Paternal drug use: before and during pregnancy

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Objective: Exploratory investigation on drug use by fathers before and during pregnancy with regard to the number of pregnancies.

Research design and methods: Data of Dutch community pharmacies were used in which fathers were linked to children. The prevalence of the 15 most prescribed drug groups were calculated per trimester for one trimester preconception and three trimesters during pregnancy. Drugs with possible harmful effect on the semen and/or embryo based on recent safety issues were analyzed for two trimesters before conception. Descriptive statistics was used.

Results: During the four trimesters, fathers had used one or more drugs in 73% of the pregnancies. Per trimester, drug use ranged from 35 to 39%, with the highest prevalence in the third trimester, statistically significant for the use of one or two drugs. Drugs used most frequently belong to ‘anti-inflammatory and antirheumatic products’. Drugs such as SSRIs with possible harmful effect on the semen and/or embryo are used in 1.4% by fathers before conception.

Conclusion: A proportion of 73% of fathers used drugs before and during pregnancy, increasing toward the third trimester. To increase the knowledge on possible effects, organizations like EUROCAT and (EN)(O)TIS might be encouraged to also collect paternal drug use.

Keywords: drugs, paternal, pregnancy, teratogenicity

1. Introduction

Little is known of the influence of paternal drug exposure on pregnancy outcome. There is some evidence that some medicinal products used by male patients can effect fertility or embryo toxicity [1]. Use of drugs preconception by fathers might be of influence on the offspring due to different mechanisms such as presence of the drug in seminal fluid and genetic or epigenetic action with direct influence on the spermatogenesis. Presence of drugs in seminal fluid could interfere with embryonic or fetal development because of a direct effect on the uterus or the vaginal mucosa during sexual intercourse [1,2] during pregnancy. Certain drugs for oncologic indications such as cyclophosphamide, and 6-mercaptopurine have been known for their negative effect on sperm quality [1]. Children of fathers who survived cancer had more major congenital anomalies than children whose father did not have a history of cancer [3].

Recently, it was detected that α-reductase inhibitors dutasteride and finasteride cause a decline in sperm quality by decrease of the blood level of dihydrotestosterone [4]. Another study showed abnormal DNA fragmentation in sperm caused by paroxetine [5]. Abnormal DNA fragmentation can lead to diminished fertility and is associated with an increased risk of diseases in the offspring [6].

A drug utilization study [7] using Dutch as well as Danish drug prescription data showed that approximately one-third of the fathers used medicinal products
6 months before conception. A publication from Norway [8], showed drug use by 25% of the fathers in 3 months before conception. Teratology Information Services (TIS) [9-11] report that approximately 0.2 – 2% of the questions concern paternal exposure.

During the recent years, there have been discussions on the effects on semen and/or offspring regarding frequently used drugs by fathers. Regulatory authorities had reason for concern regarding drug use by fathers based on studies and case reports for products such as selective serotonin reuptake inhibitors (SSRIs) [5] and finasteride [4].

Spermatogenesis takes approximately 74 days [12]. To cover the susceptible period, the data of at least 3 months preconception should be used for information on paternal drug use.

Studies on congenital anomalies focus merely on drug use by mothers. This is similar for pregnancy registries or congenital anomaly databases for collecting data on drug use by mothers. This was reason for investigating drug use among fathers.

The aim of this study is to explore the use of medicinal products by fathers before and during pregnancy. The main question was: which drug groups are most frequently prescribed to fathers in the 3 months before and during pregnancy. Secondary, the use of drugs of concern was investigated for 6 months prior conception only, because of the known influence on the sperm quality.

2. Materials and methods

2.1 Database

For this study, data of Dutch community pharmacies obtained from the InterAction Database (IADB.nl) [13] are used. IADB.nl is a database containing prescriptions of a population of approximately 500,000 individuals from the Netherlands. The data consist of among others personal characteristics (an anonymous identifier, gender and date of birth) and for drugs the Anatomical Therapeutical Chemical (ATC) code [14], the dispensing date, the number of days the prescription is valid and the prescriber [15].

Because Dutch patients commonly register with one pharmacy and mainly obtain their prescription medication from this pharmacy; medication histories of patients can be considered nearly complete [16].

In the database, fathers were linked to children by selecting children between 0 and 5 years of age and males 15 and 50 years older than the child and registered on the same address under the condition that there is only one male person of this age group registered on this address. Situations with more than one male 15 – 50 years of age present at the same address of the linked child were excluded.

For this study, prescription data covering the period of 1994 up to and including 2009 are used. Prevalence of drug use is measured per trimester (91 days). Prevalence per trimester is defined as the number of pregnancies in which the father used one or more drugs. The prevalence of the 15 most prescribed drug groups per trimester as percentage of pregnancies in which the father used one or more drugs of this therapeutic group in the certain trimester.

2.2 Statistics

Descriptive statistics are used to calculate the prevalence of the number of pregnancies in which the father used one or more medicinal products. Also the prevalence with 95% confidence interval (95% CI) of the 15 most prescribed drug groups per trimester as percentage of pregnancies in which the father used one or more drugs of this therapeutic group in the certain trimester.

3. Results

For the period of 1994 – 2009, the database contained data of 25,954 pregnancies for which information of fathers was available. The number of pregnancies linked to fathers using one or more drugs are presented in Table 1 and Figure 1.

A total of 7745 out of 18,209 fathers were included more than once during the study period, because of multiple pregnancies.

During the four trimesters, in 18,841 (73%) of the pregnancies fathers had used one or more drugs. The prevalence of drug use per trimester varies between 34.9 and 38.8%. The highest prevalence (38.8%) is in the third trimester of pregnancy which is statistically significant compared with the trimester before pregnancy.

The 15 most prescribed therapeutic drugs to men fathered a child, based on the ATC mean groups, sorted by frequency of use before conception are presented in Table 2. The order is almost similar for all trimesters.

Drugs prescribed to fathers with the highest prevalence belong to the therapeutic drug group of ‘anti-inflammatory and antirheumatic products’ (ATC = M01), followed by ‘antibacterials for systemic use’ (ATC = J01), ‘corticosteroid, dermatological preparations’ (ATC = D07) and ‘drugs for acid-related disorders’ (ATC = A02). These drugs, except for ‘drugs for acid-related disorders’ also have the highest prevalence in the third trimester.

Drugs for which there have been safety issues on fertility, semen disorders or congenital anomalies regarding use by fathers are presented in Table 3.

4. Discussion

The highest prevalence of drugs prescribed to fathers was observed during the third trimester of the pregnancy. However, individual drug groups may show a different pattern of use. Drugs with safety issues on fertility or semen disorders concerns 1 – 1.5% of the fathers.
Table 1. Number of pregnancies in which the father used one or more medicinal products, in the defined trimesters with a total number of pregnancies of 25,954.

<table>
<thead>
<tr>
<th></th>
<th>Pre conception (-3 to 0 months)</th>
<th>First trimester (1 - 3 months)</th>
<th>Second trimester (4 - 6 months)</th>
<th>Third trimester (7 - 9 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of pregnancies in which the father used one or more medicinal products during the specific period</td>
<td>9073 (35.0)</td>
<td>9062 (34.9)</td>
<td>9501 (36.6)</td>
<td>10066 (38.8)</td>
</tr>
<tr>
<td>One type of medicinal product</td>
<td>5258 (57.9)</td>
<td>5363 (59.2)</td>
<td>5493 (57.8)</td>
<td>5853 (58.1)</td>
</tr>
<tr>
<td>Two types of medicinal products</td>
<td>2209 (24.3)</td>
<td>2108 (23.3)</td>
<td>2317 (24.4)</td>
<td>2427 (24.1)</td>
</tr>
<tr>
<td>Three types of medicinal products</td>
<td>884 (9.7)</td>
<td>910 (10.0)</td>
<td>963 (10.1)</td>
<td>1001 (9.9)</td>
</tr>
<tr>
<td>Four types of medicinal products</td>
<td>399 (4.4)</td>
<td>359 (4.0)</td>
<td>394 (4.1)</td>
<td>413 (4.1)</td>
</tr>
<tr>
<td>Five or more medicinal products</td>
<td>323 (3.6)</td>
<td>322 (3.6)</td>
<td>332 (3.5)</td>
<td>372 (3.7)</td>
</tr>
</tbody>
</table>

![Figure 1. Number of pregnancies in which the father used one or more drugs during the specific period.](image)

Table 2. Top 15 of most prescribed therapeutic medicinal product groups by fathers sorted on the first trimester following birth (n = 25,955 pregnancies).

<table>
<thead>
<tr>
<th>ATC</th>
<th>Therapeutic drug group</th>
<th>Preconception</th>
<th>First trimester</th>
<th>Second trimester</th>
<th>Third trimester</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% (95% CI)</td>
<td>% (95% CI)</td>
<td>% (95% CI)</td>
<td>% (95% CI)</td>
<td>% (95% CI)</td>
</tr>
<tr>
<td>1</td>
<td>M01 Anti-inflammatory and antirheumatic products</td>
<td>6.0 (5.7 - 6.3)</td>
<td>6.0 (5.7 - 6.3)</td>
<td>6.8 (6.5 - 7.1)*</td>
<td>6.8 (6.5 - 7.1)*</td>
</tr>
<tr>
<td>2</td>
<td>J01 Antibacterials for systemic use</td>
<td>5.8 (5.5 - 6.1)</td>
<td>5.8 (5.5 - 6.0)</td>
<td>5.8 (5.5 - 6.1)</td>
<td>6.5 (6.2 - 6.8)*</td>
</tr>
<tr>
<td>3</td>
<td>D07 Corticosteroids, dermatological preparations</td>
<td>4.0 (3.8 - 4.2)</td>
<td>4.0 (3.8 - 4.3)</td>
<td>4.0 (3.7 - 4.2)</td>
<td>4.5 (4.2 - 4.7)</td>
</tr>
<tr>
<td>5</td>
<td>D01 Nasal preparations</td>
<td>3.0 (2.8 - 3.2)</td>
<td>2.9 (2.7 - 3.1)</td>
<td>3.4 (3.1 - 3.6)</td>
<td>3.4 (3.2 - 3.6)</td>
</tr>
<tr>
<td>7</td>
<td>R03 Drugs for obstructive airway diseases</td>
<td>3.0 (2.8 - 3.2)</td>
<td>2.9 (2.7 - 3.1)</td>
<td>3.3 (3.0 - 3.5)</td>
<td>3.3 (3.0 - 3.5)</td>
</tr>
<tr>
<td>8</td>
<td>R06 Antihistamines for systemic use</td>
<td>2.7 (2.5 - 2.9)</td>
<td>2.7 (2.5 - 2.9)</td>
<td>2.8 (2.6 - 3.0)</td>
<td>3.0 (2.9 - 3.3)</td>
</tr>
<tr>
<td>9</td>
<td>N05 Psycholeptics</td>
<td>2.6 (2.4 - 2.7)</td>
<td>2.5 (2.3 - 2.7)</td>
<td>2.6 (2.4 - 2.8)</td>
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</tr>
<tr>
<td>9</td>
<td>D01 Antifungals for dermatological use</td>
<td>2.3 (2.1 - 2.5)</td>
<td>2.4 (2.2 - 2.6)</td>
<td>2.6 (2.4 - 2.8)</td>
<td>2.8 (2.6 - 3.0)*</td>
</tr>
<tr>
<td>10</td>
<td>S01 Ophthalmologicales</td>
<td>2.2 (2.0 - 2.4)</td>
<td>2.4 (2.2 - 2.6)</td>
<td>2.5 (2.3 - 2.7)</td>
<td>2.6 (2.4 - 2.8)*</td>
</tr>
<tr>
<td>11</td>
<td>N02 Analgesics</td>
<td>2.1 (1.9 - 2.2)</td>
<td>2.1 (1.9 - 2.3)</td>
<td>2.1 (1.9 - 2.2)</td>
<td>1.9 (1.7 - 2.1)</td>
</tr>
<tr>
<td>12</td>
<td>N06 Psychoanaleptics</td>
<td>2.1 (1.9 - 2.1)</td>
<td>2.1 (1.9 - 2.3)</td>
<td>2.2 (2.0 - 2.3)</td>
<td>2.3 (2.1 - 2.5)</td>
</tr>
<tr>
<td>13</td>
<td>D02 Emollients &amp; protectives</td>
<td>1.1 (1.0 - 1.3)</td>
<td>1.1 (1.0 - 1.2)</td>
<td>1.2 (1.1 - 1.3)</td>
<td>1.2 (1.1 - 1.4)</td>
</tr>
<tr>
<td>14</td>
<td>R05 Cough and cold preparations</td>
<td>1.1 (1.0 - 1.2)</td>
<td>1.1 (1.0 - 1.2)</td>
<td>1.2 (1.1 - 1.3)</td>
<td>1.2 (1.1 - 1.3)</td>
</tr>
<tr>
<td>15</td>
<td>A10 Drugs used in diabetes</td>
<td>0.8 (0.7 - 0.8)</td>
<td>0.8 (0.6 - 0.9)</td>
<td>0.8 (0.7 - 0.9)</td>
<td>0.9 (0.8 - 1.0)</td>
</tr>
</tbody>
</table>

*Prevalence is significantly higher, compared the preconception.

ATC: Anatomical Therapeutical Chemical code; CI: Confidence interval.
It is to be expected that chronically used drugs such as anti-
-inflammatory drugs, analgesics and drugs for obstructive
airway diseases remain stable during the period of pregnancy. This
was more or less the matter for the latter two drug groups.
For the drug group ‘anti-inflammatory and antirheumatic
drugs’, however, there was a significant increase from the sec-
ond trimester during pregnancy onwards. Explanations for
this phenomenon should be investigated.

Approximately 6% of the fathers use anti-inflammatory
and antirheumatic drugs despite that only 0.7% of the male
Dutch population suffers from rheumatic arthritis [17]. It
seems that these drugs are more widely used. It is known
that non-steroidal anti-inflammatory drugs (NSAIDs) are
used as painkillers in general. A study on drug use for rheuma-
toid arthritis peri-pregnancy in both mothers and fathers
showed that the use of these drugs among fathers was 0.8%
in the 3 months before conception [18]. Antirheumatic drugs
use in fathers in this study [18] was NSAIDs by 53% and pred-
nisolone by 27%; showing that drugs with a known (human)
teratogenicity are seldom prescribed for fathers.

During the third trimester of pregnancy there was an
increased use of psycholeptics (including antipsychotic and
anxiolytic drugs) while psychoanalectics (including antide-
pressants) did show a steady increase over all trimesters.
Psychological stress in first-time expecting fathers [19] might
explain the increase of psycholeptic drug use. The increase
of psychoanalectics during pregnancy should be investigated,
however Paulson and Bazemore [20] showed a higher preva-
ience of depression during pregnancy in expecting fathers
compared with the overall prevalence of depression in men,
but the highest depression rates in men were seen
3 – 6 months postpartum.

Comparing our study results with previous drug prescription
studies [7,8] among fathers in the trimester before conception, we
found in the IADB population approximately 2 – 2.8 times
higher use for corticosteroids, dermatological preparations,
drugs for acid-related disorders, drugs for obstructive airway
diseases, psycholeptics and antifungals for dermatological use
(Table 4). For drug groups for chronic use, such as drugs used
for diabetes, obstructive airway diseases and musculoskeletal
disorders it was more or less similar (Table 4).

The products with a possible harmful effect on fertility
and/or the embryo did not belong to the top 15 drug groups
used by fathers except the SSRIs.

Limitation of the study is the indirect link between fathers
and children. However, it may be presumed that eventual
misclassification of the father will be very limited. The effect
on the data might be negligible because prescribing drugs to
fertile male patients mostly lacks caution. Furthermore, infor-
mation on drugs obtained during hospital stay or over-the-
counter drugs is not included in the database which can result
in underestimation of drug use.

There have been investigations on fathers exposed to herbi-
cides, pesticides, radiation and other occupational exposures
and effects to offspring, whether decreased fertility, spontane-
ous abortions, prematurity or congenital anomalies, but expo-
sure to drugs is hardly investigated. Besides investigating
maternal drug exposure, paternal drug exposure should also
be investigated. The data available on paternal drug exposure
deal mainly with impaired fertility and sperm abnormalities.

There is scarce information on paternal drug exposure and
congenital anomalies. There are some studies about the risk of
congenital anomalies in the offspring of fathers with a history
of cancer. A cohort study [3] with data from the Danish and
Swedish Birth registries linked with Danish and Swedish cancer
registries, hospital discharge registers and congenital anomaly
registers showed that there is a significant increase in the risk
of major congenital anomalies in children from fathers with a
history of cancer. However, a study [21] in fathers who survived
childhood cancer did not identify adverse outcomes in the
offspring of fathers treated with chemotherapy in childhood.

There is only limited literature on paternal exposure to spe-
cific drugs, either case reports or small cohort studies. Publica-
tions identified were on methotrexate [22], lamivudine [23],
thiopurines [2,24] such as mercaptopurine [25] and azathiop-
rine, ribavirin [26] and the combination of ribavirin–IFN-
alpha B2 combination [27], antirheumatics [18] such as methotrex-
ate, sulfasalazin and biologics, finasteride [28], paroxetine [5]
and testosterone gel [29]. The results of these studies are often
contradictory. For instance, two studies on mercaptopurine
use by fathers report an increase of pregnancy-related compli-
cations [25] or congenital anomalies [2] while another study
found no increased risk [24].

An Editorial in 1992 by Davis et al. [30] concluded that
because of the absence of records regarding prefertilization
paternal exposures and their confrontation with adverse preg-
nancy and antenatal health outcomes detailed information on
prefertilization exposures of both parents should be obtained.
Also Lee et al. [11] concluded that there is an ongoing need for

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Table 3. Six months prevalence of drugs in fathers
with recent safety issues regarding use by fathers.

<table>
<thead>
<tr>
<th>ATC</th>
<th>Drug</th>
<th>6 months preconception N (per 1000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A07EC01</td>
<td>Sulfasalazine</td>
<td>15 (0.6)</td>
</tr>
<tr>
<td>D11AX10</td>
<td>Finasteride 1 mg</td>
<td>6 (0.2)</td>
</tr>
<tr>
<td>G04CB01</td>
<td>Finasteride 5 mg</td>
<td>1 (0.0)</td>
</tr>
<tr>
<td>L01BB02</td>
<td>Finasteride</td>
<td>7 (0.3)</td>
</tr>
<tr>
<td>L04AA13</td>
<td>Leflunomide</td>
<td>0</td>
</tr>
<tr>
<td>N06AB03</td>
<td>Escitalopram</td>
<td>5 (0.3)</td>
</tr>
<tr>
<td>N06AB04</td>
<td>Sertraline</td>
<td>5 (0.3)</td>
</tr>
<tr>
<td>N06AB05</td>
<td>Fluoxetine</td>
<td>54 (2.1)</td>
</tr>
<tr>
<td>N06AB06</td>
<td>Paroxetine</td>
<td>188 (7.2)</td>
</tr>
<tr>
<td>N06AB07</td>
<td>Tolcapone</td>
<td>53 (2.0)</td>
</tr>
<tr>
<td>N06AB10</td>
<td>Escitalopram</td>
<td>3 (0.1)</td>
</tr>
</tbody>
</table>

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ATC: Anatomical Therapeutical Chemical code; SSRI: Selective serotonin reuptake inhibitor.
information on paternal drug exposure. The majority of the published studies and case reports so far are from TIS of countries with birth registries. It should be noted that organizations like (EN)(O)TIS have few data on paternal exposure because maternal exposure is more obvious. In addition, gynecologists, midwives and general practitioners should encourage counseling on paternal exposure besides maternal exposure.

5. Conclusions

A large proportion of fathers used drugs before and during pregnancy with an increase toward the third trimester. Reason for certain patterns in use and specifically the increase for the total use in the third trimester have to be investigated. To increase the knowledge on possible paternal contribution to congenital anomalies, organizations like EUROCAT and (EN)(O)TIS might be encouraged to collect information on paternal drug use before and during pregnancy.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

Table 4. Number of prescriptions to fathers over the last 3 months before conception.

<table>
<thead>
<tr>
<th>ATC</th>
<th>Therapeutic drug group</th>
<th>IADB % (95% CI)</th>
<th>Engeland et al. 2008 % (95% CI)</th>
<th>Schirm et al. 2004 NL data % (95% CI)</th>
<th>Schirm et al. 2004 DK data % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M01</td>
<td>Anti-inflammatory and antirheumatic products</td>
<td>6.0 (5.7–6.3)</td>
<td>5.6 (5.5–5.8)</td>
<td>7.6 (6.8–8.3)</td>
<td>6.1 (5.9–6.3)</td>
</tr>
<tr>
<td>J01</td>
<td>Antibacterials for systemic use</td>
<td>5.8 (5.5–6.1)</td>
<td>5.8 (5.6–5.9)</td>
<td>6.3 (5.7–6.9)</td>
<td>14.3 (14.0–14.6)</td>
</tr>
<tr>
<td>D07</td>
<td>Corticosteroid, dermatological preparations</td>
<td>4.0 (3.8–4.2)</td>
<td>1.7 (1.5–1.8)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>A02</td>
<td>Drug for acid-related disorders</td>
<td>3.2 (3.1–3.4)</td>
<td>1.4 (1.3–1.5)</td>
<td>2.5 (2.2–3.0)</td>
<td>1.6 (1.5–1.8)</td>
</tr>
<tr>
<td>R01</td>
<td>Nasal preparations</td>
<td>3.0 (2.8–3.2)</td>
<td>2.5 (2.5–2.6)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>R03</td>
<td>Drugs for obstructive airway diseases</td>
<td>3.0 (2.8–3.2)</td>
<td>1.9 (1.8–2.0)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>R06</td>
<td>Antihistamines for systemic use</td>
<td>2.7 (2.5–2.9)</td>
<td>3.2 (3.1–3.3)</td>
<td>2.0 (1.7–2.4)</td>
<td>2.0 (1.9–2.1)**</td>
</tr>
<tr>
<td>N05</td>
<td>Psycholeptics</td>
<td>2.6 (2.4–2.7)†</td>
<td>1.8 (1.7–1.8)</td>
<td>2.0 (1.7–2.5)</td>
<td>0.3 (0.3–0.4)</td>
</tr>
<tr>
<td>D01</td>
<td>Antifungals for dermatological use</td>
<td>2.3 (2.1–2.5)</td>
<td>0.8 (0.7–0.8)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>S01</td>
<td>Ophthalmologicals</td>
<td>2.4 (2.2–2.6)</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>N02</td>
<td>Analgesics</td>
<td>2.1 (1.9–2.3)</td>
<td>2.6 (2.5–2.7)†</td>
<td>3.4 (3.0–3.9)</td>
<td>1.3 (1.2–1.4)</td>
</tr>
<tr>
<td>N06</td>
<td>Psychoanaleptics</td>
<td>2.1 (1.9–2.3)</td>
<td>1.4 (1.3–1.4)‡</td>
<td>1.3 (1.0–1.6)</td>
<td>0.4 (0.4–0.5)</td>
</tr>
<tr>
<td>R05</td>
<td>Cough and cold preparations</td>
<td>1.1 (1.0–1.2)</td>
<td>1.3 (1.3–1.4)</td>
<td>1.7 (1.4–2.0)†</td>
<td>0.3 (0.3–0.4)**</td>
</tr>
<tr>
<td>D02</td>
<td>Emollients and protectives</td>
<td>1.0 (0.9–1.2)</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>A10</td>
<td>Drugs used in diabetes</td>
<td>0.8 (0.7–0.9)</td>
<td>0.6 (0.6–0.7)</td>
<td>0.5 (0.4–0.7)</td>
<td>0.6 (0.5–0.6)</td>
</tr>
</tbody>
</table>

*Six months prior conception.
†Restricted to ATC N02A, opioids.
‡Restricted to ATC N06A, antidepressants.
§Statistically significant higher than the current study.
#Current study statistically significant higher.
**Statistically significant lower than the other studies.
††Statistically significant higher than the studies of Engeland or the DK data.
ATC: Anatomical Therapeutical Chemical code; CI: Confidence interval; IADB: InterAction DataBase.
NL data: IADB.nl data.
DK data: Pharmacoepidemiological prescription database of North Jutland in Denmark.
Bibliography

Papers of special note have been highlighted as either of interest (*) or of considerable interest (**) to readers.

   * Basic knowledge, excellent overview.

   ** Created awareness on the risks of drug use.


   * Was one of the main reasons to perform our study, created our awareness.


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