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# Trends in prescription drug use during pregnancy and postpartum in Norway, 2005 to 2015

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## Abstract

**Purpose:** To explore trends in use of maternal medication 3 months prior to, during and 3 months after pregnancy.

**Methods:** Data on births from the Medical Birth Registry of Norway were linked to the Norwegian Prescription Database, identifying women's use of medications around pregnancy. All women giving birth in Norway during 2005 to 2015 (638 532 singleton births to 414 567 women) were included. Proportions of pregnant women using different medications in association with pregnancy, and annual relative change in medication use during 2005 to 2015, were calculated.

**Results:** In Norway, 60% of pregnant women used prescription medications during pregnancy (2005-15), increasing from 57% in 2005 to 62% in 2015. The annual relative increase was 0.9% (95% CI: 0.8-1.0). In the first trimester, approximately 17% of the women used medications regarded as potentially teratogenic during 2005 to 2015, increasing from 15% to 19%. Overall, this proportion was higher in the first than in the second (8.9%) and third (8.0%) trimesters, and higher than in the 3 months after pregnancy (14%). The annual relative increase of medications regarded as potentially teratogenic in the first trimester was 2.5% (95% CI: 2.3-2.7).

**Conclusions:** The proportion of women using potentially teratogenic medications in the first trimester of pregnancy have increased during the last decade. Clinicians need to be aware of the possibility of pregnancy when prescribing potentially teratogenic medication to women of fertile age and focus this in the consultations. The increasing trends call for the need of routine surveillance of adverse birth outcomes linked to medication use in pregnancy.

KEYWORDS

medication, pharmacoepidemiology, population based, pregnancy

## 1 | INTRODUCTION

Since the Thalidomide-disaster in the 1960s, there has been concern about possible serious adverse effects of medication use during pregnancy.[1] Information on adverse effects for both children and women of medication use in association with pregnancy has been limited, because pregnant women are usually excluded from clinical trials due to fear of harmful effects.[2,3] A number of recommendations

**Abbreviations:** ATC, Anatomical Therapeutic Chemical; CI, Confidence interval; MBRN, Medical Birth Registry of Norway; NorPD, Norwegian Prescription Database; SSRI, Selective serotonin reuptake inhibitors; TCA, Tricyclic antidepressants



  

have, however, been given for better surveillance of use and adverse effects of medications in pregnancy,[4] and websites on the safety of such medication use have been established.[5-8] Women may suffer from chronic diseases, such as diabetes type I and epilepsy, where medication use during pregnancy is necessary.[9,10] The use of some antiepileptics has been associated with risk of birth defects.[9]

We have previously described the use of medications during pregnancy in Norwegian women during 2004 to 2006, and reported that 57% of the women were dispensed prescription medications.[11] A web-based study from 2014 showed that the majority of women in Europe, North and South America and Australia used at least 1 medication during pregnancy.[12] Around 60% to 70% of women use prescribed drugs during pregnancy, most frequently drugs for pain conditions, heartburn, and upper airways disorders.[12] Mitchell et al explored the use of prescribed medicines in pregnant women in the US during 1978 to 2008, by using interview data.[13] They observed an increasing use of prescribed medicines during pregnancy. Gagne et al studied the use of prescribed drugs during pregnancy in a population-based study in Emilia-Romagna, Italy.[14] They found that 70% of women used at least 1 prescribed drug during pregnancy.

Many studies have addressed the teratogenicity of different drugs (listed in van Gelder et al[15]), although a considerable proportion of pregnant women use potentially teratogenic drugs.[16] The conclusions on which drugs that are teratogenic have been inconsistent, possibly due to use of different classification systems. In 2014, van Gelder et al summarised the literature on risks of medications suspected to be associated with teratogenic mechanisms but observed that the number of epidemiologic studies was limited and that many of the studies were small.[15,17] In a separate study, they found that in the Netherlands in the period 1998 to 2009, a large and nearly constant proportion of women (18%) used potentially teratogenic medications during the first trimester of pregnancy.[17]

The main aim of this study was to explore the use of maternal medication prior to and during pregnancy and after giving birth, and to examine whether the medication use in association with pregnancy has changed in recent years. An additional aim was to explore the use of potentially teratogenic medications, including antiepileptics.

**KEY POINTS**

- Use of drugs in association with pregnancy is widespread.
- Maternal use of drugs prior to and during pregnancy may have adverse effects on birth outcomes.
- In this registry-based study, we examined more than 600 000 Norwegian pregnancies during 2004 to 2015 and described the use of prescribed drugs.
- Approximately 60% of mothers are using drugs during pregnancy.
- The proportion of mothers using potentially teratogenic medications in the first trimester have increased from 15% to 19% during the last decade.

## 2 | MATERIAL AND METHODS

This study was based on data from 2 registries; the Norwegian Prescription Database (NorPD) and the Medical Birth Registry of Norway (MBRN).[18]

The NorPD contains information on all prescription medications, dispensed at pharmacies to individual patients treated in ambulatory care from January 1st, 2004 in the entire Norwegian population (5.3 million individuals in 2018).[19] In NorPD, the information available for each dispensed drug is the trade name, pharmaceutical form, strength, package size, number of packages, reimbursement code, and dispensing date. No information on the usage is, however, included. The medications are classified according to the Anatomical Therapeutic Chemical (ATC) classification system.[20]

The MBRN is based on compulsory notification and contains information on all births in Norway since 1967, including spontaneous abortions and stillbirths from 12 to 16 weeks' gestation (approximately 2.8 million births in 2016).[21] In addition, the register includes data on terminations of pregnancy for foetal anomaly or high risk of foetal anomaly after 12 weeks gestation.

### 2.1 | Study population

In the present study, only singleton pregnancies lasting at least 12 weeks and starting at April 1st, 2004 or later with births in the period 2005 to 2015, were included in the main analyses. Similar analyses were, however, performed in pregnancies with multiples, and tables for these are included in the Supporting Information (Supplementary tables 2-5). Both registries are based on the unique personal identification number assigned to all citizens of Norway, making accurate record linkage possible.

### 2.2 | Exposure

We defined exposure as dispensed prescription medications. The exposure period was subdivided into the last 3 months before pregnancy, first trimester of pregnancy (week 0-12), second trimester of pregnancy (week 13-26), third trimester of pregnancy (week 27 onwards), and the first 3 months after pregnancy. The 3 trimesters were defined as *the whole pregnancy*. We assumed that medications were used the trimesters they were dispensed.

Medications associated with teratogenic mechanisms according to van Gelder et al were tabulated.[15,22] The grouping is displayed in Supplementary Table 1.

### 2.3 | Statistical analysis

All groups of medication tabulated in our previous publication were displayed.[11]

Also, use of each of the 5 most common antiepileptics in Norway was explored—carbamazepine (ATC code N03AF01), valproic acid (N03AG01), lamotrigine (N03AX09), gabapentin (N03AX12), and pregabalin (N03AX16), because some of these have been regarded as

teratogenic. Gabapentin and pregabalin were not included among the medications termed as potentially teratogenic by van Gelder et al.[15]

In addition to calculating the proportions using specific medications for different years of birth (2005-2015), log-binomial regression was used to estimate the annual relative change in medication use with 95% confidence intervals (CIs). The estimates were adjusted for maternal age (<20, 20-34, 35-44, and ≥ 45 years). Sub-analyses including only primiparous women were performed. Robust estimation of variances accounted for correlations between births to the same woman.

The data were analysed using IBM SPSS Statistics 24 and Stata/SE 14.0.

## 3 | RESULTS

Altogether 638 532 singleton pregnancies (in 414 567 mothers) were included in the main analyses (Table 1). Approximately 43% of the pregnancies were in primiparous women. In total, 60% of women used prescription medications during pregnancy, increasing from 57% for women giving birth in 2005 to 2006 to 62% for women giving birth in 2014 to 2015 (Table 2). During pregnancy, progesterone (first trimester), penicillins, and antihistamines for systemic use were the most frequent used drugs. The annual relative increase of use of all prescribed medications was 0.9% (95% CI: 0.8-1.0), adjusted for maternal age (not tabulated). The proportion increased in all maternal age groups (<20, 20-34, 35-44, and ≥45 years). The use of medication was lower in the first trimester of pregnancy than in the 3-month period before pregnancy and was even lower in the next trimesters (second and third trimester—Figure 1 and Table 2). In mothers younger than 45, the use of medications was, however, higher in the 3 months after pregnancy than in the 3 months before pregnancy, also when disregarding oral contraceptives (data not shown). In all the 5 periods (3 months before pregnancy, 3 trimesters of pregnancy, and the first 3 months after pregnancy), the use of prescription medication increased by calendar year (Figure 1). The use of medication before and during pregnancy was most frequent in the oldest women (≥45 years) (data not shown).

**TABLE 1** Characteristics of singleton pregnancies, Norway, 2005 to 2015

| | Number | % |
|---|---|---|
| Year of birth | | |
| 2005-6 | 111 261 | 17.4 |
| 2007-8 | 115 822 | 18.1 |
| 2009-10 | 120 240 | 18.8 |
| 2011-12 | 117 883 | 18.5 |
| 2013-14 | 115 684 | 18.1 |
| 2015 | 57 642 | 9.0 |
| Maternal age | | |
| <20 | 12 462 | 2.0 |
| 20-34 | 503 586 | 78.9 |
| 35-44 | 121 619 | 19.0 |
| ≥45 | 865 | 0.1 |
| Maternal parity | | |
| 0 | 271 391 | 42.5 |
| 1 | 229 321 | 35.9 |
| 2 | 97 935 | 15.3 |
| ≥3 | 39 885 | 6.2 |
| Maternal country of birth[a] | | |
| Missing | 8301 | 1.3 |
| Norway | 483 802 | 75.8 |
| High-income country | 32 237 | 5.0 |
| Low/intermediate-income country | 114 192 | 17.9 |
| Total | 638 532 | 100.0 |

[a]Categorisation based on the classification used in the project Global Burden of Disease (see Murray et al).[23]

In the first trimester, 35.0% of women used prescription medication, increasing from 32.7% in 2005 to 37.3% in 2015. The annual relative increase was 1.4% (95% CI: 1.3-1.5). Most of this increase was due to increased use of antihistamines for systemic use (ATC code R06A) and medications for functional gastrointestinal disorders (A03), mostly the antiemetic metoclopramide (A03FA01).

In Figure 2, the prevalence of use in the first trimester and the relative changes in use from 2005 to 2015 are illustrated for the most common groups of potentially teratogenic medications. Overall, maternal use of potentially teratogenic medications in the first trimester increased during 2005 to 2015. The use increased both for medications used in fertility treatment, for oxidative stress and for medications, other than SSRI, used for serotonin signalling disturbances. For the latter group, the use decreased during 2014 to 2015, after an increase during 2005 to 2013. The use of medications for vascular disruption was stable.

Overall, the proportion using potentially teratogenic medications was highest in the 3 months before pregnancy (23%) but was higher in the first trimester (17%) than in the second (8.9%) and third (8.0%) trimesters, and even higher in the first trimester than in the 3 months after pregnancy (14%), Table 3. In the first trimester, the use of potentially teratogenic medications increased from 15% in 2005 to 19% in 2015; the annual relative increase was 2.5% (2.3–2.7). Most of the increase was due to increased use of serotonin signalling disturbance medications other than SSRI (including metoclopramide) and drugs used in fertility treatment (Tables 3 and 4). The increase in the latter group was due to an increased use of progesterone (G03DA04). While 17% of the pregnancies were exposed to 1 or more potentially teratogenic drugs in the first trimester, 5.6% were exposed to more than 1 of the potentially teratogenic drugs.

The relative increase in use of potentially teratogenic medications during the 3 months before pregnancy was 0.4% (0.2-0.5) per year. In the whole pregnancy, the relative increase was 2.0% (1.9-2.2), and in the first 3 months after pregnancy, 1.7% (1.5-1.9).

Very few women were dispensed isotretinoin (included in the group of retinoids) in association with pregnancy. However, the proportion increased with calendar time. In 2005 to 2006, no women were dispensed isotretinoin during pregnancy and less than 5 women were dispensed isotretinoin during the last 3 months before pregnancy. In 2014 to 2015, less than 5 women were dispensed isotretinoin during pregnancy and 30 women were dispensed isotretinoin during the last 3 months before pregnancy.

**TABLE 2** Maternal exposure to different medications 3 months prior to pregnancy to 3 months after pregnancy ($n$ = 638 532 singleton pregnancies), Norway, 2005 to 2015

| | Whole Period *n* | % | 3 Months Before Conception % | 1. Trimester % | 2. Trimester % | 3. Trimester % | Whole Pregnancy % | 3 Months After Pregnancy % |
|---|---|---|---|---|---|---|---|---|
| **Alimentary tract and metabolism (A)** | **102 592** | **16.1** | **3.6** | **6.6** | **4.2** | **4.2** | **11.3** | **4.8** |
| Antacids and medications for peptic ulcer (A02) | 21 370 | 3.3 | 1.2 | 1.0 | 0.7 | 1.1 | 2.3 | 0.6 |
| Medications for functional gastrointestinal disorders (A03) | 35 632 | 5.6 | 0.4 | 3.7 | 1.2 | 0.2 | 4.7 | 0.6 |
| Antidiarrheals, intest. anti-inflam./anti-infect. agents (A07) | 18 683 | 2.9 | 0.4 | 0.3 | 0.3 | 0.4 | 0.7 | 2.3 |
| Antiobesity preparations, excl. diet products (A08) | 2922 | 0.5 | 0.3 | 0.1 | 0.0 | 0.0 | 0.2 | 0.1 |
| Medications for diabetes (A10) | 9871 | 1.5 | 0.8 | 0.7 | 0.6 | 1.0 | 1.3 | 0.4 |
| **Blood and blood forming organs (B)** | **51 869** | **8.1** | **1.2** | **2.9** | **2.8** | **3.0** | **6.2** | **2.3** |
| Antithrombotic agents (B01) | 20 332 | 3.2 | 0.4 | 1.5 | 1.5 | 1.4 | 2.4 | 1.3 |
| Vitamin B12 and folic acid (B03B) | 19 550 | 3.1 | 0.5 | 1.1 | 0.8 | 0.8 | 2.4 | 0.5 |
| **Cardiovascular system (C)** | **52 404** | **8.2** | **1.1** | **0.8** | **0.8** | **1.9** | **2.9** | **5.5** |
| Vasoprotectives (C05) | 37 336 | 5.8 | 0.4 | 0.3 | 0.4 | 1.2 | 1.7 | 4.2 |
| Beta-blockers (C07) | 10 395 | 1.6 | 0.3 | 0.3 | 0.3 | 0.5 | 0.8 | 1.0 |
| Agents acting on the renin-angiotensin system (C09) | 1913 | 0.3 | 0.2 | 0.1 | 0.0 | 0.0 | 0.1 | 0.1 |
| **Dermatologicals (D)** | **94 428** | **14.8** | **4.0** | **3.0** | **3.1** | **2.7** | **7.6** | **5.8** |
| Antifungals for dermatological use (D01) | 25 302 | 4.0 | 0.5 | 0.4 | 0.6 | 0.5 | 1.4 | 2.1 |
| Antibiotics and chemother. for dermotological use (D06) | 21 027 | 3.3 | 0.8 | 0.5 | 0.5 | 0.5 | 1.5 | 1.2 |
| Dermal corticosteroids (D07) | 43 469 | 6.8 | 1.9 | 1.5 | 1.7 | 1.4 | 4.0 | 2.0 |
| Anti-acne preparations (D10) | 11 196 | 1.8 | 0.7 | 0.5 | 0.4 | 0.2 | 0.9 | 0.4 |
| **Genito urinary system and sex hormones (G)** | **273 144** | **42.8** | **13.1** | **6.6** | **1.4** | **1.1** | **8.6** | **31.4** |
| Gynaecological anti-infectives (G01) | 25 307 | 4.0 | 0.8 | 0.7 | 1.0 | 1.0 | 2.5 | 0.8 |
| Other gynecologicals (G02) | 47 999 | 7.5 | 0.7 | 0.2 | 0.0 | 0.0 | 0.2 | 6.8 |
| Sex hormones (G03) | 222 329 | 34.8 | 11.8 | 5.8 | 0.3 | 0.1 | **6.0** | **24.7** |
| **Systemic hormonal preparations, excl. sex hormones and insulins (H)** | **88 434** | **13.8** | **3.9** | **2.8** | **2.3** | **2.4** | **4.1** | **10.3** |
| Posterior pituitary lobe hormones (H01B) | 54 857 | 8.6 | 0.2 | 0.0 | 0.0 | 0.1 | 0.2 | 8.4 |
| Thyroid therapy (H03) | 17 443 | 2.7 | 1.7 | 1.8 | 2.0 | 2.0 | 2.6 | 1.7 |
| **Anti-infectives for systemic use (J)** | **287 541** | **45.0** | **11.5** | **10.2** | **12.8** | **13.7** | **29.5** | **16.7** |
| Antibacterials for systemic use (J01) | 274 351 | 43.0 | 10.2 | 9.5 | 12.2 | 12.9 | 27.9 | 16.1 |
| Tetracyclines (J01A) | 10 714 | 1.7 | 1.1 | 0.4 | 0.0 | 0.0 | 0.4 | 0.2 |
| Beta-lactam antibacterials, penicillins (J01C) | 229 909 | 36.0 | 6.4 | 7.4 | 10.3 | 10.9 | 23.8 | 12.9 |
| Sulfonamides and trimethoprim (J01E) | 21 320 | 3.3 | 1.0 | 0.4 | 0.5 | 0.8 | 1.6 | 0.9 |
| Macrolides, lincosamides, and streptosamins (J01F) | 43 864 | 6.9 | 2.2 | 1.2 | 1.0 | 0.8 | 2.8 | 2.3 |
| Other antibacterials (J01X) | 22 684 | 3.6 | 0.4 | 0.7 | 1.3 | 1.4 | 3.1 | 0.3 |

(Continues)

**TABLE 2** (Continued)

| | Whole Period *n* | % | 3 Months Before Conception % | 1. Trimester % | 2. Trimester % | 3. Trimester % | Whole Pregnancy % | 3 Months After Pregnancy % |
|---|---|---|---|---|---|---|---|---|
| **Antineoplastic and immunomodulating agents (L)** | **6556** | **1.0** | **0.9** | **0.2** | **0.1** | **0.1** | **0.3** | **0.2** |
| **Musculo-skeletal system (M)** | **68 152** | **10.7** | **5.7** | **2.0** | **0.3** | **0.2** | **2.4** | **3.8** |
| Anti-inflammatory and antirheumatic products, non-steroids (M01A) | 65 224 | 10.2 | 5.5 | 1.9 | 0.3 | 0.1 | 2.2 | 3.6 |
| Muscle relaxants (M03) | 1596 | 0.2 | 0.2 | 0.1 | 0.0 | 0.0 | 0.1 | 0.0 |
| **Nervous system (N)** | **101 130** | **15.8** | **8.5** | **5.4** | **3.3** | **3.1** | **8.5** | **5.1** |
| Opioids (N02A) | 41 718 | 6.5 | 2.9 | 1.4 | 1.0 | 1.1 | 3.0 | 1.7 |
| Antiepileptics (N03) | 4788 | 0.7 | 0.5 | 0.4 | 0.3 | 0.3 | 0.5 | 0.4 |
| Antipsychotics (N05A) | 8238 | 1.3 | 0.4 | 0.7 | 0.3 | 0.2 | 1.0 | 0.2 |
| Anxiolytics, hypnotics, and sedatives (N05B or N05C) | 21 450 | 3.4 | 1.9 | 1.0 | 0.4 | 0.5 | 1.6 | 0.8 |
| Antidepressants (N06A) | 18 165 | 2.8 | 2.0 | 1.2 | 0.6 | 0.6 | 1.5 | 1.0 |
| **Antiparasitic products, insecticides, and repellents (P)** | **16 705** | **2.6** | **0.9** | **0.3** | **0.2** | **0.1** | **0.6** | **1.2** |
| Antiprotozoals (P01) | 15 938 | 2.5 | 0.9 | 0.3 | 0.1 | 0.1 | 0.5 | 1.2 |
| **Respiratory system (R)** | **156 493** | **24.5** | **8.8** | **8.6** | **7.7** | **7.2** | **18.1** | **5.1** |
| Nasal preparations (R01) | 54 067 | 8.5 | 3.1 | 2.1 | 2.2 | 1.9 | 5.3 | 1.7 |
| Anti-asthmatics (R03) | 31 264 | 4.9 | 2.0 | 1.7 | 1.9 | 1.9 | 3.7 | 1.2 |
| Cough and cold preparations (R05) | 39 795 | 6.2 | 2.2 | 1.3 | 1.3 | 1.3 | 3.7 | 0.7 |
| Antihistamines (R06) | 87 701 | 13.7 | 3.9 | 5.2 | 3.9 | 3.6 | 10.4 | 2.6 |
| **Sensory organs and various (S + V)** | **73 718** | **11.5** | **3.3** | **2.5** | **2.7** | **2.5** | **6.8** | **3.4** |
| **Total[a] 2005-6** | **92 059** | **82.7** | **39.2** | **32.8** | **28.5** | **28.8** | **57.3** | **56.7** |
| **Total[a] 2014-15** | **97 616** | **84.5** | **41.4** | **37.2** | **32.7** | **33.5** | **61.5** | **57.8** |
| **Total[a]** | **533 556** | **83.6** | **40.6** | **35.0** | **30.6** | **31.2** | **59.5** | **57.0** |
| **Total[a] excl. ATC-group G** | **498 175** | **78.0** | **36.7** | **34.2** | **30.5** | **31.2** | **59.0** | **44.1** |

[a]Number of mothers exposed to 1 or more of the drugs above.

In Figure 3, the prevalence of use in the first trimester and the relative changes in use from 2005 to 2015 are illustrated for the most common antiepileptics in Norway. Use of lamotrigine was much more common than the use of the other drugs, and more than doubled during 2005 to 2015.

The maternal use of drugs in multiple pregnancies is shown in Supplementary tables 2 and 3. In addition, the maternal use of drugs in multiple pregnancies is compared with the maternal use of drugs in singleton pregnancies (Supplementary tables 4 and 5). Especially, the maternal use of drugs used in fertility treatment (progesterone) and antineoplastic and immunomodulating agents were more frequent in multiple pregnancies.

## 4 | DISCUSSION

A large proportion of women use prescription medications during pregnancy (62% in 2015, increasing from 57% in 2005). Most of the medications were not regarded as teratogenic. However, 19% of women giving birth in 2015 used medications regarded as potentially teratogenic during the first trimester of pregnancy, significantly more than the corresponding 15% in 2005.

### 4.1 | Comparisons with other studies

A cross-sectional, multinational web-based study from 2014 on self-reported medication use in pregnancy showed that the majority of women in Europe, North and South America, and Australia used at least 1 medication during pregnancy.[12] The majority of medications used around pregnancies, however, was not teratogenic. In a population-based study (in British Columbia) with births during 2002 to 2011, Smolina et al observed that the proportion of pregnant women filling a prescription during pregnancy increased from 60% to 66%,[24] which is similar to our findings. In a Health Insurance and Assessment Service database in Korea during 2007 to 2011, however, the use of pregnancy-contraindicated medications in pregnancy was moderately reduced.[25]

Van Gelder et al observed that 24% and 18% of pregnant Dutch women in 1998 to 2009 used at least 1 medication associated with a teratogenic mechanism during the 3 months before pregnancy and in the first trimester, respectively.[17] We found similar figures among

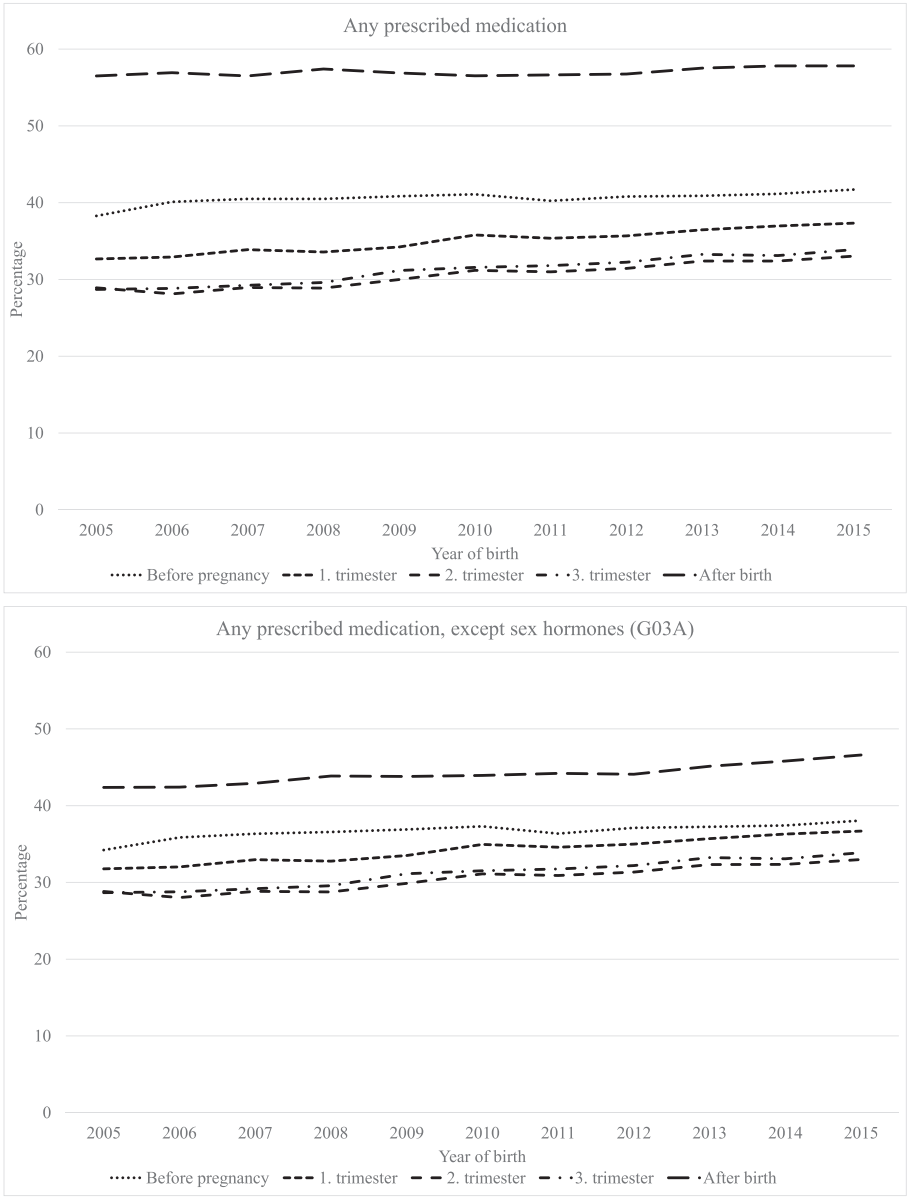


**FIGURE 1** Prescription medication in association with singleton pregnancies by year of birth, Norway, 2005 to 2015

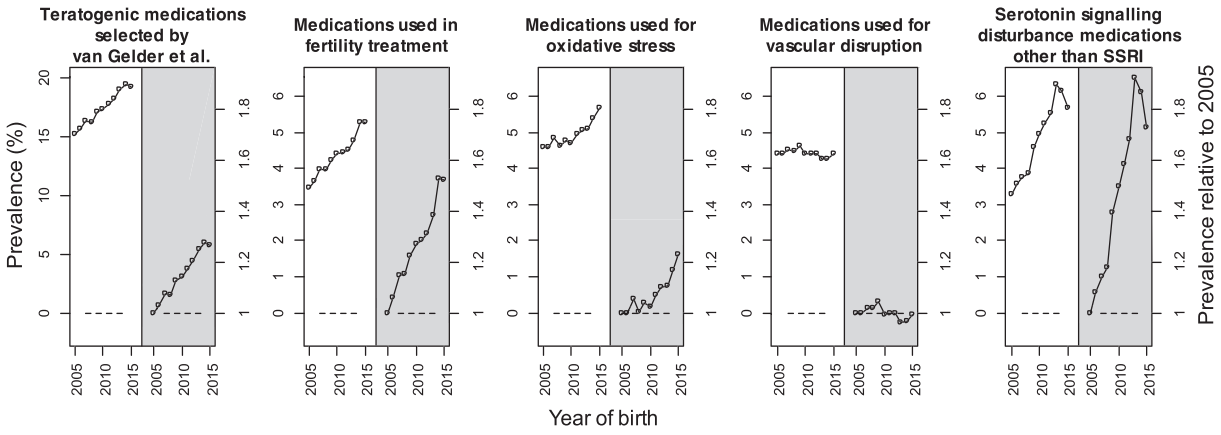


**FIGURE 2** Prevalence of maternal use and relative change in the use of potentially teratogenic medications in the first trimester of pregnancy, Norway, 2005 to 2015.[15,22] Singleton pregnancies

**TABLE 3** Maternal exposure to potentially teratogenic medications 3 months prior to pregnancy to 3 months after pregnancy ($n$ = 638 532 singleton pregnancies), Norway, 2005 to 2015[15,22]

| Potentially Teratogenic Mechanism | Whole Period | | 3 Months Before Conception | 1. Trimester | 2. Trimester | 3. Trimester | Whole Pregnancy | 3 Months After Pregnancy |
|---|---|---|---|---|---|---|---|---|
| | *n* | % | % | % | % | % | % | % |
| Folate antagonism | | | | | | | | |
| Antiepileptics | 3291 | 0.5 | 0.4 | 0.3 | 0.3 | 0.3 | 0.4 | 0.3 |
| DHFR inhibitors | 21 596 | 3.4 | 1.1 | 0.6 | 0.7 | 1.0 | 1.8 | 1.0 |
| Other drugs | 4509 | 0.7 | 0.5 | 0.3 | 0.1 | 0.1 | 0.4 | 0.1 |
| Neural crest cell disruption | | | | | | | | |
| Retinoids | 3516 | 0.6 | 0.3 | 0.1 | 0.0 | 0.0 | 0.2 | 0.1 |
| Isotretinoin | 104 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| Endocrine disruption | | | | | | | | |
| Oral contraceptives | 57 392 | 9.0 | 5.8 | 1.1 | 0.1 | 0.0 | 1.2 | 2.8 |
| Drugs used in fertility treatment | 43 229 | 6.8 | 4.8 | 4.4 | 0.2 | 0.1 | 4.5 | 0.4 |
| Oxidative stress | 106 782 | 16.7 | 4.6 | 4.9 | 4.4 | 4.3 | 10.9 | 4.3 |
| Vascular disruption | 110 802 | 17.4 | 8.8 | 4.4 | 2.6 | 2.6 | 7.4 | 6.2 |
| ACE inhibitors/AT II receptor antagonists | 1913 | 0.3 | 0.2 | 0.1 | 0.0 | 0.0 | 0.1 | 0.1 |
| HMG-CoA reductase inhibitors | 819 | 0.1 | 0.1 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| HDAC inhibitors | 630 | 0.1 | 0.1 | 0.0 | 0.0 | 0.0 | 0.1 | 0.1 |
| COX inhibitors | 65 276 | 10.2 | 5.5 | 1.9 | 0.3 | 0.1 | 2.2 | 3.6 |
| NMDA receptor antagonists | 5778 | 0.9 | 0.5 | 0.2 | 0.1 | 0.1 | 0.3 | 0.3 |
| Serotonin signalling disturbance | | | | | | | | |
| SSRI | 13 329 | 2.1 | 1.4 | 0.9 | 0.5 | 0.5 | 1.1 | 0.8 |
| Other medication | 53 564 | 8.4 | 2.3 | 4.8 | 1.8 | 0.5 | 6.0 | 1.4 |
| GABA receptor antagonists | 10 053 | 1.6 | 0.8 | 0.5 | 0.2 | 0.2 | 0.8 | 0.4 |
| Carbonic anhydrase inhibition | 301 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| Total[a] | 278 028 | 43.5 | 23.1 | 17.5 | 8.9 | 8.0 | 25.7 | 13.7 |
| Total[b] | 221 347 | 34.7 | 14.7 | 13.1 | 8.7 | 7.9 | 21.7 | 11.2 |

Reductase; GABA, aminobutyric acid; HDAC, histone deacetylase; HMG-CoA, hydroxymethylglutaryl-coenzyme A; NMDA, N-methyl-d-aspartate; SSRI, selective serotonin-reuptake inhibitor.

[a]Number of mothers exposed to 1 or more of the drugs above.

[b]Number of mothers exposed to 1 or more of the drugs above, excluding oral contraceptives and drugs used in fertility treatment.

Norwegian women (23% and 17%, respectively). However, while van Gelder et al observed higher proportions of use in the last 2 trimesters of pregnancy than in the first trimester, the proportion using these medications in Norwegian women was halved in the second and third trimester compared with the first. Furthermore, van Gelder et al observed a slight decrease in the proportion of women using potentially teratogenic medications during first trimester in 1998 to 2005 and a slight increase thereafter. We observed a steady increase during 2005 to 2015, mostly due to increases in the use of metoclopramide and progesterone. Use of metoclopramide did not increase risk for major congenital malformations or fetal death in a large Danish study.[26] Use of progesterone has been associated with increased risk of hypospadias.[15]

Overall, we observed a higher proportion of women using potentially teratogenic medication in the first trimester than in the remaining 2 trimesters, and even higher than in the 3 months after pregnancy. This is mostly explained by drugs used in fertility treatment in the first trimester. In addition, a number of women receive medication before their pregnancy is acknowledged, which indicates the need for clinicians to focus on these issues when prescribing potentially teratogenic medication to women of fertile age.

Antiepileptics have previously been associated with increased risk of birth defects.[9,27] In Norway, the most common antiepileptic medication is lamotrigine. The use of lamotrigine in the first trimester of pregnancy increased during 2005 to 2015. The use of lamotrigine has also increased in the general population.[28] Lamotrigine use has, however, not been associated with birth defects.[9,27]

Isotretinoin is a highly teratogenic drug.[29,30] In Norway, guidelines have been introduced to prevent that the medication is used in or shortly before pregnancy, and pregnancy is an absolute contraindication for all oral retinoids in the EU.[31-33] Even though adviced against, a few women dispensed isotretinoin shortly before and during pregnancy in our data set. None of these women had a pregnancy termination due to a fetal anomaly after 12 weeks gestation. However, we do not have data on women who may have terminated their pregnancy before 12 weeks or due to fear of birth defects induced by isotretinoin intake.

## 4.2 | Study strengths and limitations

We assumed that medications were used the trimesters they were dispensed. We know the date of dispensing drug, but we do not know

**TABLE 4** Annual relative change[a] in maternal use of potentially teratogenic medications from 3 months prior to pregnancy to 3 months after pregnancy, Norway, 2005 to 2015.[15,22] Singleton pregnancies

| | 3 Months Before Conception | | 1. Trimester | | 2. Trimester | | 3. Trimester | | Whole Pregnancy | | 3 Months after Pregnancy | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Teratogenic Mechanism | Annual relative change (%) | 95% CI | Annual relative change (%) | 95% CI | Annual relative change (%) | 95% CI | Annual relative change (%) | 95% CI | Annual relative change (%) | 95% CI | Annual relative change (%) | 95% CI |
| Endocrine disruption | | | | | | | | | | | | |
| Medications used in fertility treatment | 2.1 | 1.7–2.5 | 3.8 | 3.4–4.2 | 19 | 17–22 | 44 | 37–51 | 4.3 | 3.9–4.7 | 2.8 | 1.5–4.1 |
| Oxidative stress | 1.5 | 1.2–1.9 | 1.9 | 1.5–2.2 | 1.0 | 0.7–1.4 | 0.9 | 0.5–1.3 | 1.2 | 1.0–1.4 | 3.5 | 3.1–3.9 |
| Vascular disruption | −0.2 | −0.5-0.0 | −0.4 | −0.8-0.0 | 0.6 | 0.1–1.1 | 0.7 | 0.2–1.2 | −0.1 | −0.4-0.1 | 1.5 | 1.2–1.8 |
| Serotonin signalling disturbance | | | | | | | | | | | | |
| Other medications than SSRI | 2.4 | 1.9–3.0 | 6.7 | 6.3–7.1 | 8.1 | 7.5–8.8 | 8.5 | 7.3–9.8 | 6.7 | 6.3–7.0 | 3.0 | 2.3–3.7 |
| Total potentially teratogenic medication | 0.4 | 0.2–0.5 | 2.5 | 2.3–2.7 | 2.7 | 2.5–3.0 | 2.2 | 1.9–2.5 | 2.0 | 1.9–2.2 | 1.7 | 1.5–1.9 |

[a]Adjusted for maternal age (<20, 20-34, 35-44, and ≥ 45).

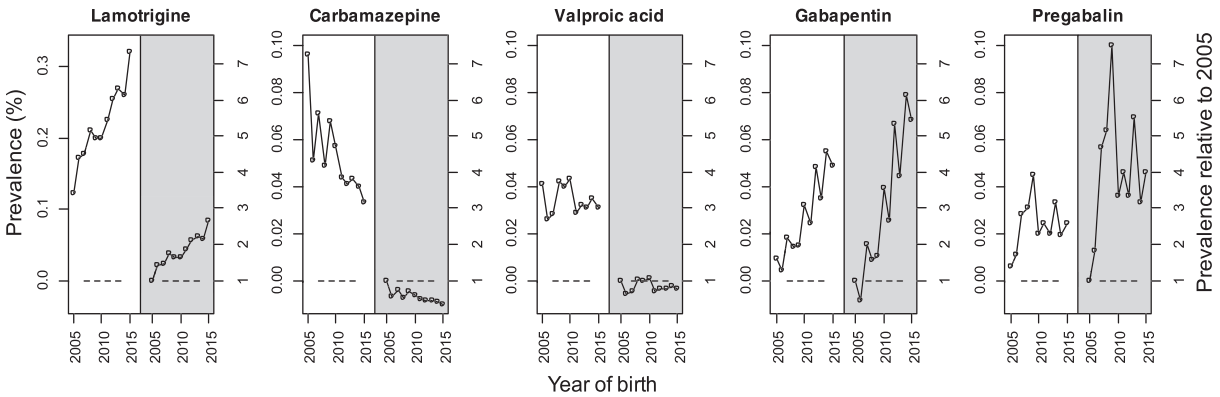


**FIGURE 3** Prevalence of maternal use and relative change in the use of antiepileptics in the first trimester of pregnancy, Norway, 2005 to 2015. Singleton pregnancies

when or whether the dispensed drugs are used. Eg, a woman getting dispensed drugs in 1 period of pregnancy may use it in another period.

The teratogenicity of different drugs is based on an extensive literature review up to December 2012 performed by van Gelder et al where 250 studies were assessed.[15] There are different conclusions regarding the teratogenicity of different drugs, and for many drugs the evidence for teratogenicity is sparse. Many of these drugs have shown small teratogenic effects, as is the case for antidepressants.[34-38]

The classification of drugs carried out in this study is somewhat broad, and results could have differed if another classification was used.

The health care system in Norway covers all citizens, independent of socioeconomic status. Drugs are completely or partially reimbursed. In 2016, prescribed drugs constituted 87% (measured in defined daily doses) of all drugs dispensed in Norway and are included in NorPD.[39]

We used population-based registries with information on all births and prescriptions for the entire Norwegian population in the period 2005 to 2015. Notification to the registers is compulsory, and the problem of selection bias is therefore negligible. Because the registries are based on personal identification numbers and contain dates of births and dispensing dates, it was possible to study use of medications during specific periods of pregnancy.

We examined prescribed drugs as recorded in the NorPD. The NorPD includes information on all prescribed medications dispensed to individual patients from all pharmacies in Norway. Neither medications given to individuals when in hospitals or institutions nor over-the-counter drugs are not registered in NorPD at an individual level. However, we do not believe this will influence the main results of our study.

Since NorPD was established in 2004, a relatively short calendar period was available for evaluating trends in use of medication during pregnancy. Further, over-the-counter medications were not included in our study. The present study explores medication use around pregnancy. To explore the incidence of different birth outcomes associated with specific medications, a much larger cohort is needed. Hence, such explorations are left to larger studies, such as Furu et al and the EUROmediCAT project.[2,36]

Women suffering from chronic diseases, such as diabetes type I and epilepsy, will need to use medication also during pregnancy.[9,10] Some women with severe disorders during pregnancy may also need to use specific drugs for the treatment in spite of being pregnant. We have no information on severity of the illnesses or any risk assessments that have been done when considering need of treatment against risk for the fetus.

## 5 | CONCLUSION

The proportion of women using prescription medications during pregnancy and the proportion of women using potentially teratogenic medications in the first trimester of pregnancy have increased in Norway during the last decade. Clinicians need to be aware of the possibility of pregnancy when prescribing potentially teratogenic medication to women of fertile age, and focus this in the consultations. The increasing trends indicate a need of routine surveillance of adverse birth outcomes linked to the use of medication in pregnancy, especially when potentially teratogenic medication is concerned.

### ETHICS STATEMENT

The Norwegian Data Inspectorate was notified before the MBRN and NorPD were linked, as required by the Norwegian law for national health registries.

### FINANCIAL DISCLOSURE

The authors have no financial relationships relevant to this article to disclose.

### CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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