, there was a difference in terms of educational level; on average, the women in the study had higher education than the general birthing population in each country. In addition, participants in Sweden,

Austria, Iceland and Italy were slightly more often primiparous, whereas the responders in Australia, USA, The Netherlands, Slovenia and Croatia were somewhat older than the general birthing population.

Total medication use

After exclusion of vitamins, mineral supplements and iron, use of at least one medication either prescribed or OTC at any time during pregnancy was reported by 7,678 out of 9,459 women (81.2%). Figure 2 depicts prevalence estimates of total medication use during pregnancy by region and country of residence. The extent of OTC medication use, as well as medication use for acute/short-term illnesses and chronic/long-term disorders is also outlined. The highest prevalence of total medication use during pregnancy was observed in The Netherlands (95.1%), Iceland (93.0%) and Finland (92.3%). The overall prevalence estimates of medication use in pregnancy according to timing and drug class (ATC level 1 and 2) are presented in Appendix 5. Medications for the nervous system (ATC class N) were the most commonly used during pregnancy (57.5%), mostly due to paracetamol (acetaminophen) and its combinations.

A corollary analysis according to pregnancy status showed that pregnant women reported in a significantly lower degree than new mothers any medication use during pregnancy (78.8% vs. 84.0%, p-value<0.001), as well as OTC medication use (63.0% vs. 71.5%, p-value<0.001) and medication use for acute/short-term illnesses (66.2% vs. 70.9%, p-value<0.001). In contrast, the difference in medication use for chronic/long-term disorders was not significant (17.4% vs. 16.5%, p-value=0.271). None of the rates differed significantly when women in the third trimester of pregnancy were compared to new mothers.

Medication use according to indication

Headache, heartburn, pain, nausea and UTIs constituted the leading indications for use of medication during pregnancy among the acute/short-term illnesses analyzed. Hypothyroidism, asthma, allergy and depression were the leading indications for chronic/long-term medication use. Observed prevalence rates of these disorders, overall and by region of residency, are presented in Appendices 6 and 7, respectively, along with rates of total and specific medication use. Table 1 outlines prevalence estimates of OTC medication use during pregnancy by region and indication for use. Only the most common medication groups reported are presented. Inter-region variations in rates and types of medication used during pregnancy were observed both for acute/short-term illnesses (e.g. nausea and UTIs), chronic/long-term disorders (e.g. asthma and depression) and OTC medications (e.g. nasal spray).

Factors associated with medication use

Factors associated with medication use during pregnancy according to type of medication utilized are presented in table 2. Use of chronic/long-term medications during pregnancy was reported in a significant larger extent by women in Northern Europe (aOR: 1.68, 95% CI: 1.46-1.94), North America (aOR: 1.80, 95% CI: 1.42-2.28) and Australia (aOR: 2.76, 95% CI: 2.03-3.76) compared to women in Western Europe. Older women or housewives, those with low education or with an unplanned pregnancy, were the ones most often reporting use of chronic/long-term medication. Sub-analysis on individual region level revealed that women not having the official language of the country of residency as mother tongue were less likely to report chronic/long-term medication use in Western (aOR: 0.55, 95% CI: 0.34-0.87) and Northern Europe (aOR: 0.50, 95% CI: 0.31-0.83), but not in the other regions.

Table 1: Use of OTC medication at any time during pregnancy by ATC level, indication for use and region (n=9,459) [*†]

OTC medication use, overall and by drug groups	REGION						
	Western Europe n=3,201 *n (%)*	**Northern Europe n=2,820** *n (%)*	**Eastern Europe n=2,342** *n (%)*	**North America n=533** *n (%)*	**South America n=346** *n (%)*	**Australian n=217** *n (%)*	**Total n=9,459** *n (%)*
OTC painkillers, total	**1,714 (53.5)**	**1,773 (62.9)**	**734 (31.3)**	**284 (53.3)**	**127 (36.7)**	**151 (69.9)**	**4,783 (50.6)**
By drug group							
Paracetamol (incl. combinations) (N02BE)	1,655 (51.7)	1,735 (61.5)	630 (26.9)	263 (49.3)	87 (25.1)	146 (67.3)	4,516 (47.7)
Non-steroideal antiinflammatory drugs (M01A)	70 (2.2)	182 (6.5)	68 (2.9)	40 (7.5)	59 (17.1)	7 (3.2)	426 (4.5)
Acetylsalicylic acid (incl. combinations) (N02BA)	7 (0.2)	11 (0.4)	32 (1.4)	2 (0.4)	2 (0.6)	1 (0.5)	55 (0.6)
Metamizole (N02BB02)	-	6 (0.2)	31 (1.3)	1 (0.2)	12 (3.5)	-	50 (0.5)
OTC antacids, total	**1,011 (31.6)**	**883 (31.3)**	**583 (24.9)**	**129 (24.2)**	**48 (13.9)**	**76 (35.0)**	**2,730 (28.9)**
By drug group							
Antacids (aluminium, salts combinations, antiflatulents)	472 (14.7)	550 (19.5)	508 (21.7)	47 (8.8)	36 (10.4)	54 (24.9)	1,667 (17.6)
Alginic acid complex/sucralfate/bismuth (A02BX)	606 (18.9)	421 (14.9)	87 (3.7)	4 (0.8)	1 (0.3)	17 (7.8)	1,136 (12.0)
H_2 receptor antagonists (A02BA)	20 (0.6)	20 (0.7)	16 (0.7)	57 (10.1)	10 (2.9)	17 (7.8)	137 (1.4)
Antacids with calcium (A02AC)	23 (0.7)	12 (0.4)	10 (0.4)	69 (12.9)	2 (0.6)	10 (4.6)	126 (1.3)
Proton pump inhibitors (A02BC)	38 (1.2)	52 (1.8)	-	10 (1.9)	2 (0.6)	5 (0.3)	107 (1.1)
OTC nasal sprays/drops, total	**272 (8.5)**	**742 (26.3)**	**451 (19.3)**	**35 (6.6)**	**7 (2.0)**	**14 (6.5)**	**1,521 (16.1)**
By drug group							
Sympathomimetic nasal decongestants (R01AA/R01BB)	204 (6.4)	683 (24.2)	365 (15.6)	20 (3.8)	3 (0.9)	4 (1.8)	1,279 (13.5)
Nasal corticosteroids (R01AD)	31 (1.0)	49 (1.7)	12 (0.5)	5 (0.9)	2 (0.6)	10 (4.6)	109 (1.2)
Nasal immunostimulants (low dose interferon) (L03A)	-	-	28 (1.2)	-	-	-	28 (0.3)
OTC laxatives, total	**240 (7.5)**	**227 (8.0)**	**237 (10.1)**	**50 (9.4)**	**8 (2.3)**	**19 (8.8)**	**781 (8.3)**
By drug group							
Osmotically acting laxatives (A06AD)	159 (5.0)	171 (6.1)	197 (8.4)	2 (0.4)	2 (0.6)	8 (3.7)	539 (5.7)
Contact laxatives (A06AB)	28 (0.9)	44 (1.6)	18 (0.8)	7 (1.3)	6 (1.7)	2 (0.9)	105 (1.1)

OTC medication use, overall and by drug groups	REGION						
	Western Europe n=3,201 *n (%)*	Northern Europe n=2,820 *n (%)*	Eastern Europe n=2,342 *n (%)*	North America n=533 *n (%)*	South America n=346 *n (%)*	Australian n=217 *n (%)*	Total n=9,459 *n (%)*
Enemas (A06AG)	3 (0.1)	25 (0.9)	34 (1.5)	4 (0.8)	-	2 (0.9)	68 (0.7)
Softeners, emollients (A06AA)	8 (0.2)	-	-	38 (7.1)	-	6 (2.8)	52 (0.5)
OTC antinauseants, total	**263 (8.2)**	**273 (9.7)**	**41 (1.8)**	**60 (11.3)**	**28 (8.1)**	**40 (18.4)**	**705 (7.5)**
By drug group							
First generation antihistamines (R06A)	141 (4.4)	256 (9.1)	7 (1.5)	55 (10.3)	5 (1.4)	5 (2.3)	469 (5.0)
Metoclopramide/domperidone/bromopride (A03FA)	113 (3.5)	5 (0.2)	18 (0.8)	2 (0.4)	19 (5.5)	27 (12.4)	184 (1.9)
Total OTC medication use	**2,163 (67.6)**	**2,155 (76.4)**	**1,347 (57.5)**	**342 (64.2)**	**156 (45.1)**	**168 (77.4)**	**6,331 (66.9)**

Abbreviations: OTC: Over-The-Counter medications.

*Countries are grouped into regions as shown in Figure 1.

†Sums of percentages do not add up to total medication use as only most common medication groups are presented. Rates do not include mineral supplements, vitamins, iron, and herbal or alternative medicine products.

Table 2: Factors associated with medication use in pregnancy (n=9,459)*

	Medication use					
	For acute/short-term illnesses (n=6,469)		For chronic/long-term disorders (n=1,604)		OTC (n=6,331)	
	n (%)	*aOR (95% CI)*	*n (%)*	*aOR (95% CI)*	*n (%)*	*aOR (95% CI)*
Region of residency†						
Western Europe	2,224 (69.5)	Reference	462 (14.4)	Reference	2,163 (67.6)	Reference
Northern Europe	1,954 (69.3)	0.96 (0.86-1.08)	593 (21.0)	**1.68 (1.46-1.94)**	2,155 (76.4)	**1.54 (1.36-1.74)**
Eastern Europe	1,474 (62.9)	**0.69 (0.61-0.78)**	322 (13.7)	1.03 (0.87-1.21)	1,347 (57.5)	**0.60 (0.53-0.67)**
North America	403 (75.6)	**1.28 (1.03-1.60)**	119 (22.3)	**1.80 (1.42-2.28)**	342 (64.2)	**0.81 (0.66-0.99)**
South America	250 (82.3)	1.03 (0.79-1.34)	38 (11.0)	0.70 (0.48-1.01)	156 (45.1)	**0.34 (0.27-0.44)**
Australia	164 (75.6)	1.29 (0.93-1.79)	70 (32.3)	**2.76 (2.03-3.76)**	168 (77.4)	**1.57 (1.12-2.20)**
Maternal age (years)						
≤20	232 (70.5)	1.22 (0.93-1.60)	761 (14.7)	**0.58 (0.39-0.87)**	205 (62.3)	1.05 (0.81-1.36)
21-30	3,531 (68.2)	Reference	33 (10.0)	Reference	3,461 (66.8)	Reference
31-40	2,576 (68.6)	0.90 (0.82-1.00)	764 (20.4)	**1.44 (1.27-1.63)**	2,531 (67.4)	**0.85 (0.77-0.94)**
≥41	130 (66.3)	0.73 (0.54-1.00)	46 (23.5)	**1.61 (1.13-2.29)**	134 (68.4)	0.86 (0.62-1.19)
Previous children						
No	3,082 (65.5)	Reference	735 (15.6)	Reference	2,949 (62.6)	Reference
Yes	3,387 (71.3)	**1.34 (1.22-1.47)**	869 (18.3)	1.08 (0.96-1.21)	3,382 (71.2)	**1.58 (1.44-1.74)**
Marital status						
Married/cohabiting	6,066 (68.5)	Reference	1,503 (17.0)	Reference	5,960 (67.3)	Reference
Single/divorced/others	403 (66.3)	0.91 (0.75-1.10)	101 (16.6)	1.06 (0.83-1.35)	371 (61.0)	0.91 (0.75-1.10)
Working status						
Employed, but not as HCP	3,737 (66.8)	Reference	905 (16.2)	Reference	3,667 (65.6)	Reference
HCP	934 (74.4)	**1.41 (1.23-1.63)**	240 (19.1)	1.13 (0.96-1.33)	944 (75.2)	**1.42 (1.23-1.64)**
Student	592 (69.1)	1.11 (0.94-1.31)	128 (14.9)	1.04 (0.84-1.30)	578 (67.4)	1.10 (0.93-1.30)
Housewife	608 (72.6)	1.14 (0.96-1.35)	170 (20.3)	**1.34 (1.10-1.63)**	577 (68.9)	1.05 (0.88-1.24)
Job seeker	281 (66.0)	0.96 (0.78-1.20)	66 (15.5)	1.03 (0.78-1.36)	258 (60.6)	0.85 (0.68-1.05)
Other than above	311 (65.2)	0.91 (0.75-1.12)	94 (19.7)	**1.29 (1.01-1.65)**	302 (63.3)	0.91 (0.74-1.12)
Educational level						

	Medication use					
	For acute/short-term illnesses (n=6,469)		For chronic/long-term disorders (n=1,604)		OTC (n=6,331)	
	n (%)	*aOR (95% CI)*	*n (%)*	*aOR (95% CI)*	*n (%)*	*aOR (95% CI)*
Less than high school	331 (72.7)	1.17 (0.93-1.49)	92 (20.2)	**1.51 (1.15-1.97)**	317 (69.7)	**1.32 (1.04-1.67)**
High school	1,864 (68.7)	Reference	428 (15.8)	Reference	1,779 (65.6)	Reference
More than high school	3,574 (68.4)	0.99 (0.89-1.11)	916 (17.5)	1.04 (0.91-1.20)	3,489 (66.8)	1.07 (0.96-1.19)
Others, unspecified	700 (65.7)	0.82 (0.70-0.96)	168 (15.8)	0.94 (0.77-1.16)	746 (70.0)	1.13 (0.97-1.33)
Alcohol use after awareness of pregnancy						
No	5,270 (67.1)	Reference	1,322 (16.8)	Reference	5,133 (65.3)	Reference
Yes	1,144 (75.7)	**1.59 (1.39-1.81)**	270 (17.9)	1.11 (0.95-1.29)	1,150 (76.1)	**1.95 (1.71-2.23)**
Smoking during pregnancy						
No	5,835 (68.5)	Reference	1,441 (16.9)	Reference	5,716 (67.0)	Reference
Yes, but less than before pregnancy	530 (69.0)	1.08 (0.91-1.27)	130 (16.9)	1.01 (0.82-1.25)	511 (66.5)	1.06 (0.90-1.26)
Yes, the same or more than before pregnancy	88 (67.7)	0.95 (0.64-1.40)	28 (21.5)	1.19 (0.74-1.90)	89 (68.5)	1.21 (0.81-1.82)
Planned pregnancy						
Yes	5,836 (68.4)	Reference	1,427 (16.7)	Reference	5,727 (67.2)	Reference
No	616 (68.4)	0.96 (0.82-1.12)	173 (19.2)	**1.29 (1.06-1.56)**	587 (65.1)	1.00 (0.85-1.17)
First language different from the official main language in the country of residency						
No	6,089 (68.5)	Reference	1,530 (17.2)	Reference	5,972 (67.1)	Reference
Yes	363 (67.2)	0.93 (0.76-1.12)	71 (13.1)	**0.66 (0.50-0.86)**	347 (64.3)	0.89 (0.74-1.08)

Abbreviation: HCP: health care provider.

[*]Numbers may not add up due to missing values. Missing values are less than 5% of the total. Mineral supplements, vitamins, iron, herbal or alternative medicine products are not included in the medication use estimates.

[†]Countries are grouped into regions as shown in Figure 1.

DISCUSSION

This is the first ~~internet~~web-based study examining patterns and factors associated with medication use during pregnancy on a multinational level. In all regions, approximately eight out of ten women reported use of at least one medication, either prescribed or OTC, during the course of their pregnancy. This finding is in line with previous research conducted in Europe, North America, South America and Australia,[4,20-25] though our estimates were somewhat higher in some of the Eastern European countries, e.g. Serbia, than those observed in a previous study.[5] Different recruitment strategies, i.e. web~~internet~~-based in our study versus maternity care unit-/community pharmacy-based in the previous study could explain such discrepancy.

Overall, analgesics, antacids, nasal decongestants/antiallergics and systemic antibiotics were the medication groups dominating the drug utilization scenario, as also shown by previous research.[4,20-22] However, our study also provides insights into the proportion of medicated women among those suffering from a specific illness during pregnancy across the six regions. We found that approximately seven out of ten women who reported UTIs were treated with antibiotics during pregnancy. This related to all regions, except Eastern Europe where it was only four out of ten women. Since women may perceive dysuria without ascertainment of bacteriuria in the urine as UTI, an over-reporting of the illness could have occurred. Yet, a sub-optimal treatment of UTIs during pregnancy in Eastern Europe cannot be ruled out. The inter-country variability in the types of antibiotics used for UTIs could simply be explained by differences in prescribing practice,[26] presence of screening for bacteriuria in early pregnancy, or specific antibiotic resistance patterns.

Even though nausea was the condition affecting most women in all six regions, the corresponding proportions of medicated nausea were generally low. This scenario is probably due to two main factors: a) the predominantly mild character of nausea and the possibility of non-pharmacological management (e.g. dietary advices); b) the reluctance of general practitioners to prescribe antinauseants even though safety profile assessments are in place.[27,28] As also shown in previous studies,[4,29] use of serotonin antagonists in North America and Australia is increasing also in pregnancy compared to the other regions, eliciting the need of sound studies assessing the safety profile of this drug group in pregnancy.

In most regions, the self-reported prevalence of hypothyroidism was somewhat higher than the reported hormone substitution rate. Because of its known association with adverse pregnancy outcomes,[30] the unexpected finding of potential sub-optimal treatment of hypothyroidism during pregnancy deserves attention. It could probably be due to a lack of information about hypothyroidism typology and its diagnostic ascertainment in our study.

In our study, depression was self-reported and not based on any psychometric assessment, thus the observed substantial inter-regional variability in the extent of this disorder and related medication use could have certainly been affected by women's attitudes in reporting. Our estimate of medication use for depression in Australia was higher than that observed in a recent study (10.6% versus 2.1%).[31] However, the similarity in self-reported depression itself (11.5% versus 15.6%) suggests that our population might mostly comprise women who did not discontinue their pharmacological therapy once they became pregnant. Our estimates for North America and Western Europe were in line with recent literature showing an increase in antidepressant use in pregnancy during the last years.[4,32] Selective serotonin reuptake inhibitors (SSRIs) were the most widely used antidepressant class. Recent meta-analyses have shown that antidepressants, including SSRIs, do increase the risk of poor neonatal adaptation

syndrome, specific cardiovascular malformations and persistent pulmonary hypertension of the newborn.[33-35] However, the clinical impact of the latter two outcomes, in absolute terms, is small and the risk of pharmacotherapy should always be weighted versus the risk of undertreated depression in pregnancy.

In most regions approximately 60-70% of women reported use of at least one OTC medication during the course of their pregnancies, mostly for pain conditions, heartburn and upper airways disorders, indicating a substantially high rate of self-medication during pregnancy. This estimate aligns with previous research carried out in North America.[17] Of note, self-medication with OTC sympathomimetic nasal decongestants was more extensive in Northern and Eastern Europe than in the remaining regions; this could be explained by the time of the year when the data collection was performed.

Region of residency was an important factor associated with medication use during pregnancy. As also shown by Cleary et al.,[36] we found that rates of medication use among women originally from Eastern Europe and South America were significantly lower than those observed in Western Europe, North America and Australia. Such geographical differences could be due to culture, variations in prenatal care assistance or access to medications in the various regions and the related costs.

Women working as health care providers, consuming alcohol during pregnancy, or with previous children were those more likely to use short-term and OTC medications, possibly reflecting higher confidence in self-treatment and use of medications in general in the former instance, and less anxiety for the pregnancy outcome in the latter two instances.
Contrary to previous studies indicating an association between higher maternal education and more prevalent use of medication during pregnancy,[14,17,23] we found that lower education

was associated with a higher use of OTC medications as well as medication for chronic/long-term disorders (30-50% increased risk). Results of similar magnitude (30% increased risk) were also observed by Olesen et al.[37], whereas Stokholm et al. [38] identified a stronger association (2.3-fold increased risk) between low maternal education and use of antibiotic for respiratory tract infections during pregnancy. One factor negatively associated with chronic/long-term medication use was not having the official language of the country of residency as mother tongue. This tendency was detected in Western and Northern Europe, rising concerns about the potential health risks for immigrant women in these two regions. As shown by Hämeen-Anttila et al., 57% of pregnant women have perceived information needs about medications during pregnancy.[39] Thus, identification of potential users or non-users of medication during pregnancy might be of clinical relevance. Indeed, this may allow tailored evidence-based information about medication safety or outcome of sub-optimal medication of severe medical conditions in pregnancy.

Strengths and limitations

The main strength is that data collection was performed uniformly across all participating countries, allowing for inter-country comparison of the prevalence of medication use during pregnancy. By quantifying the extent of self-medication with OTC drugs and medication use according to self-reported indication, it was possible to determine the leading causes for medication use among pregnant women. Categorization of maternal characteristics positively associated with the various types of medications used during pregnancy enabled us to identify which groups of women are more likely to need information about medication use during pregnancy. The utilization of an anonymous web-based questionnaire enabled us to reach a large proportion of the birthing population in several countries worldwide. However, we cannot exclude the possibility that the women who decided to participate in the study differed

from the general birthing population in other ways that our analysis could not control for. In most participating countries the study sample was large enough to warrant calculation of prevalence estimates with a precision of 5%. However, less precise estimates were permitted by the study sample in Austria, Iceland and The Netherlands (precision of 9-11%), as well as in Australia, Canada, Croatia, Serbia, Slovenia, and USA (precision of 6-7%).

One main limitation of the study is the lack of validity of the self-reported diagnoses. All disorders were self-reported by the participants and hence dependent on the women's perception of the medical condition. Similarly, information about medication use during pregnancy was dependent on the accuracy of the women's reporting and recall. For new mothers, data were registered retrospectively; hence a risk of recall bias cannot be ruled out. In specific countries (Australia, Canada, France, Russia, The Netherlands, and USA) the study sample was a small proportion of the general birthing population; hence the generalizability of our findings for these specific countries should be interpreted with caution.

The questionnaire was only available through internet websites; by using this kind of approach a conventional response rate cannot be calculated and a selection bias of the target population cannot be ruled out. However, recent epidemiological studies indicate reasonable validity of web-based recruitment methods.[40,41] Also, the penetration rate of the internet either in households or at work is relatively high among women in childbearing age.[42-46] Hence, the degree to which our findings can be extrapolated to the target population is based on the representativeness of the respondents to the general birthing populations in each country. The sample in each country had a somewhat higher educational level than the general birthing populations. Such a limitation might have led to ~~biased estimates of the association between maternal education and medication use during pregnancy~~an underestimation of the prevalence of medication during pregnancy. Since many ailments requiring pharmacotherapy

occur in mid or late pregnancy, inclusion of pregnant women at early gestation in the total material has somewhat inflated the prevalence of non-users of medications during pregnancy. Also, women with specific disorders or in need of information about medication use during pregnancy might have been more likely to consult internet websites and therefore participate in this study.

CONCLUSIONS

Use of medications for acute/short-term illnesses and chronic/long-term disorders as well as use of OTC medications, were common during pregnancy. The extent of medicated illnesses and types of medications used for the different indications varied across the six regions. This was especially relevant for acute/short-term illnesses such as nausea and UTIs, but also for chronic/long-term disorders such as hypothyroidism or depression. Women with higher age or lower educational level, housewives, or women with an unplanned pregnancy were those most often reporting chronic/long-term medication use, as opposed to immigrants residing in Western and Northern Europe who reported the least use of this medication category. Future research should definitely focus on this specific group of women, but also address more insights into the outcome of sub-optimal medication of severe conditions in pregnancy.

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AUTHOR'S CONTRIBUTION: AL, OS and HN conceived the idea for the study and participated in its design and coordination. AL drafted the manuscript and analyzed the data. MJT, KZ, ACM, MEM, MD, AP, KHA, AR, RGJ, MO, DK, GR, HJ, AP and IB contributed to the data collection. All authors contributed to the interpretation of the results and revised the manuscript critically for important intellectual content. All the authors read and approved the final manuscript.

DATA SHARING STATEMENT: No additional data are available. Researchers can apply for data access for subprojects within the overall aims of the main study 'The Multinational Medication Use in Pregnancy Study'.

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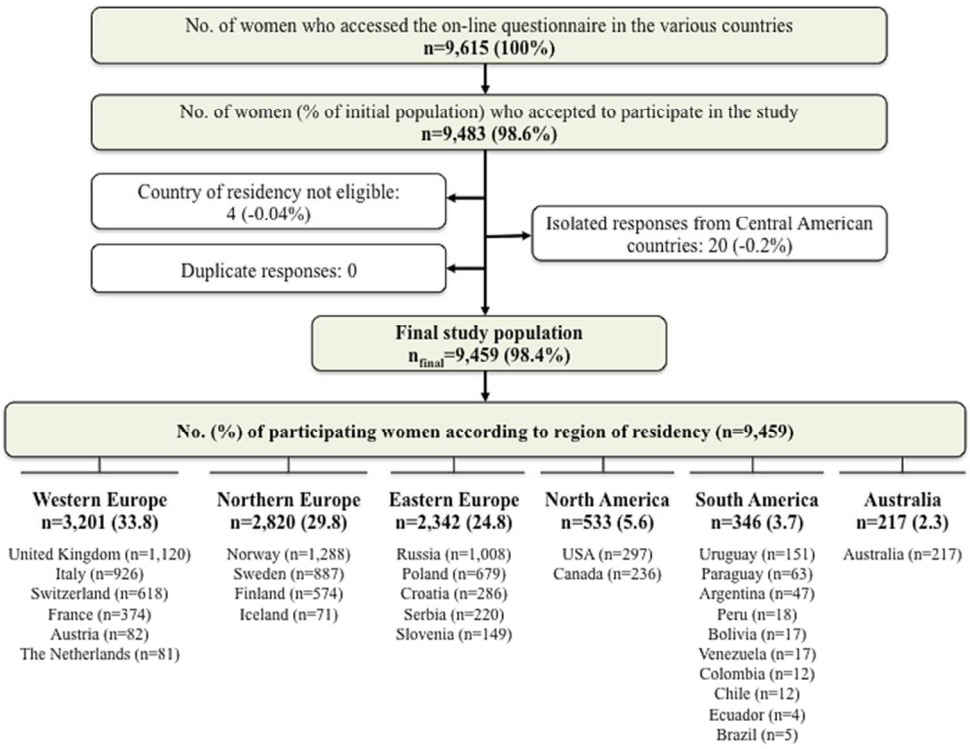

Figure 1 shows the participant flow-chart to achieve the final sample analyzed
60x45mm (300 x 300 DPI)

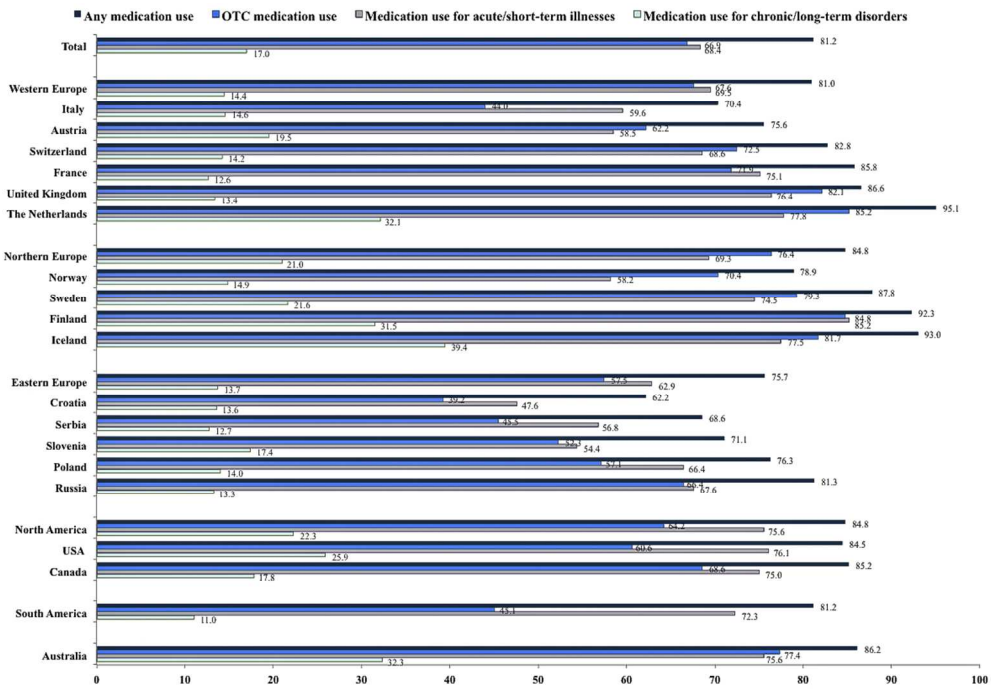

Figure 2 shows the proportion of respondents (%) reporting use of any medication, over-the-counter (OTC) medication, medication for acute/short-term illnesses and medication for chronic/long-term disorders during pregnancy according to region and country of residency. The observed estimates do not include vitamins, mineral supplements, iron, and herbal or alternative medicine products.
100x69mm (300 x 300 DPI)

Appendix 1: Survey questionnaire

Internet questionnaire

Medication use in pregnancy with focus on attitudes, perception of risk and mental health

The Multinational Medication Use in Pregnancy Study

INFORMATION ABOUT YOURSELF

1. In which country do you live? **Country:**_____	**In which region/province do you live?** **Region:** _____
2. Are you pregnant right now? □ Yes	□ No
(If yes in Q2) In which pregnancy week are you? **From 1 to 44** **(If yes in Q2) Is it a multiple pregnancy?** □ No □ Yes (e.g. twins, triplets, etc)	**(If No in Q2) How old is your newborn child (in weeks)?** **0-4 / 5-8 / 9-12 / 13-16 / 17-20 / 21-24 / 25-28 / > 29** **(If No in Q2) Do you breast feed your child?** □ Yes □ No
3. How many children do you already have from before? □ None □ One □ Two □ More than two	
4. What is your marital status? □ Married □ Cohabitant □ Single □ Divorced/Separated □ Other	
5. What is the highest education you have completed? □ Primary school (8-9 years of education) □ High-school (11-13 years of education) □ University □ Other education	
6. What was your work situation when you became pregnant? □ Student □ Housewife □ Health care personnel, i.e., physician, nurse, or pharmacist □ Employed in another sector □ Job seeker □ None of the above	
7. Is English your mother tongue? □ Yes □ No **(If No in Q7 above) What is your mother tongue**? _____	
8. Your age: Years, from 15 to 55	

INFORMATION ABOUT YOUR PREGNANCY

9. (If pregnant) Are you attending any pregnancy/birth preparation course or similar?

□ Yes
□ No, but I am planning to attend
□ No, I am not going to attend it

10. (If pregnant) What are your thoughts about how the experience of giving birth is going to be?

Please indicate your thoughts in a scale from 1 to 6, where **1 corresponds to absolutely terrible and 6 to absolutely fantastic**

Absolutely terrible	1 □	2 □	3 □	4 □	5 □	6 □	Absolutely fantastic

11. Was your pregnancy planned?

□ Yes
□ No, but it was not completely unexpected
□ No, it was not planned

12. Did you contact any healthcare provider due to infertility?

□ Yes
□ No

(If Yes in Q12 above) Did you, in this pregnancy, become pregnant secondarily to infertility treatment?

□ Yes
□ No

13. Have you taken folic acid? (alone or as part of multivitamins)

□ Yes, before pregnancy
□ Yes, before and during pregnancy
□ Yes, only during pregnancy
□ No
□ cannot remember

14. Did you smoke cigarettes before becoming pregnant?

□ Yes, regularly
□ Yes, occasionally
□ No, never

(If yes in Q14 as regularly/occasionally) Do you/did you smoke during pregnancy?

□ Yes, more than before
□ Yes, approximately the same
□ Yes, but less
□ No

(If yes) How many cigarettes (on average) do you/did you smoke per day?

□ < 1
□ 1-5
□ 6-10
□ > 11

15. Did you drink any alcohol after finding out that you were pregnant?

□ Yes
□ No
□ Cannot remember

(If yes) How much did you drink (in units)?
1 alcohol unit is equivalent to:
one 25ml single measure of whisky (ABV 40%),
or a third of a pint of beer (ABV 5-6%)
or half a standard (175ml) glass of red wine (ABV 12%).

□ More than 1-2 units per week
□ 1-2 units per week
□ 1-4 units per month
□ 1-2 units during the pregnancy
□ Can not remember

HEALTH DISORDERS AND MEDICATIONS DURING PREGNANCY

16. Have you experienced any of the disorders listed below during this pregnancy? If you use or have used any medicines in relation to [each health disorder listed] please enter the names of the medicines. In which weeks of pregnancy have you used them?

Health disorder		Medicine	Period of use (pregnancy weeks)
Nausea	□ Yes □ No	(If Nausea ticked) If you use or have used any medicines in relation to nausea, please enter the names of the medicines	□ week 0-12 □ week 13-24 □ week 25- delivery
Heartburn or reflux problems	□ Yes □ No	(If Heartburn ticked) If you use or have used any medicines in relation to heartburn or reflux problem, please enter the names of the medicines	□ week 0-12 □ week 13-24 □ week 25- delivery
Constipation	□ Yes □ No	(If Constipation ticked) If you use or have used any medicines in relation to constipation, please enter the names of the medicines	□ week 0-12 □ week 13-24 □ week 25- delivery
Common cold	□ Yes □ No	(If common cold ticked If you use or have used any medicines in relation to common cold, please enter the names of the medicines	□ week 0-12 □ week 13-24 □ week 25- delivery
Urinary tract infections	□ Yes □ No	(If UTI ticked) If you use or have used any medicines in relation to urinary tract infections, please enter the names of the medicines	□ week 0-12 □ week 13-24 □ week 25- delivery
Other infections	□ Yes □ No	(If other infections ticked) If you use or have used any medicines in relation to other infections, please enter the names of the medicines	□ week 0-12 □ week 13-24 □ week 25- delivery
Pain in neck or back or pelvic girdle	□ Yes □ No	(If pain ticked) If you use or have used any medicines in relation to pain in neck or back or pelvic girdle, please enter the names of the medicines	□ week 0-12 □ week 13-24 □ week 25- delivery
Headache	□ Yes □ No	(If headache ticked) If you use or have used any medicines in relation to headache, please enter the names of the medicines	□ week 0-12 □ week 13-24 □ week 25- delivery
Sleeping problems	□ Yes □ No	(If sleeping problems ticked) If you use or have used any medicines in relation to sleeping problems, please enter the names of the medicines	□ week 0-12 □ week 13-24 □ week 25- delivery

17. Have you been on sick leave during this pregnancy?	
□ Yes	□ No

18. (If yes in Q17) What was the reason for it? In which pregnancy weeks have you been on sick leave?

Reason of the sick leave	**Sick leave period (pregnancy week)**
_____ _____	□ week 0-12 □ week 13-24 □ week 25-delivery

19. Below, some common over-the-counter (OTC) medicines are mentioned. Please indicate whether you have used any of them during pregnancy.

Please enter the name of all *X* medicines you have used.
In which pregnancy weeks have you used them?

		Name of the medicine(s) you have used	**Period of use (pregnancy week)**
Pain killers (*e.g. paracetamol*)	□ Yes □ No	(If painkillers ticked) Please enter the name of all pain killers you have used during pregnancy.	□ week 0-12 □ week 13-24 □ week 25- delivery
Nasal spray/drops (excluding salt water solution) (*e.g. Otrivine, Vicks Sinex decongestant Nasal spray*)	□ Yes □ No	(If nasal spray ticked) Please enter the name of all nasal sprays/drops you have used during pregnancy.	□ week 0-12 □ week 13-24 □ week 25- delivery
Medication against heartburn (*e.g. Gaviscon or Rennie*)	□ Yes □ No	(If OTC for heartburn ticked) Please enter the name of all medications you have used against heartburn during pregnancy.	□ week 0-12 □ week 13-24 □ week 25- delivery
Medication against nausea/travel sickness (*e.g. Cetirizine, Sea-Legs)*	□ Yes □ No	(If OTC for nausea ticked) Please enter the name of all medications you have used against nausea during pregnancy.	□ week 0-12 □ week 13-24 □ week 25- delivery
Medication against constipation (*e.g.Lactulose, Dulcolax)*	□ Yes □ No	(If OTC for constipation ticked) Please enter the name of all medications you have used against constipation during pregnancy.	□ week 0-12 □ week 13-24 □ week 25- delivery

20. Did you take any herbal preparations during pregnancy (e.g. ginger, echinacea, valerian, cranberries)**?**

□ Yes □ No □ Cannot remember

(If yes) Please provide the name of all herbal preparations you have taken during pregnancy**.**
(If yes) What was the reason for taking herbal preparations (health disorder, illness)?
(If yes) In which pregnancy weeks did you take herbal preparations?

Name of herbal preparation used	**Reason for use (health disorder, illness)**	**Period of use (pregnancy week**
_____ _____ _____	_____ _____ _____	□ week 0-12 □ week 13-24 □ week 25- delivery
_____ _____ _____	_____ _____ _____	□ week 0-12 □ week 13-24 □ week 25- delivery

21. (If you used herbal preparations during pregnancy) Who recommended to you to take herbal preparations during pregnancy? (You may tick more than one answer)

□ My own initiative
□ Family/friends
□ Physician
□ Midwife/Nurse
□ Pharmacy personnel
□ Herbal shop personnel
□ Internet
□ Magazines, media, etc.
□ Other (please specify:_____)

22. Did you use homeopathic products during pregnancy?

□ Yes □ No □ Cannot remember

(If yes in Q22 above) What was the reason for use?

_____

A BIT MORE ABOUT MEDICATION USE DURING PREGNANCY

23. Have you deliberately avoided taking an over-the-counter medicine during your pregnancy?

□ Yes □ No □ Cannot remember

(If yes in Q23 above) Which medicine was it?

_____

(If yes in Q23 above) What was the reason for doing so?

_____

_____

24. Have you deliberately chosen not to use a medicine prescribed by a doctor because you were pregnant?

□ Yes □ No □ Can not remember

(If yes in Q24 above) Which medicine was it?

_____

(If yes in Q24 above) What was the reason for doing so?

_____

_____

YOUR NEEDS FOR INFORMATION

25. Did you need information about medicines during the course of your pregnancy?
□ Yes □ No □ Cannot remember

26. (If yes in Q25) Whom did you turn to for information? (*You may tick more than one answer*)
□ Family/friends
□ Physician
□ Midwife/Nurse
□ Pharmacy personnel
□ Herbal shop personnel
□ Drug formulary/information leaflet
□ Poison information centre
□ Teratology information service
□ National center of information on medicines
□ Internet
□ Magazines, media, etc
□ Other (please specify:_____)

27. (if yes in Q25) If you have obtained information from various sources, was such information similar?
□ Yes, completely similar
□ Yes, as a whole (only the wording or detail level was somewhat different)
□ No, part of the information was different
□ No, the information was completely contradictory

28. (If No – last 2 options in Q27) If there were discrepancies among the sources, what did it mean to you? (*You may tick more than one answer*)
□ Nothing
□ I became anxious
□ I decided not to use the medication
□ I sought for a new information source (Which new source have you consulted? _____)
□ I chose to rely on one source and ignore the conflicting one (On which source have you relied? _____Which source have you ignored? _____)

29. How often do you have someone help you read hospital materials?
□ Always
□ Often
□ Sometimes
□ Occasionally
□ Never

30. How confident are you filling out medical forms by yourself?
□ Extremely
□ Quite a bit
□ Somewhat
□ A little bit
□ Not at all

31. How often do you have problems learning about your medical condition because of difficulty understanding written information?
□ Always
□ Often
□ Sometimes
□ Occasionally
□ Never

The following section will pop-up only if the subject has reported to be suffering from a chronic disease

I. MEDICATIONS FOR CHRONIC DISEASES DURING PREGNANCY

If you use or have used medicines for a chronic disease during your pregnancy fill out this part of the questionnaire (I, II, III) and provide some information about those medicines you use daily.

Some chronic diseases are asthma, allergy, hypothyroidism (low thyroid hormone), rheumatic diseases (incl. rheumatoid arthritis, psoriatic arthritis), diabetes (type I or II), epilepsy, depression, anxiety, cardiovascular diseases (incl. hypertension, high cholesterol, and heart diseases)

Do you suffer of any chronic disease? □ Yes □ No

(If Yes above) Please indicate whether you suffer of any of the following chronic diseases.

		If you use or have used medicines for *X* during your pregnancy, please enter the name of the medicines.	**In which weeks of pregnancy did you use them?**
Asthma	□ Yes □ No	(If Asthma ticked) If you use or have used medicines for asthma during pregnancy, please enter the names of the medicines.	□ week 0-12 □ week 13-24 □ week 25-delivery
Allergy	□ Yes □ No	(If Allergy ticked) If you use or have used medicines for allergy during pregnancy, please enter the names of the medicines.	□ week 0-12 □ week 13-24 □ week 25-delivery
Hypothyroidism (low thyroid hormone)	□ Yes □ No	(If Hypothyroidism ticked) If you use or have used medicines for hypothyroidism during pregnancy, please enter the names of the medicines.	□ week 0-12 □ week 13-24 □ week 25-delivery
Rheumatic disorders (incl. rheumatoid arthritis, psoriatic arthritis)	□ Yes □ No	(If Rheumatic disorders ticked) If you use or have used medicines for rheumatic disorder during pregnancy, please enter the names of the medicines.	□ week 0-12 □ week 13-24 □ week 25-delivery
Diabetes (type I or II)	□ Yes □ No	(If Diabetes ticked) If you use or have used medicines for diabetes during pregnancy, please enter the names of the medicines.	□ week 0-12 □ week 13-24 □ week 25-delivery
Epilepsy	□ Yes □ No	(If Epilepsy ticked) If you use or have used medicines for epilepsy during pregnancy, please enter the names of the medicines.	□ week 0-12 □ week 13-24 □ week 25-delivery
Depression	□ Yes □ No	(If Depression ticked) If you use or have used medicines for depression, please enter the names of the medicines.	□ week 0-12 □ week 13-24 □ week 25-delivery
Anxiety	□ Yes □ No	(If Anxiety ticked) If you use or have used medicines for anxiety during pregnancy, please enter the names of the medicines.	□ week 0-12 □ week 13-24 □ week 25-delivery

		If you use or have used medicines for *X* during your pregnancy, please enter the name of the medicines.	In which weeks of pregnancy did you use them?
Cardiovascular diseases (incl. hypertension, high cholesterol, heart diseases)	□ Yes □ No	(If Cardio disease ticked) If you use or have used medicines for cardiovascular diseases during pregnancy, please enter the names of the medicines.	□ week 0-12 □ week 13-24 □ week 25-delivery
Others (If Others ticked) (Please specify which other disease(s): _____)	□ Yes □ No	(If Other disease ticked) If you use or have used medicines for your chronic disease during pregnancy, please enter the names of the medicines.	□ week 0-12 □ week 13-24 □ week 25-delivery

Section II will pop-up only if the subject has reported to be suffering of a chronic disease

II. YOUR VIEWS ABOUT PRESCRIBED MEDICINES

In this section of the survey questionnaire, the **Belief About Prescribed Medicine Questionnaire (BMQ-Specific)** was presented (Horne R, Weinman J, Hankins M. The beliefs about medicines questionnaire: The development and evaluation of a new method for assessing the cognitive representation of medication. Psychol Health. 1999;14(1):1-24).

Section III will pop-up only if the subject has reported to be suffering of a chronic disease. There will be one single scale for each chronic condition reported

III. QUESTION ABOUT YOUR USE OF MEDICATIONS FOR X DURING PREGNANCY AND/OR POSTPARTUM

In this section of the survey questionnaire, the **8-item Morisky Medication Adherence Questionnaire (MMAS-8)** was presented (*Morisky DE, Green LW, Levine DM. Concurrent and predictive validity of a self-reported measure of medication adherence. Medical care. 1986;24(1):67-74*).

Do you have any other comments about your medication use during pregnancy?

_____

_____

_____

_____

_____

YOUR VIEWS ABOUT MEDICATIONS

In this section of the survey questionnaire, the **Belief About Medicine Questionnaire (BMQ-General)** was presented (*Horne R, Weinman J, Hankins M. The beliefs about medicines questionnaire: The development and evaluation of a new method for assessing the cognitive representation of medication. Psychol Health. 1999;14(1):1-24*).

32. Below are some statements about use of medicines in pregnancy. Please specify how much you agree or disagree with these statements by ticking where appropriate. (*You may only tick once per line*)					
	Strongly agree	**Agree**	**Uncertain**	**Disagree**	**Strongly disagree**
I have a higher threshold for using medicines when I am pregnant than when I'm not pregnant	○	○	○	○	○
Even though I am ill and could have taken medicines, it is better for the foetus that I refrain from using them	○	○	○	○	○
Pregnant women should preferably use herbal remedies than conventional medicines	○	○	○	○	○

YOUR ASSESSMENT OF PREGNANCY RISKS

33. Among 100 healthy women in a healthy environment, how many do you think will give birth to a child with a birth defect?

_____

34. Here below is a list with various medicines, food and other substances.
Please indicate how harmful you think they are for the foetus in a scale from 0 to 10, where 0 corresponds to 'not harmful' and 10 to 'very harmful'.

If you have not heard before about such substance, tick 'unknown substance'.

	Unknown substance	0	1	2	3	4	5	6	7	8	9	10
Paracetamol/acetaminophen	o	o	o	o	o	o	o	o	o	o	o	o
Antibiotics (*e.g. Penicillins*)	o	o	o	o	o	o	o	o	o	o	o	o
Antidepressants	o	o	o	o	o	o	o	o	o	o	o	o
Thalidomide	o	o	o	o	o	o	o	o	o	o	o	o
Swine influenza vaccine	o	o	o	o	o	o	o	o	o	o	o	o
OTC medicines against nausea/travel sickness	o	o	o	o	o	o	o	o	o	o	o	o
Ginger	o	o	o	o	o	o	o	o	o	o	o	o
Cranberries	o	o	o	o	o	o	o	o	o	o	o	o
Blue veined cheese *(e.g. Gorgonzola)*	o	o	o	o	o	o	o	o	o	o	o	o
Eggs	o	o	o	o	o	o	o	o	o	o	o	o
Alcohol during the 1. trimester (*e.g. wine, beer, spirits*)	o	o	o	o	o	o	o	o	o	o	o	o
Smoking (*e.g. cigarettes*)	o	o	o	o	o	o	o	o	o	o	o	o
Dental X-ray	o	o	o	o	o	o	o	o	o	o	o	o

HOW YOU ARE FEELING NOW

In this section of the survey questionnaire, the **Edinburgh Postnatal Depression Scale (EPDS)** was presented (*Cox J, Holden J, Sagovsky R. Detection of postnatal depression. Development of the 10-item edinburgh postnatal depression scale. The British Journal of Psychiatry. 1987 June 1, 1987;150(6):782-6*).

HOW YOU SEE YOURSELF

In this section of the survey questionnaire, the **Big Five Inventory (BFI)** was presented (*John OP, Srivastava S, editors. The big five trait taxonomy: History, measurement, and theoretical perspectives: New York: Guilford; 1999; John OP, Robins RW, Pervin LA. Handbook of personality: Theory and research: The Guilford Press; 2008*).

Appendix 2: Websites used for recruitment and internet penetration rates in each country where data were collected

Country	*Website used for recruitment*	*Internet penetration rates (%)*
EUROPE		
	Western Europe	
Austria	www.schwangerschaft.at; www.schwangerschafts-blog.at; www.fratz.at; www.netdoctor.at; www.babycenter.at; www.baby-boom.at; www.ekiz-dachverband.at; www.babyguide.at	93* [1]
France	www.aufeminin.com (*Including ipad application to website subscribers*)	91* [1]
Italy	*Pregnancy Forums*: www.gravidanzaonline.it; www.forumsalute.it; www.mammole.it; www.pianetamamma.it; www.miobambino.it *Targeted email to pregnancy forum subscribers*: www.gravidanzaonline.it	70* [1]
Switzerland	www.bebe-bebe.com; www.swissmom.ch	84* [2]
The Netherlands	www.lareb.nl; www.gezondzwangerzijn.nl; www.babybytes.nl	98* [1]
United Kingdom	*Targeted email to pregnancy forum subscribers*: www.bounty.com *Pregnancy Forums*: www.pregnancyforum.co.uk; www.pregnancyforum.org.uk	93* [1]
	Northern Europe	
Finland	www.vauva.fi; www.meidanperhe.fi; www.kaksplus.fi	99* [1]
Iceland	*Pregnancy Forums*: www.bland.is	100* [1]
Norway	www.barnimagen.com; www.klikk.no; www.jormorsiri.no; www.tryggmamamedisin.no	99* [1]
Sweden	www.barntotal.se; www.minbebis.com; www.se.babycenter.com; www.socmed.gu.se	99* [1]
	Eastern Europe	
Croatia	www.cybermed.hr	80* [1] (data from 2010)
Poland	www.zzief.umlub.pl *Pregnancy Forums*: www.ebrzuszek.pl; www.babyboom.pl; www.zapytajpolozna.pl; www.planujemydziecko.pl; www.twoja-ciaza.com.pl	84* [1]
Russia	www.babyblog.ru; www.littleone.ru	48* [2]

Country	*Website used for recruitment*	*Internet penetration rates (%)*
	Pregnancy Forums: www.woman.ru; www.9months.ru; www.bemam; www.280dney.ru; www.iampregnant.ru www.pregnancy.org.ua; www.baby.ru; www.mama66.ru; www.spuzom.ru	
Serbia	www.ringeraja.rs	52* [1] (data from 2009)
Slovenia	*Pregnancy Forums*: www.med.over.net	92* [1]
AMERICAS		
	North America	
Canada	www.otispregnancy.org; Facebook page of OTIS; www.babyontheway.com.ca *Pregnancy Forums*: www.babycentre.com.ca; www.thecradle.com; www.talk.sheknows.com; www.parenting.com	94† [3]
USA	www.otispregnancy.org; Facebook page of OTIS; www.justmommies.com *Pregnancy Forums*: www.babyandbump.com www.thecradle.com; www.talk.sheknows.com; www.parenting.com	80§ [4]
	Central America	
Belize	www.otispregnancy.org; Facebook page of OTIS	23[2]
Costa Rica		43[2]
El Salvador		25[2]
Guatemala		16[2]
Honduras		16[2]
Nicaragua		14[2]
Panama		43[2]
	South America	
Argentina	www.otispregnancy.org; Facebook page of OTIS	67[2]
Bolivia		30[2]
Brazil	*Pregnancy Forums*: www.semanaasemana.com; www.univision.com; www.elembarazo.net	46[2]
Chile		59[2]
Colombia		59[2]
Ecuador		44[2]
Paraguay		24[2]
Peru		37[2]
Uruguay		56[2]
Venezuela		41[2]

Country	*Website used for recruitment*	*Internet penetration rates (%)*
	AUSTRALIA	
Australia	www.mothersafe.org.au; www.bubhub.com.au *Pregnancy Forums*: www.abds.org.au; www.birth.com.au	83[ζ] [5]

[*]Indicates the frequency of internet access - at least once a week, including every day - among individuals aged 25- 34 years. Differences between men and women were relatively small. Slightly more than two thirds of men (70%) and 65% of women used the Internet regularly.
[†]Indicates individuals aged 16-45 years who used the internet for personal use.
[§]Indicates individuals > 18 years old, access from anywhere; household internet for women is equal to 68.1%; higher percentages are observed for people aged 25-54 years.
[ζ]Indicates households with access to the internet at home.

Sources of internet penetration rates:

1. Seybert H. Internet use in households and by individuals in 2011. Eurostat Statistics in focus; 2011.
2. Internet World Stats. Usage and population statistics. Available at: http://www.internetworldstats.com/. Accessed 29 December, 2013.
3. Statistics Canada. Individual Internet use and E-commerce (2010). Available at: http://www.statcan.gc.ca/daily-quotidien/111012/dq111012a-eng.htm. Accessed 20 November, 2012.
4. United States Census Bureau. The 2012 Statistical Abstract. Information & Communications: Internet Publishing and Broadcasting and Internet Usage. Available at: http://www.census.gov/compendia/statab/cats/information_communications/internet_publishing_and_broadcasting_and_internet_usage.html. Accessed 13 November, 2012.
5. Australian Bureau of Statistics. Household Use of Information Technology, Australia, 2010-11 Available at: http://www.abs.gov.au/ausstats/abs@.nsf/Latestproducts/8146.0Main%20Features12010-11?opendocument&tabname=Summary&prodno=8146.0&issue=2010-11&num=&view=. Accessed 13 November, 2012.

Appendix 3: Socio-demographic characteristics of the study population and general birthing population on individual country

Appendix 3a: Socio-demographic characteristics in Western European countries (Switzerland, Italy and United Kingdom (UK))

	Study sample in Switzerland n=618	General birthing population in Switzerland LB=80,808[1]	Study sample in Italy n=926	General birthing population in Italy LB=546,606[1]	Study sample in the UK n=1,120	General birthing population in UK* LB=723,165[2]
	(%)	(%)	(%)	(%)	(%)	(%)
No. of respondents/No. live births¶	4.6%		1.0%		0.9%	
Mean Age +/- sd	31.6 +/- 4.3	31.4[3]	32.3 +/- 5.0	31.3[4]	30.5 +/- 5.2	29.6[2]
Marital status						
In marriage	80.0	80.7[3]	68.8	75.1[1]	63.3	53.2[2]
Outside marriage	20.0	19.3[3]	31.2	31.5[1]	36.7	46.8[2]
Parity						
No previous children	53.2	-	59.7	48.7[5]	48.0†	41.9[2] †
Educational level						
Less than high school	11.0	11.7[6]	7.0	25.2[6]	0.6	16.5[2]
High school	13.6	49.2[6]	47.2	49.2[6]	27.9	37.2[2]
More than high school	47.2	39.1[6]	44.3	25.6[6]	52.1	46.3[2]
Other	28.2	-	1.5	-	19.3	-
Women smoking before pregnancy	25.1	25.4[7]	34.2	33.3[4]	25.2	25.7[7]
Women smoking during pregnancy	5.5	6.6[8]	10.5	22.7[9]	7.1‡	13.2[10] ‡
Use of alcohol during pregnancy	20.7	29.9[8]	17.9	17.7[9]	28.3	24.0[11] §

Abbreviations: LB: Number of live births per year.

*The figures shown here are statistic estimates for England and Wales. Scotland and Northern Ireland have separate statistical reports. Since more than 85% of the study population in UK were resident in England and about 8% in Wales, we are only showing national statistic data for these two parts of the UK.

¶The ratio "No. of respondents/No. live births" is calculated as the proportion (%) of pregnancies included in the study among live births in the country in two months (period of data collection).

†Among married women only – as provided by the Statistics Bureau in the UK.

‡Among women resident in England only (as provided by the Statistics Bureau in the UK, data on 4th Quarter of 2011).

§Women reporting at least one occasion during pregnancy of consuming more than four drinks in a day.

Appendix 3b: Socio-demographic characteristics in Western European countries (Austria, France and The Netherlands)

	Study sample in Austria n=82 (%)	General birthing population in Austria LB=78,109[1] (%)	Study sample in France n=374 (%)	General birthing population in France LB=824,263[1] (%)	Study sample in The Netherlands n=81 (%)	General birthing population in The Netherlands LB=180,060[1] (%)
No. of respondents/No. live births*	0.6%		0.3%		0.3%	
Mean Age +/- sd	30.6 +/- 4.6	30.0[12]	29.6 +/- 4.9	30.1[13]	32.0 +/- 6.4	31.0[14]
Marital status						
In marriage	48.8	59.6[15]	48.9	45.0[1]	69.1	58.2[14]
Outside marriage	51.2	40.4[15]	51.1	55.0[1]	30.8	41.8[14]
Parity						
No previous children	63.4	47.96[15]	52.9	44.2[16]	38.3	46.4[14]
Educational level						
Less than high school	9.8	13.3[6]	1.6	15.4[6]	9.9	15.9[6]
High-school	32.9	64.1[6]	25.1	37.4[6]	66.7	40.2[6]
More than high school	40.2	22.7[6]	57.0	47.2[6]	23.5	43.9[6]
Other	17.1	-	16.3	-	-	-
Women smoking before pregnancy	31.7	32.1[17]	39.3	39.0[16]	34.6	29.5[7]
Women smoking during pregnancy	4.9	-	14.2	28.0[16]	14.8	17.1[18]
Use of alcohol during pregnancy	13.4	-	11.5	52.0[19]	11.1	16-35[14]

Abbreviations: LB: Number of live births per year.

*The ratio "No. of respondents/No. live births" is calculated as the proportion (%) of pregnancies included in the study among live births in the country in two months (period of data collection).

Appendix 3c: Socio-demographic characteristics in Northern European countries (Norway, Finland and Sweden)

	Study sample in Norway n=1,228	General birthing population in Norway LB=60,220[1]	Study sample in Finland n=574	General birthing population in Finland LB=59,961[1]	Study sample in Sweden n=887	General birthing population in Sweden LB=111,770[1]
	(%)	**(%)**	**(%)**	**(%)**	**(%)**	**(%)**
No. of respondents/No. live births*	12.2%		5.7%		4.8%	
Mean Age +/- sd	29.0 +/- 4.6	29.8 +/- 5.3[20]	29.0+/-5.1	30.1[21]	29.8 +/- 5.3	30.3[22]
Marital status						
In marriage	39.1	46.0[20]	59.4	57.8[21]	40.7	45.8[1]
Outside marriage	60.9	53.4[20]	40.6	42.0[21]	59.3	54.2[1]
Unknown	-	0.6[20]	-	0.2[21]		
Parity						
No previous children	41.4	42.4[20]	35.5	42.2[21]	63.1	44.9[22]
Educational level						
Less than high school	4.5	14.7[6]	8.2	7.1[6]	5.2	11.1[6]
High-school	28.0	31.4[6]	36.4	44.5[6]	30.0	38.2[6]
More than high school	46.9	53.9[6]	52.6	48.4[6]	60.6	50.6[6]
Other	20.7	-	2.8	-	4.2	-
Women smoking before pregnancy	33.5	36.5[7]	36.7	19.7[7]	25.0	27.2[7]
Women smoking during pregnancy	6.8	7.0[20]	11.7	15.2[21]	5.4	6.5[22]
Use of alcohol during pregnancy	4.1	7.4[23]	13.9	-	7.2	5.9[24]

Abbreviations: LB: Number of live births per year.

*The ratio "No. of respondents/No. live births" is calculated as the proportion (%) of pregnancies included in the study among live births in the country in two months (period of data collection).

Appendix 3d: Socio-demographic characteristics in Northern European countries (Iceland)

	Study sample in Iceland n=71	General birthing population in Iceland LB=4,492[1]
	(%)	**(%)**
No. of respondents/No. live births*	9.3%	
Age range (in years)		
15-20	11.3	5.1[25]
21-25	16.9	19.3[25]
26-30	42.3	34.2[25]
31-35	15.5	27.3[25]
36-40	12.7	11.7[25]
≥41	1.4	2.4[25]
Marital status		
In marriage	31.0	35.0[25]
Outside marriage	69.0	65.0[25]
Parity		
No previous children	47.9	38.1[25]
Educational level		
Less than high school	25.4	21.4[6]
High-school	18.3	30.5[6]
More than high school	43.7	48.1[6]
Other	12.7	-
Women smoking before pregnancy	40.8	35.5[7]

Abbreviations: LB: Number of live births per year.

*The ratio "No. of respondents/No. live births" is calculated as the proportion (%) of pregnancies included in the study among live births in the country in two months (period of data collection).

Appendix 3e: Socio-demographic characteristics in Eastern European countries (Croatia, Slovenia and Serbia)

	Study sample in Croatia n=286	General birthing population in Croatia LB=41,197[1]	Study sample in Slovenia n=149	General birthing population in Slovenia LB=21,947[1]	Study sample in Serbia n=220	General birthing population in Serbia LB=65,598[1]
	n (%)	**(%)**	**n (%)**	**(%)**	**n (%)**	**(%)**
No. of respondents/No. live births*	4.2%		4.1%		2.0%	
Mean Age +/- sd	29.1 +/- 4.5†	27.7[26]	31.7 +/- 4.5	30.4[27]	29.2 +/- 3.9*	28.7[1,28]
Marital status						
In marriage	83.9	86.7[26]	47.0	43.2[27]	90.1	76.1[28]
Outside marriage	16.1	13.3[26]	53.0	56.8[27]	9.9	23.9[28]
Parity						
No previous children	50.7	46.9[26]	45.6	48.5[27]	46.8	51.1[28,29]
Educational level						
Less than high school	1.0	3.1[26]	2.0	8.5[27]	0.9	15.9[29]
High-school	36.7	52.5[26]	24.8	48.5[27]	33.6	54.9[29]
More than high school	61.2	44.4[26]	69.1	43.0[27]	61.8	29.2[29]
Other	1.0	-	4.0	-	3.6	-
Women smoking before pregnancy	50.0	34.4[26]	32.9	34.4[7]	49.1	29.9[30,31]
Women smoking during pregnancy	18.8	23.1[32]	6.7	9.6-11.2[33]	18.2	18.4[31]
Use of alcohol during pregnancy	12.6	15.5[34]	32.2	-	15.0	-

Abbreviations: LB: Number of live births per year.

* The ratio "No. of respondents/No. live births" is calculated as the proportion (%) of pregnancies included in the study among live births in the country in two months (period of data collection).

†Mean age for first child (as it is available from the Statistics Bureau reports in Croatia and Serbia).

Appendix 3f: Socio-demographic characteristics in Eastern European countries (Poland and Russia)

	Study sample in Poland n=679	General birthing population in Poland LB=388,416[1]	Study sample in Russia n=1,008	General birthing population in Russia LB=1,796,629[1]
	(%)	**(%)**	**(%)**	**(%)**
No. of respondents/No. live births*	1.0%		0.3%	
Mean Age +/- sd	27.1 +/- 4.1	28.6[35] †	27.7 +/- 4.8	27.4[36]
Marital status				
In marriage	85.0	79.4[35]	85.3	73.9[36]
Outside marriage	15.0	20.6[35]	14.7	26.1[36]
Parity				
No previous children	40.6	50.1[35]	57.9	-
Educational level				
Less than high school	1.9	8.7[35]	1.6	-
High-school	31.1	49.6[35]	9.3	-
More than high school	65.1	41.6[35]	75.1	-
Other	1.9	-	14.0	-
Women smoking before pregnancy	49.2	25.0[37]	46.1	30.8[38]
Women smoking during pregnancy	12.8	22-30[37]	9.6	4.3-6.5[39,40]
Use of alcohol during pregnancy	9.6	15.3[41]	26.0	60.0[42]

Abbreviations: LB: Number of live births per year.

* The ratio "No. of respondents/No. live births" is calculated as the proportion (%) of pregnancies included in the study among live births in the country in two months (period of data collection).

†Median age of women at birth, not mean age.

Appendix 3g: Socio-demographic characteristics in North American countries (Canada and USA)

	Study sample in Canada n=236 n (%)	General birthing population in Canada[43] LB=377,636 (%)	Study sample in The USA n=297 n (%)	General birthing population in USA[44] LB=3,999,386 (%)
No. of respondents/No. live births*	0.4%		0.04%	
Age range (in years)				
15-19	2.1	3.9[43]	4.7	9.3[44]
20-24	25.0	14.6[43]	18.2	23.8[44]
25-29	30.1	30.2[43]	28.3	28.3[44]
30-34	30.5	32.2[43]	29.3	24.1[44]
35-39	11.0	15.6[43]	15.2	11.6[44]
40-44	1.3	3.1[43]	4.0	2.7[44]
≥45	-	0.2[43]	0.3	0.2[44]
Mean Age +/- sd	28.3 +/- 5.2	29.6[43]	29.3 +/- 6.1	-
Marital status				
In marriage	42.4	60.4[43]	67.0	59.2[45]
Outside marriage	57.6	28.8[43]	33.0	39.9[45]
Unknown	-	10.8[43]	-	0.9[45]
Parity				
No previous children	48.3	43.3[43]	41.1	40.1[44]
Educational level				
Less than high school	1.3	8.4[46]	2.7	17.4[47]
High-school	24.6	-	25.3	24.4[47]
More than high school	67.8	69.6[46]	62.0	58.2[47]
Other	6.4	-	10.1	-

	Study sample in Canada n=236 n (%)	General birthing population in Canada[43] LB=377,636 (%)	Study sample in The USA n=297 n (%)	General birthing population in USA[44] LB=3,999,386 (%)
Women smoking before pregnancy	29.2	22.0[48]	28.3	21.5[49]
Women smoking during pregnancy	16.1	13.4[46]	8.1	10.2[50]
Use of alcohol during pregnancy	16.1	10.5[46]	17.5	15.5[49]

Abbreviations: LB: Number of live births per year.

*The ratio "No. of respondents/No. live births" is calculated as the proportion (%) of pregnancies included in the study among live births in the country in two months (period of data collection).

Appendix 3h: Socio-demographic characteristics in Australia

	Study sample in Australia n=217	General birthing population in Australia[51] LB=301,617
	n (%)	**(%)**
No. of respondents/No. live births*	0.4%	
Mean Age +/- sd	31.1 +/- 5.7	30.7[51]
Marital status		
In marriage	70.5	65.8[51]
Outside marriage	29.5	34.2[51]
Parity		
No previous children	47.9	43.8[51]
Educational level		
Less than high school	0.5	20.6† [52]
High-school	29.0	
More than high school	63.1	56.0[53]
Other	7.4	-
Women smoking before pregnancy	29.1	29.9[54]
Women smoking during pregnancy	14.3	14.5[55]
Use of alcohol during pregnancy	27.2	29.0[56]

Abbreviations: LB: Number of live births per year.

*The ratio "No. of respondents/No. live births" is calculated as the proportion (%) of pregnancies included in the study among live births in the country in two months (period of data collection).

†Refers to the educational levels "high school" and "less than high school" grouped together.

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Appendix 4: Sample size calculation (using 5% precision with 95% confidence interval) for the population survey on region and individual country levels.

	Study sample	Population size*	Expected prevalence				
			Any medication use=80%	*Any medication use=70%*	*OTC medication use=60%*	*Chronic medication use=30%*	*Chronic medication use=15%*
			Required sample size				
Western Europe	3,201	Not known	246	323	369	323	196
United Kingdom	1,120	120,528	245	322	368	322	196
Italy	926	91,101	245	322	367	322	195
Switzerland	618	13,468	241	315	359	315	193
France	374	137,377	245	322	368	322	196
Austria†	82	13,018	241	315	359	315	193
The Netherlands†	81	30,010	244	319	364	319	195
Northern Europe	2,820	Not known	246	323	369	323	196
Norway	1,228	10,037	240	313	356	313	192
Sweden	887	18,628	243	317	362	317	194
Finland	574	9,994	240	313	356	313	192
Iceland†	71	749	185	225	247	225	155
Eastern Europe	2,342	Not known	246	323	369	323	196
Russia	1,008	299,438	246	322	368	322	196
Poland	679	64,736	245	321	367	321	195
Croatia§	286	6,866	237	308	350	308	190
Serbia¶	220	10,933	240	313	357	313	192
Slovenia**	149	3,658	230	297	335	297	186
North America	533	Not known	246	323	369	323	196
USA§	297	666,564	246	323	369	323	196
Canada††	236	62,939	245	321	367	321	195
South America¶¶	346	Not known	246	323	369	323	196
Australia§§	217	50,270	245	321	366	321	195

Sample size calculations were performed in Epi Info ™ 7 available at: Center for DiseaseControl and Prevention (CDC), Epi Info. URL: http://wwwn.cdc.gov/epiinfo/. Accessed 2013 Dec 31.

*The population size indicates the number of live births in the country in two months (corresponds to the period of data collection) (cf. Appendix 3 for annual estimates of live births in each country). For the all regions except Australia, the population size is very large but not known exactly (i.e. infinite population). Infinite population size is therefore assumed in the calculation of the required sample size.

†The sample size allows for prevalence estimates with a precision of 9% (expected prevalence=80%), 10% (expected prevalence=70% and 30%), 11% (expected prevalence=60%) and 8% (expected prevalence=15%).

§The sample size allows for prevalence estimates with a precision of 6% (expected prevalence=70%, 60% and 30%).

¶The sample size allows for prevalence estimates with a precision of 6% (expected prevalence=80%) and 7% (expected prevalence=70%, 60% and 30%).

**The sample size allows for prevalence estimates with a precision of 7% (expected prevalence=80%), 8% (expected prevalence=70%, 60% and 30%) and 6% (expected prevalence=15%).

††The sample size allows for prevalence estimates with a precision of 6% (expected prevalence=80%, 70% and 30%) and 7% (expected prevalence=60%).

¶¶The sample size allows for prevalence estimates with a precision of 6% (expected prevalence=60%).

§§The sample size allows for prevalence estimates with a precision of 6% (expected prevalence=80%) and 7% (expected prevalence=70%, 60% and 30%).

Appendix 5: Overall medication use on 1st and 2nd ATC level according to timing of use in pregnancy (n=9,459)*

	Anatomical Therapeutic Chemical (ATC) classification index 1st and 2nd levels	Anytime during pregnancy n (%)	1st trimester n (%)	2nd trimester n (%)	3rd trimester n (%)
A	**Alimentary tract and metabolism**	**4,275 (45.2)**	**2,786 (29.5)**	**3,390 (35.8)**	**3,160 (33.4)**
A01	Stomatological preparations	62 (0.7)	42 (0.4)	52 (0.5)	46 (0.5)
A02	*Drugs for acid related disorders*	3,242 (34.3)	2,034 (21.5)	2,634 (27.8)	2,615 (27.6)
A03	Drugs for functional gastrointestinal disorders	650 (6.9)	543 (5.7)	512 (5.4)	381 (4.0)
A04	Antiemetics and antinauseants	136 (1.4)	124 (1.3)	114 (1.2)	81 (0.9)
A05	Bile and liver therapy	24 (0.3)	15 (0.2)	17 (0.2)	16 (0.2)
A06	*Laxatives*	978 (10.3)	696 (7.4)	835 (8.8)	735 (7.8)
A07	Antidiarrheals, intestinal antiinflammatory/antiinfective agents	89 (0.9)	61 (0.6)	69 (0.7)	57 (0.6)
A09	Digestives, incl. enzymes	9 (0.1)	7 (0.1)	8 (0.1)	3 (0.0)
A10	Drugs used in diabetes	85 (0.9)	57 (0.6)	58 (0.6)	45 (0.5)
-	Unspecified medications for nausea	6 (0.1)	5 (0.1)	4 (0.0)	3 (0.0)
B	**Blood and blood forming organs**	**148 (1.6)**	**89 (0.9)**	**102 (1.1)**	**79 (0.8)**
B01	*Antithrombotic agents*	135 (1.4)	78 (0.8)	95 (1.0)	72 (0.8)
B02	Antihemorrhagics	5 (0.1)	4 (0.0)	2 (0.0)	3 (0.0)
B05	Blood substitutes and perfusion solutions	7 (0.1)	5 (0.1)	5 (0.1)	2 (0.0)
B06	Other hematological agents	3 (0.0)	2 (0.0)	2 (0.0)	3 (0.0)
C	**Cardiovascular system**	**202 (2.1)**	**132 (1.4)**	**161 (1.7)**	**133 (1.4)**
C01	Cardiac therapy	7 (0.1)	4 (0.0)	5 (0.1)	4 (0.1)
C02	*Antihypertensives*	56 (0.6)	34 (0.4)	42 (0.4)	31 (0.3)
C03	Diuretics	6 (0.1)	5 (0.1)	3 (0.0)	2 (0.0)
C04	Peripheral vasodilators	3 (0.0)	3 (0.0)	3 (0.0)	3 (0.0)
C05	Vasoprotectives	44 (0.5)	24 (0.3)	35 (0.4)	31 (0.3)
C07	*Beta blocking agents*	74 (0.8)	51 (0.5)	59 (0.6)	51 (0.5)
C08	Calcium channel blockers	21 (0.2)	16 (0.2)	18 (0.2)	13 (0.1)
C09	Agents acting on the renin-angiotensin system	4 (0.0)	2 (0.0)	2 (0.0)	2 (0.0)

Anatomical Therapeutic Chemical (ATC) classification index 1st and 2nd levels		Anytime during pregnancy n (%)	1st trimester n (%)	2nd trimester n (%)	3rd trimester n (%)
C10	Lipid modifying agents	5 (0.1)	3 (0.0)	4 (0.0)	4 (0.0)
-	Unspecified medications for hypertension	4 (0.0)	3 (0.0)	3 (0.0)	2 (0.0)
D	**Dermatologicals**	**162 (1.7)**	**116 (1.2)**	**127 (1.3)**	**103 (1.1)**
D01	*Antifungals for dermatological use*	38 (0.4)	28 (0.3)	33 (0.3)	27 (0.3)
D02	Emollients and protectives	14 (0.1)	11 (0.1)	12 (0.1)	10 (0.1)
D03	Preparations for treatment of wounds and ulcers	4 (0.0)	3 (0.0)	3 (0.0)	3 (0.0)
D04	Antipruritics, incl. antihistamines, anaesthetics, etc.	6 (0.1)	3 (0.0)	5 (0.1)	4 (0.0)
D05	Antipsoriatics	3 (0.0)	1 (0.0)	1 (0.0)	1 (0.0)
D06	Antibiotics and chemotherapeutics for dermatological use	21 (0.2)	15 (0.2)	16 (0.2)	13 (0.1)
D07	*Corticosteroids, dermatological preparations*	56 (0.6)	40 (0.4)	39 (0.4)	31 (0.3)
D08	Antiseptics and disinfectants	14 (0.1)	9 (0.1)	10 (0.1)	9 (0.1)
D09	Medicated dressings	5 (0.1)	5 (0.1)	5 (0.1)	3 (0.0)
D10	Anti-acne preparations	4 (0.0)	4 (0.0)	4 (0.0)	2 (0.0)
D11	Other dermatological preparations	1 (0.0)	-	1 (0.0)	1 (0.0)
-	Unspecified medications for skin disorders	5 (0.1)	4 (0.0)	4 (0.0)	3 (0.0)
G	**Genitourinary system and sex hormones**	**488 (5.2)**	**318 (3.4)**	**394 (4.2)**	**303 (3.2)**
G01	*Gynaecological antiinfective and antiseptics*	406 (4.3)	255 (2.7)	337 (3.6)	258 (2.7)
G02	Other gynecologicals	13 (0.1)	10 (0.1)	10 (0.1)	8 (0.1)
G03	Sex hormones and modulators of the genital system	68 (0.7)	55 (0.6)	50 (0.5)	36 (0.4)
G04	Urologicals	12 (0.1)	8 (0.1)	7 (0.1)	8 (0.1)
H	**Systemic hormonal preparations, excl. sex hormones and insulins**	**486 (5.1)**	**304 (3.2)**	**346 (3.7)**	**262 (2.8)**
H01	Pituitary and hypothalamic hormones and analogues	4 (0.0)	4 (0.0)	3 (0.0)	4 (0.0)
H02	Corticosteroids for systemic use	93 (1.0)	64 (0.7)	78 (0.8)	63 (0.7)
H03	*Thyroid therapy*	397 (4.2)	242 (2.6)	273 (2.9)	201 (2.1)
J	**Anti-infective for systemic use**	**1,381 (14.6)**	**874 (9.2)**	**1,107 (11.7)**	**943 (10.0)**
J01	*Antibacterials for systemic use*	1,325 (14.0)	840 (8.9)	1,061 (11.2)	908 (9.6)
J02	Antimycotics for systemic use	23 (0.2)	16 (0.2)	21 (0.2)	17 (0.2)

Anatomical Therapeutic Chemical (ATC) classification index 1st and 2nd levels		Anytime during pregnancy n (%)	1st trimester n (%)	2nd trimester n (%)	3rd trimester n (%)
J05	Antivirals for systemic use	39 (0.4)	27 (0.3)	30 (0.3)	26 (0.3)
J06	Immune sera and immunoglobulins	4 (0.0)	2 (0.0)	3 (0.0)	4 (0.0)
J07	Vaccines	10 (0.1)	5 (0.1)	8 (0.1)	5 (0.1)
L	**Antineoplastic and immunomodulating agents**	**134 (1.4)**	**83 (0.9)**	**117 (1.2)**	**97 (1.0)**
L01	Antineoplastic agents	4 (0.0)	3 (0.0)	4 (0.0)	1 (0.0)
L03	*Immunostimulants*	96 (1.0)	58 (0.6)	86 (0.9)	78 (0.8)
L04	Immunosuppressants	34 (0.4)	22 (0.2)	27 (0.3)	18 (0.2)
M	**Musculo-skeletal system**	**571 (6.0)**	**416 (4.4)**	**437 (4.6)**	**380 (4.0)**
M01	*Antiinflammatory and antirheumatic products*	515 (5.4)	378 (4.0)	396 (4.2)	342 (3.6)
M02	Topical products for joint and muscular pain	54 (0.6)	37 (0.4)	41 (0.4)	41 (0.4)
M03	Muscle relaxants	8 (0.1)	8 (0.1)	4 (0.0)	1 (0.0)
M05	Drugs for treatment of bone diseases	1 (0.0)	-	1 (0.0)	-
M09	Other drugs for disorders of the musculo-skeletal system	2 (0.0)	2 (0.0)	2 (0.0)	2 (0.0)
-	Unspecified medications for headache	2 (0.0)	1 (0.0)	1 (0.0)	1 (0.0)
N	**Nervous system**	**5,441 (57.5)**	**3,638 (38.5)**	**4,247 (44.9)**	**3,449 (36.5)**
N01	Anaesthetics	13 (0.1)	10 (0.1)	7 (0.1)	8 (0.1)
N02	*Analgesics*	5,297 (56.0)	3,562 (37.7)	4,171 (44.1)	3,387 (35.8)
N03	Antiepileptics	76 (0.8)	46 (0.5)	49 (0.5)	42 (0.4)
N05	*Psycholeptics*	210 (2.2)	173 (1.8)	164 (1.7)	138 (1.5)
N06	*Psychoanaleptics*	275 (2.9)	211 (2.2)	213 (2.3)	179 (1.9)
N07	Other nervous system drugs	6 (0.1)	4 (0.0)	5 (0.1)	3 (0.0)
-	Unspecified analgesics/medications for the nervous system	52 (0.5)	38 (0.4)	43 (0.5)	35 (0.4)
P	**Antiparasitic products, insecticides and repellents**	**26 (0.3)**	**20 (0.2)**	**22 (0.2)**	**16 (0.2)**
P01	*Antiprotozoals*	25 (0.3)	20 (0.2)	22 (0.2)	16 (0.2)
P02	Anthelmintics	1 (0.0)	-	-	-
R	**Respiratory system**	**2,609 (27.6)**	**1,878 (19.9)**	**2,047 (21.6)**	**1,702 (18.0)**
R01	*Nasal preparations*	1,547 (16.4)	1,079 (11.4)	1,229 (13.0)	1,046 (11.1)

Anatomical Therapeutic Chemical (ATC) classification index 1st and 2nd levels		Anytime during pregnancy n (%)	1st trimester n (%)	2nd trimester n (%)	3rd trimester n (%)
R02	Throat preparations	167 (1.8)	110 (1.2)	131 (1.4)	122 (1.3)
R03	*Drugs for obstructive airway diseases*	396 (4.2)	269 (2.8)	304 (3.2)	242 (2.6)
R05	Cough and cold preparations	152 (1.6)	103 (1.1)	125 (1.3)	101 (1.1)
R06	*Antihistamines for systemic use*	912 (9.6)	777 (8.2)	740 (7.8)	580 (6.1)
R07	Other respiratory system products	3 (0.0)	2 (0.0)	3 (0.0)	3 (0.0)
-	Unspecified medications of the respiratory system	142 (1.5)	101 (1.1)	118 (1.2)	99 (1.0)
S	**Sensory organs**	**45 (0.5)**	**33 (0.3)**	**38 (0.4)**	**28 (0.3)**
S01	*Ophthalmologicals*	33 (0.3)	24 (0.3)	28 (0.3)	23 (0.2)
S02	Otologicals	5 (0.1)	3 (0.0)	4 (0.0)	2 (0.0)
S03	Ophthalmological and otological preparations	3 (0.0)	2 (0.0)	2 (0.0)	2 (0.0)
-	Unspecified medications for eye disorders	5 (0.1)	4 (0.0)	5 (0.1)	2 (0.0)
V	**Various**	15 (0.2)	10 (0.1)	11 (0.1)	9 (0.1)
Total medication use (any ATC)		**7,678 (81.2)**	**4,710 (49.8)**	**5,538 (58.5)**	**4,663 (49.3)**

*The most common medication groups within each ATC class are in italics. Exposure timing is defined as follows: 1st trimester (gestational weeks 0-12), 2nd trimester (gestational week 13-24), 3rd trimester (gestational week 25 and up to childbirth).

Appendix 6: Prevalence of acute/short-term illnesses and most common medications used at any time during pregnancy by ATC level, indication for use and region (n=9,459) [*†]

	REGION						
Prevalence of acute/short-term illnesses in pregnancy and related medication use, overall and by drug groups	**Western Europe n=3,201** *n (%)*	**Northern Europe n=2,820** *n (%)*	**Eastern Europe n=2,342** *n (%)*	**North America n=533** *n (%)*	**South America n=346** *n (%)*	**Australia n=217** *n (%)*	**Total n=9,459** *n (%)*
Prevalence of headache	1,699 (53.1)	1,657 (58.8)	1,138 (48.6)	373 (70.0)	197 (56.9)	147 (67.7)	5,211 (55.1)
Medication use for headache, total	**1,027 (32.1)**	**1,057 (37.5)**	**522 (22.3)**	**226 (42.4)**	**121 (35.0)**	**109 (50.2)**	**3,062 (32.4)**
By drug group							
Paracetamol (incl. combinations) (N02BE)	994 (31.1)	1,009 (35.8)	372 (15.9)	206 (38.6)	92 (26.6)	101 (46.5)	2,774 (29.3)
Non-steroidal antiinflammatory drugs (M01A)	28 (0.9)	78 (2.8)	37 (1.6)	18 (3.0)	18 (5.2)	2 (0.9)	179 (1.9)
Acetylsalicylic acid (incl. combinations) (N02BA)	7 (0.2)	4 (0.1)	81 (3.5)	1 (0.2)	4 (1.2)	2 (0.9)	99 (1.0)
Opioid analgesics (N02A)	14 (0.4)	46 (1.6)	3 (0.1)	3 (0.6)	-	13 (6.0)	79 (0.8)
Selective serotonin (5-HT_1) agonists (N02CC)	6 (0.2)	22 (0.8)	2 (0.1)	3 (0.6)	-	1 (0.5)	34 (0.4)
Prevalence of heartburn	2,196 (68.6)	1,875 (66.5)	1,425 (60.8)	374 (70.2)	248 (71.7)	141 (65.0)	6,259 (66.2)
Medication use for heartburn, total	**984 (30.7)**	**885 (31.4)**	**525 (22.4)**	**202 (37.9)**	**88 (25.4)**	**72 (33.2)**	**2,756 (29.1)**
By drug group							
Antacids (aluminium, salts combinations, antiflatulents)	384 (12.0)	503 (17.8)	440 (18.8)	51 (9.6)	63 (18.2)	20 (9.2)	1,461 (15.4)
Alginic acid complex/sucralfate/bismuth (A02BX)	569 (17.8)	332 (11.8)	86 (3.7)	4 (0.8)	3 (0.9)	14 (6.5)	1,008 (10.7)
Proton pump inhibitors (A02BC)	77 (2.4)	86 (3.0)	4 (0.2)	13 (2.4)	3 (0.9)	7 (3.2)	190 (2.0)
Antacid with calcium (A02AC)	20 (0.6)	13 (0.5)	10 (0.4)	123 (23.1)	2 (0.6)	9 (4.1)	177 (1.9)
H_2 receptor antagonists (A02BA)	27 (0.8)	27 (1.0)	7 (0.3)	45 (8.4)	5 (1.4)	38 (17.5)	149 (1.6)
Prevalence of pain	2,150 (67.2)	2,067 (73.3)	1,484 (63.4)	369 (69.2)	248 (71.7)	157 (72.4)	6,475 (68.5)
Medication use for pain, total	**533 (16.7)**	**426 (15.1)**	**147 (6.3)**	**110 (20.6)**	**80 (23.1)**	**59 (27.2)**	**1,355 (14.3)**
By drug group							
Paracetamol (incl. combinations) (N02BE)	444 (13.9)	374 (13.3)	65 (2.8)	99 (18.6)	44 (12.7)	55 (25.3)	1,081 (11.4)

Prevalence of acute/short-term illnesses in pregnancy and related medication use, overall and by drug groups	REGION						
	Western Europe n=3,201 *n (%)*	Northern Europe n=2,820 *n (%)*	Eastern Europe n=2,342 *n (%)*	North America n=533 *n (%)*	South America n=346 *n (%)*	Australia n=217 *n (%)*	Total n=9,459 *n (%)*
Non-steroidal antiinflammatory drugs (M01A)	19 (0.6)	36 (1.3)	21 (0.9)	11 (2.1)	24 (6.9)	3 (1.4)	114 (1.2)
Opioid analgesics (N02A)	39 (1.2)	51 (1.8)	2 (0.1)	4 (0.8)	-	12 (5.5)	108 (1.1)
Prevalence of nausea	2,324 (72.6)	2,244 (79.6)	1,503 (64.2)	409 (76.7)	238 (68.8)	173 (79.7)	6,891 (72.9)
Medication use for nausea, total	**413 (12.9)**	**380 (13.5)**	**140 (6.0)**	**128 (24.0)**	**71 (20.5)**	**39 (18.0)**	**1,171 (12.4)**
By drug group							
First generation antihistamines (R06A)	150 (4.7)	259 (9.2)	21 (0.9)	84 (15.9)	9 (2.6)	4 (1.8)	527 (5.6)
Metoclopramide/domperidone/bromopride (A03FA)	134 (4.2)	69 (2.4)	27 (1.2)	10 (1.9)	45 (13.0)	25 (11.5)	310 (3.3)
Serotonin antagonists (A04AA)	4 (0.1)	8 (0.3)	1 (0.0)	28 (5.3)	1 (0.3)	11 (5.1)	53 (0.6)
Prevalence of UTI	513 (16.0)	327 (11.6)	452 (19.3)	93 (17.4)	92 (26.6)	25 (11.5)	1,502 (15.9)
Medication use for UTI, total	**315 (9.8)**	**221 (7.8)**	**192 (8.2)**	**56 (10.5)**	**63 (18.2)**	**17 (7.8)**	**864 (9.1)**
By drug group							
Unspecified penicillins (J01C-)	94 (2.9)	99 (3.5)	46 (2.0)	16 (3.0)	17 (4.9)	1 (0.5)	273 (2.9)
NOS Antibacterials for systemic use (J01-)	116 (3.6)	85 (3.0)	25 (1.1)	20 (3.8)	14 (4.0)	6 (2.8)	266 (2.8)
Penicillins with extended spectrum +/- beta-lactamase inhibitors (J01CA/J01CR)	85 (2.7)	78 (2.8)	44 (1.9)	14 (2.6)	17 (4.9)	1 (0.5)	239 (2.5)
Nitrofurantoin (J01XE)	7 (0.2)	25 (0.9)	54 (2.3)	10 (1.9)	3 (0.9)	1 (0.5)	100 (1.1)
Cephalosporins (J01D)	20 (0.6)	10 (0.4)	36 (1.5)	2 (0.4)	11 (3.2)	6 (2.8)	85 (0.9)
Total prevalence of any acute/short-term illness	**3,159 (98.7)**	**2,803 (99.4)**	**2,299 (98.2)**	**523 (98.1)**	**341 (98.6)**	**214 (98.6)**	**9,339 (98.7)**
Total medication use for any acute/short-term illness	**2,224 (69.5)**	**1,954 (69.3)**	**1,474 (62.9)**	**403 (75.6)**	**250 (72.3)**	**164 (75.6)**	**6,469 (68.4)**

*Countries are grouped into regions as shown in Figure 1.

†Sums of percentages do not add up to total medication use as only most common medication groups are presented. Rates do not include mineral supplements, vitamins, iron, and herbal or alternative medicine products.

Abbreviations: UTI: Urinary tract infection; NOS: Not otherwise specified.

Appendix 7: Prevalence of chronic/long-term disorders and most common medications used at any time during pregnancy by ATC level, indication for use and region (n=9,459) [*†]

	REGION						
Prevalence of chronic/long-term disorders in pregnancy and related medication use, overall and by drug groups	**Western Europe n=3,201** *n (%)*	**Northern Europe n=2,820** *n (%)*	**Eastern Europe n=2,342** *n (%)*	**North America n=533** *n (%)*	**South America n=346** *n (%)*	**Australia n=217** *n (%)*	**Total n=9,459** *n (%)*
Prevalence of hypothyroidism	130 (4.1)	118 (4.2)	105 (4.5)	22 (4.1)	11 (3.2)	6 (2.8)	392 (4.1)
Medication use for hypothyroidism, total	**118 (3.7)**	**113 (4.0)**	**96 (4.1)**	**21 (3.9)**	**9 (2.6)**	**6 (2.8)**	**363 (3.8)**
By drug group							
Thyroid hormone, levothyroxine (H03AA01)	117 (3.7)	112 (4.0)	89 (3.8)	21 (3.9)	9 (2.6)	6 (2.8)	354 (3.7)
Prevalence of asthma	163 (5.1)	193 (6.8)	58 (2.5)	43 (8.1)	12 (3.5)	24 (11.1)	493 (5.2)
Medication use for asthma, total	**122 (3.8)**	**133 (4.7)**	**38 (1.6)**	**35 (6.6)**	**8 (2.3)**	**24 (11.1)**	**360 (3.8)**
By drug group							
Inhalant selective beta-2 agonists (R03AC)	94 (2.9)	66 (2.3)	26 (1.1)	32 (6.0)	7 (2.0)	24 (11.1)	249 (2.6)
Adrenergics and other drugs for COPD (R03AK)	33 (1.0)	46 (1.6)	10 (0.4)	3 (0.6)	2 (0.6)	7 (3.2)	101 (1.1)
Inhalant glucocorticoids (R03BA)	28 (0.9)	40 (1.4)	13 (0.6)	12 (2.3)	-	4 (1.8)	97 (1.0)
Systemic selective beta-2 agonists (R03CC)	-	30 (1.1)	-	2 (0.4)	-	-	32 (0.3)
Prevalence of allergy	205 (6.4)	372 (13.2)	163 (7.0)	51 (9.6)	20 (5.8)	23 (10.6)	834 (8.8)
Medication use for allergy, total	**66 (2.1)**	**171 (6.1)**	**65 (2.8)**	**24 (4.5)**	**13 (3.8)**	**17 (7.8)**	**356 (3.8)**
By drug group							
Second generation antihistamines (R06A)	29 (0.9)	104 (3.7)	27 (1.2)	17 (3.2)	4 (1.2)	5 (2.3)	186 (2.0)
Nasal corticosteroids (R01AD)	11 (0.3)	32 (1.1)	17 (0.7)	-	-	7 (3.2)	67 (0.7)
First generation antihistamines (R06A)	13 (0.4)	29 (1.0)	10 (0.4)	9 (1.7)	6 (1.7)	4 (1.8)	71 (0.8)
Prevalence of depression	95 (3.0)	144 (5.1)	29 (1.2)	52 (9.8)	4 (1.2)	25 (11.5)	349 (3.7)
Medication use for depression, total	**61 (1.9)**	**100 (3.5)**	**11 (0.5)**	**29 (5.4)**	**1 (0.3)**	**23 (10.6)**	**225 (2.4)**
By drug group							
SSRI antidepressants (N06AB)	44 (1.4)	82 (2.9)	6 (0.3)	14 (2.6)	-	14 (6.5)	160 (1.7)
SNRIs/mianserin/trazodone/mirtazapine/bupropion	9 (0.3)	11 (0.4)	1 (0.0)	15 (2.8)	-	7 (3.2)	43 (0.5)

Prevalence of chronic/long-term disorders in pregnancy and related medication use, overall and by drug groups	REGION						
	Western Europe n=3,201 *n (%)*	Northern Europe n=2,820 *n (%)*	Eastern Europe n=2,342 *n (%)*	North America n=533 *n (%)*	South America n=346 *n (%)*	Australia n=217 *n (%)*	Total n=9,459 *n (%)*
Anxiolytics, benzodiazepine (N05BA)	6 (0.2)	2 (0.1)	5 (0.2)	-	-	1 (0.5)	14 (0.1)
Antipsychotics quetiapine/olanzapine (N05AH)	2 (0.1)	4 (0.1)	-	3 (0.6)	-	3 (1.4)	12 (0.1)
Total prevalence of any chronic/long-term disorder	**617 (19.3)**	**831 (29.5)**	**576 (24.6)**	**154 (28.9)**	**51 (14.7)**	**72 (33.2)**	**2,301 (24.3)**
Total medication use for any chronic/long-term disorder	**462 (14.4)**	**593 (21.0)**	**322 (13.7)**	**119 (22.3)**	**38 (11.0)**	**70 (32.3)**	**1,604 (17.0)**

*Countries are grouped into regions as shown in Figure 1.

†Sums of percentages do not add up to total medication use as only most common medication groups are presented. Rates do not include mineral supplements, vitamins, iron, and herbal or alternative medicine products.

Abbreviations: COPD: Chronic obstructive pulmonary disease; SSRI: Selective serotonin re-uptake inhibitors; SNRI: Serotonin–noradrenaline reuptake inhibitors.

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation
Title and abstract	1	✗ (*a*) Indicate the study's design with a commonly used term in the title or the abstract
		✗ (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	✗ Explain the scientific background and rationale for the investigation being reported
Objectives	3	✗ State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	✗ Present key elements of study design early in the paper
Setting	5	✗ Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	✗ (*a*) Give the eligibility criteria, and the sources and methods of selection of participants
Variables	7	✗ Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	✗ For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	✗ Describe any efforts to address potential sources of bias
Study size	10	✗ Explain how the study size was arrived at
Quantitative variables	11	✗ Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	✗ (*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		✗ (*c*) Explain how missing data were addressed
		(*d*) If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	✗ (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	✗ (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
Outcome data	15*	✗ Report numbers of outcome events or summary measures
Main results	16	✗ (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		✗ (*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a

		meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	✗ Summarise key results with reference to study objectives
Limitations	19	✗ Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	✗ Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	✗ Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	✗ Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.