

# Medical care contact for infertility and related medication use during pregnancy – a European, cross-sectional web-based study

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## ABSTRACT

**Aims:** The aim of the study was two-fold: i) to determine the prevalence of medical care contact for infertility in European countries; ii) to map overall and long-term/chronic medication use during pregnancy in women who sought medical care due to infertility.

**Methods:** This is a sub-study of the Multinational Medication Use in Pregnancy Study, a cross-sectional, web-based study conducted from October 2011 to February 2012. We included 8097 participants from Europe who were pregnant or new mothers. We collected data on overall and long-term/chronic medication use, medical care seeking due to infertility, and whether women eventually conceived spontaneously or with the aid of infertility treatment.

**Results:** Medical care contact for infertility was lower in Western Europe (prevalence estimate: 10.0-15.3%), compared with Northern (15.2-17.5%) or Eastern (17.4-20.9%), but Poland had the lowest estimate (8.0%). Overall, 660 (8.2%) women sought medical care due to infertility but conceived spontaneously; 548 (6.8%) conceived aided by fertility treatment, and 6889 (85.0%) women did not seek help. Use of any medication was comparable across the three groups (range 80.4-82.5%), but women seeking help for infertility (21.8-24.6%) took more often long-term/chronic medications than women who did not (14.8%).

**Conclusion:** Medical care contacts for infertility varies greatly across European countries. Women who had medical contact due to infertility used more often chronic medications in pregnancy than women who did not, pointing to more co-morbidities and risk pregnancies.

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## INTRODUCTION

Infertility represents a worldwide public health concern. Equal and equitable access to fertility care remains a challenge in most countries, particularly in those with low-middle income (1). Pooled data from worldwide surveys show a 12-month prevalence of infertility between 3.5-16.7% in more developed countries, and 6.9-9.3% in less developed countries (2). These data additionally indicate that 56.1% and 51.2% of couples in more or less developed countries, respectively, sought medical care because of problems with conceiving, but the proportion of couples actually receiving care was substantially smaller, 22.4% (2). Nevertheless, comparisons across countries are difficult due to different methods of data collection in the individual studies.

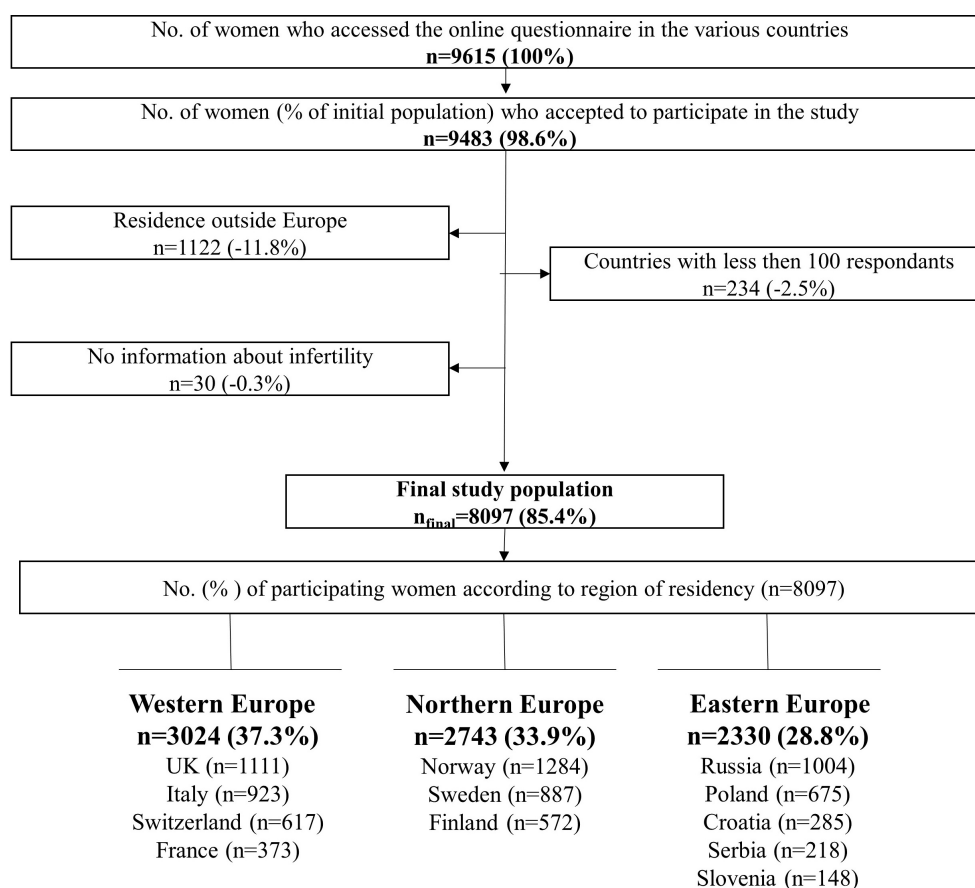
Women who undergo fertility treatment or seek medical help due to infertility are often older and have more chronic diseases than average pregnant women, and may therefore be more likely to need pharmacotherapy in pregnancy. One study showed that 12.7% of women undergoing fertility treatment filled at least one prescription for potential hazardous medications within 45 days after the beginning of a fertility cycle, compared

to 6.8% of women who conceived spontaneously (3). In addition, these two groups had comparable intake of periconception folic acid, that is about 30%, which is surprisingly low (3).

Women with fertility problems may have planned a pregnancy for years ahead. It is therefore possible that these women will be more careful in relation to smoking, drinking alcohol, or even in taking needed medications due to heightened fear for teratogenic effects on the unborn child. Yet, avoiding medications in pregnancy may sometimes jeopardize maternal-fetal health, for instance in women with diabetes, epilepsy, severe mental illnesses, or infections (4).

To date, no study has systematically characterized to what extent women seeking medical care due to infertility use medications, and in particular if differences do exist between women eventually conceiving spontaneously and those conceiving aided by fertility treatment. Filling this knowledge gaps is essential for prevention and preconception counselling, as eight out of ten women use at least one medication during the course of the pregnancy (5).

The aim of this study was two-fold: 1) to quantify the prevalence of medical care contact due to infertility in



**Figure 1.** Flow chart to achieve the final study population.

European countries; 2) to determine the overall extent and type of medications taken during pregnancy, as well as for treatment of chronic/long-term disorders, according to medical care seeking due to infertility in multiple European countries.

## MATERIALS AND METHODS

### *Study population and data collection*

This is a sub-study of the ‘Multinational Medication Use in Pregnancy Study, a multinational, cross-sectional, web-based investigation to examine patterns and correlates of medication use in pregnancy (5). Data were collected via a self-administered, anonymous, electronic questionnaire (www.questback.com) in 18 countries. Women located in Europe, North and South America and Australia who were pregnant or who had given birth less than a year ago were eligible to participate. The study was advertised on 2-3 pregnancy-related websites in each country, pregnancy forums and social media, and was open to the public for two months between October 2011 and February 2012 in each participating country. The recruitment national websites were selected for having the greatest number of daily users. The full questionnaire and further details about recruitment and the tools have been previously published (5).

Few responses were obtained from countries outside Europe, i.e. USA, Canada, Australia and South America, relative to the yearly birthing population in

the countries. Hence, this specific study was limited to women residing in Europe at the time of study participation. To ensure that the study results are more representative of the target population in Europe, we further limited the study population to those countries with at least 100 respondents. An additional exclusion criterion was missing answer on the questions related to medical care contact due to infertility. Data selection to achieve the final study sample was performed as depicted in Figure 1.

### *Medical care contact due to infertility*

Participants were asked whether they had contacted any healthcare provider due to infertility. Those who replied “yes” were additionally asked if they conceived with the aid of fertility treatment. Information from these two questions was used to define three mutually exclusive study groups: i) women who sought medical contact due to infertility and conceived aided by fertility treatment; ii) women who sought medical contact due to infertility but conceived spontaneously; iii) women who did not seek medical care due to infertility.

### *Medication use during pregnancy*

Participants were confronted with a list of the most common chronic/long-term disorders (i.e. allergy, anxiety, asthma, cardiovascular disease, depression, diabetes, epilepsy, hypothyroidism, rheumatic disorders, 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. 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)). In addition, women were asked standardized questions about medication use for specific short-term illnesses (e.g., nausea, heartburn, constipation) and over-the-counter (OTC) drugs, as described earlier (5).

We defined a medicine as a single product containing one or more active ingredients. All recorded medications were coded into the corresponding Anatomical Therapeutic Chemical (ATC) codes at the ATC 5<sup>th</sup> level (i.e. the substance level) whenever possible, otherwise into the 2<sup>nd</sup>-4<sup>th</sup> levels as appropriate, in accordance with the World Health Organization ATC index (6). Iron, mineral supplements, vitamins, herbal remedies and any type of alternative medicine were recorded separately and excluded from the estimation of medication use. Use of any medication, and medication for chronic/long-term disorders during pregnancy constituted the outcome variables.

### **Maternal characteristics**

The study collected information on multiple socio-demographics characteristics, including age, educational level, immigrant status, working status at time of conception, previous children, and marital status. Life-style factors included smoking status during pregnancy and alcohol consumption after awareness of pregnancy. Pregnancy characteristics included gestational week or weeks since childbirth at time of questionnaire response. In addition, women reported their country of residence at the time of study participation. For the latter variable, participating countries were grouped into the regions (1) Western Europe (including France, Italy, Switzerland, and the UK); (2) Northern Europe (including Finland, Norway and Sweden), (3) Eastern Europe (including Croatia, Poland, Russia, Serbia and Slovenia). In prior work, we have assessed the external validity of the study, by comparing 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 (5).

### **Data analysis and statistics**

All statistical analyses were performed using Statistical Software for Data Science (Stata SE) version 16.0. Descriptive statistics were conducted to quantify the prevalence of medical care contact due to infertility in the countries involved in the study, as well as the proportions of medication use, overall and by chronic/long-term disorders. The chi-square test was used to compare the distribution of maternal sociodemographics and medication use between two independent groups at a time, that is: i) women who sought medical contact due to infertility and conceived aided by fertility treatment

vs. women who did not seek medical care due to infertility; ii) women who sought medical contact due to infertility but conceived spontaneously vs. women who did not seek medical care due to infertility. A  $p$ -value  $< 0.05$  was considered statistically significant.

### **Ethics**

Informed consent was given by the participants by ticking the answer “yes” to the question “Are you willing to participate in the study?” The Regional Ethics Committee in Norway, region South-East, granted an ethical approval exemption for this study because of anonymity. Ethical approval or study notification to the relevant national Ethics Boards was achieved in the UK and Italy as required by the national legislation. All data were anonymous.

## **RESULTS**

### **Population characteristics**

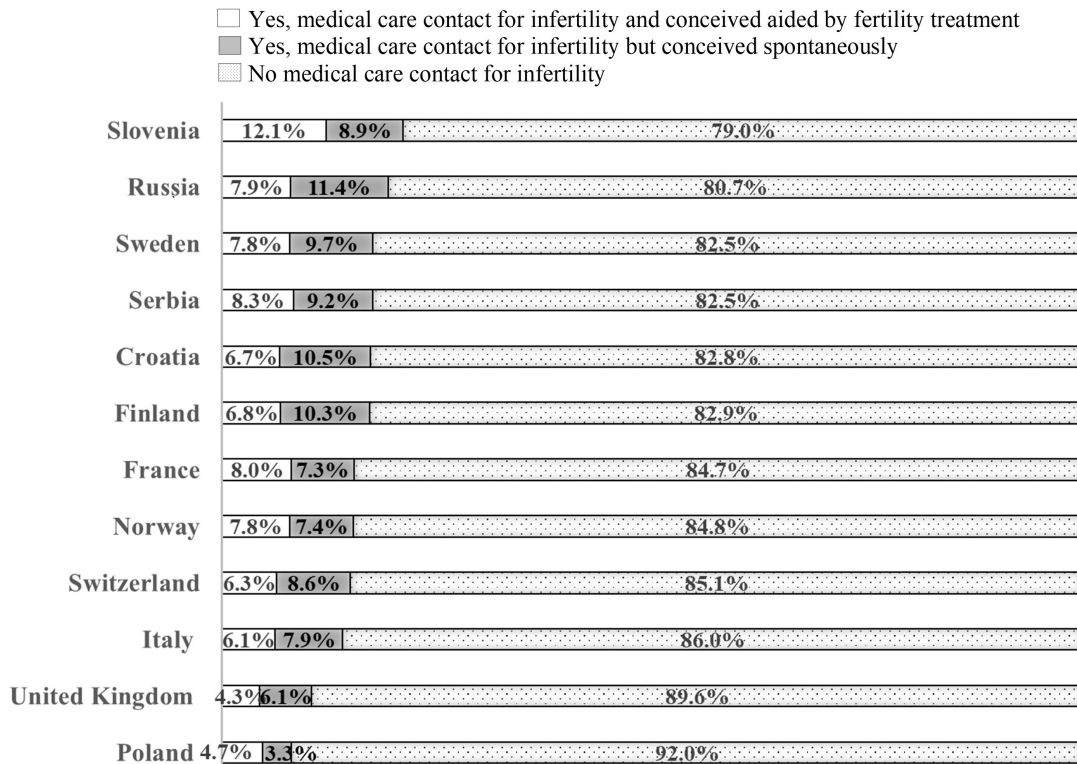
A total of 9615 women accessed the online questionnaire and reported their willingness to participate or not in the study; of these, 98.6% completed the electronic questionnaire. Figure 1 shows the data flow to achieve the final study population ( $n=8097$ ).

Figure 2 shows the prevalence of medical care contact due to infertility, according to whether women eventually conceived spontaneously or conceived aided by fertility treatment. Overall, medical care contact for infertility, irrespective of conception means, ranged from 8.0% in Poland to 21.0% in Slovenia. The estimate was slightly lower in Western European countries (10.4-15.3%), compared with the Nordic (15.2-17.5%) or Eastern European countries except Poland (17.2-21.0%). The largest proportion of women who conceived with the aid of fertility treatment ranged between 6.1% and 8.3% in most countries, but was lowest in Poland and the UK (4.1-4.3%) and highest in Slovenia (12.1%).

Table 1 shows the sociodemographic and life-style characteristics of the study population by medical care contact due to infertility. Women that sought medical help due to infertility had more often taken perinatal folate than those who did not. Women that conceived with the aid of fertility treatment were more often older, employed, married/cohabiting, and smoked or consumed alcohol during pregnancy to a lower extent than women who conceived spontaneously or did not seek care.

### **Medication use during pregnancy**

Use of any medication during pregnancy was similar between women who sought or did not seek medical care due to infertility (Table 2). There were some differences in use of specific medications across the groups; regardless of whether women conceived with the aid of fertility treatment or spontaneously, those seeking medical care for infertility were significantly more often taking antithrombotic agents, antidiabetics, laxa-



**Figure 2.** Prevalence of women seeking medical care due to infertility in European countries.

tives, thyroid hormones and systemic corticosteroids than those who did not have contact. Women who sought medical care but conceived spontaneously has a significantly greater use of sex hormones and drugs for obstructive airways diseases than women who did not seek medical care.

Table 3 shows the prevalence estimates of medication use for treatment of the most common chronic/long-term disorders. Overall, use of medication for treatment of chronic/long-term disorders was significantly higher in women who sought medical care and conceived with the aid of fertility treatment (24.6%) or spontaneously (21.8%) relative to women who did not seek care (14.8%). Thyroid hormone therapy was more than twice as high in women who sought medical help due to infertility compared to women who did not ( $p$ -value  $\leq 0.001$ ). Use of inhaled corticosteroid was significantly greater in women who sought medical care but conceived spontaneously (1.8%) compared to 0.9% in other two groups. The same pattern was observed for nasal corticosteroids. Use of medication to treat depression was comparable across the three groups.

## DISCUSSION

This is the first multinational study that explored medication use during pregnancy in women who had medical care contact due to infertility, and eventually had conceived either spontaneously or after fertility treatment. Because data were collected uniformly across countries, our estimates of medical care contact due to infertility are more comparable across countries in Europe, which

is important from a public health perspective, but also in relation to access to care. Indeed, the negative implication of later parenthood on fertility, coupled to the growing range and availability of fertility treatments, is likely to influence help seeking and access to care due to infertility in Europe (7).

Our findings show that the prevalence of medical care contact due to infertility was generally lower in Western European countries (about 10-15%) compared to both Northern (about 15-17%) and Eastern European countries (about 17-21%), with the latter ranking highest. Poland, however, was the only Eastern European country with low rate of medical contact rate due to infertility (8.0%), which ranked lowest in the entire study. This finding is in line with prior research (8), and multiple factors can explain it, e.g., lack of public financing for diagnostics and treatment of infertility in Poland, or political and religion driven measures which limit women's and couples' access to fertility treatment (9).

The high incidence of sexually transmitted infections and pregnancy terminations in most Eastern European countries have been considered as contributing factors to the higher infertility prevalence in these countries, as also observed in this study (10). It is well known that sexually transmitted infections such as Chlamydia trachomatis and Neisseria gonorrhoea can lead to infertility problems (11). Nevertheless, our estimates of medical care seeking due to infertility for the remaining countries were somewhat lower than what observed in prior research in Europe (8). This study by Olsen *et al.* (8) was conducted in 1991-1993, and so these prior

**Table 1.** Maternal sociodemographic and life-style characteristics by medical care contact due to infertility.

	Medical care contact due to infertility							
	No, n=6889		Yes, but spontaneous pregnancy, n=660		p value <sup>a</sup>	Yes, pregnancy aided by FT, n=548		p value <sup>b</sup>
	n	%	n	%		n	%	
<b>Pregnancy characteristics</b>								
<i>Pregnancy trimester</i>								
1 <sup>st</sup> trimester	941	25.8	96	25.8	0.385	77	24.8	0.904
2 <sup>nd</sup> trimester	1467	40.3	162	43.5		126	40.5	
3 <sup>rd</sup> trimester	1232	33.8	114	30.6		108	34.7	
<i>Weeks since childbirth</i>								
0-12	681	20.9	61	21.2	0.429	50	21.0	0.320
13-24	830	25.5	57	19.8		48	20.2	
≥ 25	1783	54.9	170	59.0		139	58.6	
<i>Previous children (yes); no (%)</i>	3471	50.4	326	49.4	0.627	173	31.6	≤0.001
<i>Perinatal use of folate (yes); <sup>c</sup> no (%)</i>	6234	90.5	618	93.6	0.010	535	97.7	≤0.001
<b>Sociodemographic characteristics</b>								
<i>Residence<sup>d</sup></i>								
Western Europe	2630	38.2	221	33.5	0.057	173	31.6	0.007
Northern Europe	2295	33.3	240	36.4		208	37.9	
Eastern Europe	1964	28.5	199	30.2		167	30.4	
<i>Maternal age</i>								
≤20 years	231	3.35	<5		≤0.001	<5		≤0.001
21-30 years	3937	57.1	309	46.8		210	38.3	
≥31 years	2721	39.5	347	52.6		337	61.5	
<i>Marital status</i>								
Married/cohabiting	6521	94.6	631	95.5	0.297	534	97.4	0.004
Other than above	368	5.3	29	4.4		14	2.5	
<i>Working status at conception; no (%)</i>								
Employed	4118	59.9	412	62.4	0.087	372	67.8	≤0.001
Student	639	9.3	39	5.9		22	4.0	
HCP	904	13.1	94	14.2		87	15.8	
Homemaker	563	8.2	50	7.6		22	4.0	
Job seeker/others	306	4.4	33	5.0		23	4.2	
<i>Educational attainment; no (%)</i>								
< High school	300	4.3	21	3.2	0.012	12	2.2	≤0.001
High school	1988	28.9	170	25.8		117	21.3	
> High school	3781	54.8	405	61.4		354	64.6	
<i>Immigrant status (yes); <sup>e</sup> no (%)</i>	377	5.5	48	7.3	0.053	26	4.7	0.469
<b>Life-style characteristics</b>								
Alcohol use during pregnancy (yes); <sup>f</sup> no (%)	1146	16.6	94	14.3	0.214	52	9.5	≤0.001
Smoking during pregnancy (yes); no (%)	654	9.5	59	8.9	0.668	35	6.4	0.017

Numbers may not add up due to missing values.

Abbreviations: FT=Fertility treatment; HCP= Health Care professional.

<sup>a</sup> p value for the comparison between group *fertility contact, but spontaneous pregnancy* versus *no fertility contact*

<sup>b</sup> p value for the comparison between group *fertility contact with pregnancy aided by fertility treatment* versus *no fertility contact*

<sup>c</sup> Indicates use of folate before and/or during pregnancy

<sup>d</sup> Western Europe included UK, Italy, Switzerland, France; Northern Europe included Norway, Sweden, Finland; Eastern Europe included Russia, Poland, Croatia, Serbia, Slovenia

<sup>e</sup> Women having the first language different from the official main language in the country of residence

<sup>f</sup> Indicates alcohol consumption after awareness of the pregnancy.

results may not be directly comparable to ours due to the long time difference in recruitment. In Olsen *et al.* (8), women were asked to report about medical contact due to infertility for themselves and their male partners, while our study did not enquire about the partner having problems, and this could additionally explain our lower estimates (8). This could explain the discrepancies between the studies, as fertility problems are in about a third of the cases attributable to males (12). Further-

more, we cannot exclude the risk that bias due to social desirability could have affected our results, given the sensitive nature of the question on fertility issues. Even though highly educated are more likely to seek medical help due to infertility compared to those who have lower education levels (13,14), this factor is unlikely to explain our lower estimates of medical care contact due to infertility in Western and Northern Europe, as our sample included more often women with higher educa-

**Table 2.** Overall medication use on 2<sup>nd</sup> ATC level according to medical care contact due to infertility.

Medication use by ATC, 2 <sup>nd</sup> level	Medical care contact due to infertility							
	No n=6889		Yes, but conceived spontaneously n=660			Yes, and conceived aided by FT n=548		
	n	%	n	%	p value <sup>a</sup>	n	%	p value <sup>b</sup>
<b>A Alimentary tract and metabolism</b>								
A01 Stomatological preparations	51	0.7	5	0.8	0.961	5	0.9	0.654
A02 Drugs for acid related disorders	2341	34.0	226	34.2	0.893	175	31.9	0.330
A03 Drugs for functional gastrointestinal disorders	447	6.5	39	5.9	0.562	48	8.8	0.040
A04 Antiemetics and antinauseants	70	1.0	9	1.4	0.402	6	1.1	0.860
A05 Bile and liver therapy	14	0.2	6	0.9	0.001	<5		0.432
A06 Laxatives	851	9.9	86	13.0	0.011	82	15.0	<0.001
A07 Antidiarrheals, intestinal antiinflammatory/antiinfective agents	67	1.0	6	0.9	0.874	4	0.7	0.547
A10 Drugs used in diabetes	32	0.5	9	1.4	0.003	20	3.6	<0.001
<b>B Blood and blood forming organs</b>								
B01 Antithrombotic agents	86	1.1	16	2.4	0.012	15	2.7	0.004
<b>C Cardiovascular system</b>								
C02 Antihypertensives	31	0.4	<5		0.573	5	0.9	0.383
C07 Beta blocking agents	54	0.8	7	1.2	0.448	<5		0.890
<b>D Dermatologicals</b>								
D01 Antifungals for dermatological use	25	0.4	<5		0.335	<5		0.185
D07 Corticosteroids, dermatological preparations	40	0.6	6	0.9	0.300	<5		0.661
<b>G Genitourinary system and sex hormones</b>								
G01 Gynaecological antiinfective and antiseptics	292	4.2	32	4.8	0.460	28	5.1	0.334
G03 Sex hormones and modulators of the genital system	45	0.6	11	1.7	0.004	7	1.3	0.091
<b>H Systematic hormonal preparations, excl. sex hormones and insulins</b>								
H02 Corticosteroids for systemic use	51	0.7	13	2.0	0.001	10	1.8	0.007
H03 Thyroid therapy	237	3.4	49	7.4	<0.001	51	9.3	<0.001
<b>J Anti-infective for systematic use</b>								
J01 Antibacterials for systemic use	947	13.7	99	15.0	0.373	66	12.0	0.263
<b>L Antineoplastic and immunomodulating agents</b>								
L03 Immunostimulants	77	1.1	11	1.7	0.209	8	1.5	0.468
<b>M Musculo-skeletal system</b>								
M01 Antiinflammatory and antirheumatic products	330	4.8	31	4.7	0.915	22	4.0	0.411
<b>N Nervous system</b>								
N02 Analgesics	3794	55.1	365	55.3	0.910	290	55.9	0.329
N05 Psycholeptics	136	2.0	16	2.4	0.432	9	1.6	0.589
N06 Psychoanaleptics	158	2.3	19	2.9	0.342	13	2.4	0.906
<b>R Respiratory system</b>								
R01 Nasal preparations	1193	17.3	130	19.7	0.125	108	19.7	0.244
R02 Throat preparations	135	2.0	16	2.4	0.415	11	2.0	0.938
R03 Drugs for obstructive airway diseases	248	3.6	37	5.6	0.010	14	4.4	0.349
R05 Cough and cold preparations	108	1.6	8	1.2	0.478	5	0.9	0.227
R06 Antihistamines for systemic use	588	8.5	66	10.0	0.201	51	9.3	0.535
<b>Total medication use (any ATC)</b>	<b>5541</b>	<b>80.4</b>	<b>537</b>	<b>81.4</b>	<b>0.564</b>	<b>452</b>	<b>82.5</b>	<b>0.243</b>

Abbreviation: ATC= Anatomical Therapeutic Chemical codes.

The most common medication groups within each ATC class are in italics. Medication groups used by less than three women in any of the groups, are not presented. Estimates do not include mineral supplements, vitamins, iron, and herbal or alternative medicine products.

<sup>a</sup> p-value for the comparison between group *fertility contact, but spontaneous pregnancy* versus *no fertility contact*

<sup>b</sup> p-value for the comparison between group *fertility contact with pregnancy aided by fertility treatment* versus *no fertility contact*

tion than the general birthing population.

We found a comparable prevalence of any medication use in pregnancy across groups, which was common (about 80%) regardless of medical care contact due to infertility and conception measures. This finding is in line with other studies examining prevalence of

medication use in pregnant women in USA and Europe (15-21), and suggests that having medical contact due to infertility does not relate to greater or lower medication use in pregnancy. At the same time, we observed that use of long-term/chronic medication was higher in women who sought help due to infertility (21.8-24.6%),

**Table 3.** Prevalence of medication use for chronic/long-term disorders in pregnancy, overall and by drug groups, according to medical care contact due to infertility.

	Medical care contact due to infertility							
	No n=6889		Yes, but conceived spontaneously n=660			Yes, and conceived aided by FT n=548		
	n	%	n	%	p value <sup>a</sup>	n	%	p value <sup>b</sup>
<b>Medication use for hypothyroidism, total</b>	<b>218</b>	<b>3.2</b>	<b>46</b>	<b>6.9</b>	<b>≤0.001</b>	<b>47</b>	<b>8.6</b>	<b>≤0.001</b>
Levothyroxine (H03AA01)	209	3.0	41	6.2	≤0.001	45	8.2	≤0.001
<b>Medication use for asthma, total</b>	<b>236</b>	<b>3.4</b>	<b>28</b>	<b>4.2</b>	<b>0.275</b>	<b>20</b>	<b>3.6</b>	<b>0.782</b>
Inhalant selective beta-2 agonists (R03AC)	150	2.2	20	3.0	0.158	10	1.8	0.584
Adrenergic and other drugs for COPD (R03AK)	72	1.0	7	1.1	0.970	7	1.3	0.610
Inhalant glucocorticoids (R03BA)	60	0.9	12	1.8	0.017	5	0.9	0.920
Systemic selective beta-2 agonists (R03CC)	23	0.3	5	0.8	0.087	<5		0.548
<b>Medication use for allergy, total</b>	<b>223</b>	<b>3.2</b>	<b>38</b>	<b>5.8</b>	<b>0.001</b>	<b>27</b>	<b>4.9</b>	<b>0.035</b>
Nasal corticosteroids (R01AD)	39	0.6	13	2.0	≤0.001	5	0.9	0.309
Antihistamines (R06AE)	80	1.2	11	1.7	0.256	8	1.5	0.534
Antihistamines (R06AX)	49	0.7	7	1.1	0.318	8	1.5	0.053
Ophthalmologic antiallergics (S01GX)	16	0.2	<5		0.814	<5		0.722
<b>Medication use for depression, total</b>	<b>126</b>	<b>1.8</b>	<b>15</b>	<b>2.3</b>	<b>0.421</b>	<b>13</b>	<b>2.4</b>	<b>0.366</b>
SSRI antidepressants (N06AB)	97	1.4	12	1.8	0.399	8	1.5	0.921
SNRIs/mianserin/trazodone/mirtazapine/bupropion	15	0.2	<5		0.659	<5		0.487
Anxiolytics, benzodiazepine (N05BA)	9	0.1	<5		-	<5		0.019
<b>Total medication use for any chronic/long-term disorder</b>	<b>1025</b>	<b>14.8</b>	<b>144</b>	<b>21.8</b>	<b>≤0.001</b>	<b>135</b>	<b>24.6</b>	<b>≤0.001</b>

<sup>a</sup> p-value for the comparison between group *fertility contact, but spontaneous pregnancy* versus *no fertility contact*

<sup>b</sup> p-value for the comparison between group *fertility contact with pregnancy aided by fertility treatment* versus *no fertility contact*

\*Sums of percentages do not add up to total medication use as only most common medication groups are presented. Estimates 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.

regardless of the conception measure, compared with women not seeking care (14.8%). These medications included antithrombotic agents, systemic corticosteroids, antidiabetic medications, and thyroid hormones. The more elevated use of thyroid medication in women seeking fertility help is not surprising since hypothyroidism is a known risk factor for subfertility (22). Similarly, use of antithrombotic medications is a marker for underlying cardiovascular disorders that may affect women's ability to conceive (23) or are related with recurrent pregnancy losses. However, we cannot exclude that antithrombotics were taken in conjunction with the received fertility treatment (24). Our results regarding medication use for diabetes are in line with prior research showing a link between diabetes and reduced fertility (25). Further, the higher prevalence of antidiabetic medications use in women who sought help due to infertility could be explained by metformin being used in ovulation induction (26).

The higher proportion of asthma and allergy medications, including inhaled glucocorticoids, systemic selective beta-2 agonists and nasal corticosteroids, in women with medical care contact due to infertility who however conceived spontaneously, are somewhat surprising. Indeed, these estimates of medication use were greater than in women who conceived after fertility treatment. Results of a systematic review indicate an

association between asthma and reduced fertility (number of offspring, time to pregnancy and need for fertility treatment) (27). A case-control study conducted in USA and Canada reports that women who had used asthma medication for more than 6 months had a statistically significant increased risk of infertility (magnitude of risk: 1.7) (28). Other studies also reported higher need for fertility treatment among women with asthma (29, 30), however a recent study showed that only women taking asthma medications on daily basis plus extra dosing for symptoms (i.e., combination of inhaled corticosteroid and long-acting beta-agonists) have a small reduction in fecundability (31). Taken together, these findings may suggest that most women using asthma and/or allergy medications are more likely to encounter fertility problems, but they eventually conceive spontaneously without the need of fertility treatment.

One prior study in Israel reported that 12.7% of women who underwent fertility treatment filled at least one prescription of potentially hazardous medications, compared to 6.8% of women who spontaneously got pregnant (3). Most used medications were statins, ACE inhibitors in women who underwent fertility treatment, compared to isotretinoin and tetracyclines in women who got spontaneously pregnant (3). This finding could not be substantiated in our study, as these drugs constituted very rare exposures and therefore not presented in

the results. However, given our results, we argue that women seeking care due to infertility have often underlying chronic disorders, which require treatment with medications that may be classified as potentially harmful. Yet, use of these medications may still be appropriate for the individual women to safeguard maternal-fetal health.

### **Strengths and limitations**

The study has strengths and limitations that need mentioning. One advantage is uniform data collection across countries, which facilitates comparability of estimates. The study was web-based, which enabled us to reach a high number of participants. Information about the study was available on many of internet pages frequently used by pregnant women, something that made the number of potential participants even higher. Because the study was anonymous, it is likely that women answered sensitive questions (such as alcohol use or smoking in pregnancy, and even seeking help due to fertility problems), more truthfully than what could happen in a face-to-face interview. One additional strength is that questions about medication use were phrased according to indication, including for treatment of long-term/chronic illnesses in pregnancy, which may have enhanced recall of drug use.

One study limitation is that our study population had on average higher education than the general birthing population in the countries examined, which may have affected the prevalence of medical contact for infertility or medication use in pregnancy. The study used an electronic questionnaire, which may have led to recruitment of more educated and resourceful women; this risk of selection bias limits the extent to which the results are representative of the target population. However, epidemiological studies indicate reasonable validity of web-based recruitment methods (32-35). Also, the penetration rate of the internet either in households or at work is relatively high among women in childbearing age (36). We have previously assessed the study's external validity on an individual country level and found that on average, the women in the study had higher education and were slightly more often primiparous than the general birthing populations in the various countries (5). In specific countries (i.e., France and Russia) 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 (5). Further, all disorders and medication use in this study were self-reported by participants, and thus dependent on these women's perception of the medical conditions and recall of medication use. Since many acute ailments requiring pharmacotherapy occur in mid or late pregnancy, inclusion of pregnant women at early gestation in the total material

may have reduced the prevalence of medication user during pregnancy. We have previously shown that time of recruitment does not influence the proportion of chronic/long-term medication use in this study (5). Moreover, the questions regarding infertility were only related to women and not their partners, and the study did not ask women about the infertility method used. The study did not recruit women from all European countries, and so our results may not be generalizable to the entire population of pregnant women in Europe. In addition, as the study included women who eventually got pregnant, our results on medical care seeking due to infertility do not include women with fertility problems that do not succeed to conceive.

### **CONCLUSION**

Medical care contacts for infertility varies greatly across European countries. Use of medications was common in pregnant women, regardless of whether they sought fertility help or not and of how the pregnancy was achieved. Women who had medical contact due to infertility used more often chronic medications in pregnancy than women who did not, pointing to more comorbidities and risk pregnancies. Tailored counseling regarding risks and benefits of medication use in pregnancy due to chronic diseases should be prioritized in these women, in order to enhance appropriate drug treatment and safeguard the health of both mother and her unborn child.

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### **Conflicts of interest**

The authors declare no conflict of interest.

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