General practitioners’ awareness of pregnancy: trends and association with hazardous medication use

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Title
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General practitioners’ awareness of pregnancy

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ABSTRACT

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Background
GPs have been shown to be important providers of medical care during pregnancy, however little evidence exists on their awareness of pregnancy when prescribing medication to women.

Aim
To assess GPs’ awareness of pregnancy and its association with prescribing medication with potential safety risks.

Design and Setting
Population-based study using confirmed pregnancy records linked to GP records from the PHARMO Perinatal Research Network.

Method
GPs’ awareness of pregnancy, defined as the presence of a pregnancy confirmation in the GP information system during pregnancy, was assessed from 2004 to 2020. GP prescriptions of medication with potential safety risks were selected during pregnancy and its association with GPs’ awareness of pregnancy was assessed using multivariable logistic regression.

Results
A pregnancy confirmation was present in the GP records for 48% of 140,976 selected pregnancies, increasing from 28% in 2004 to 63% in 2020. During 3% of all pregnancies, the GP prescribed highly hazardous medication with teratogenic effects that should have been (temporarily) avoided. Pregnancy was GP-confirmed for only 13% at the first occurrence of such a prescription. Comparative analyses showed that women without a pregnancy confirmation were 59% more likely to be prescribed this highly hazardous medication (OR 95%CI: 1.59 1.49-1.70) compared to those with.

Conclusion
Results of this study indicate a potential GP awareness issue at the time medication with potential safety risks is prescribed. Although pregnancy registration by GPs improved over the years, still inadequate use seems to be made of the available information systems for appropriate drug surveillance.

Keywords
Pregnancy; General practice; Inappropriate Prescribing; Awareness; Electronic Health Records
HOW THIS FITS IN

The role of Dutch general practitioners (GPs) in pregnancy care has been an item for debate for some time. GPs have been shown to be important providers of medical care during pregnancy, however little evidence exists on GPs’ awareness of pregnancy when prescribing medication to women. This study indicates a potential GP awareness issue at the time medication with potential safety risks is prescribed, placing women and their babies at avoidable risk of exposure to teratogens. Although pregnancy registration by GPs improved over the years, still inadequate use seems to be made of the available information systems for appropriate drug surveillance.
INTRODUCTION
The role of general practitioners (GPs) in pregnancy care has been an item for debate for some time in Europe.1 Although GPs act as gatekeeper to hospital- and specialist care in the Netherlands, midwives have the lead in providing pregnancy care. In case of medical or obstetric pathology, responsibility is taken over by the obstetrician.2 Currently, only 2-6% of all GPs still provide obstetric care.3 Despite their declined involvement1,4, GPs have been shown to be important providers of routine medical care for pregnant women.3 For example, they are still responsible for the large majority of drug prescriptions during pregnancy, including medication with potential safety risks in one-third of Dutch pregnancies.5,6 A substantial part of repeat prescribing by GPs occurs without any direct patient contact, thus without assessing pregnancy status or intention.7,8 This underscores the GPs’ vital role in optimisation of pregnancy care.9 Collaboration between GPs and midwives has been widely encouraged and GPs acknowledge their role in shared perinatal care.10-14

In practice, the involvement of GPs in this collaborative preconception and antenatal care needs further reinforcement, for instance by involvement in preconception care.11,12,15 Guidelines state that midwives should inform the GP about pregnancy16, however no automatic link exists between the information system of the midwife and de GP. There is little evidence on actual clinical practice in forwarding, recording and using this information.

This study aimed to fill this evidence gap, to allow for more directed future interventions targeted at preventing use of potentially harmful medication during pregnancy. Therefore, the objectives were to assess GPs’ awareness of pregnancy, the way it is registered in GP records as well as the trends over time. Furthermore, the association between GPs’ awareness and prescribing medication with potential safety risks was assessed.

METHOD
Data source
This population-based study was performed using the PHARMO Perinatal Research Network (PPRN), including linked records from the Netherlands Perinatal Registry (Perined) and the PHARMO Database Network (PHARMO).17 Perined is a nationwide registry that contains validated data from pregnancies with a gestational age of at least 16 weeks.18 PHARMO is a population-based, patient-level network of healthcare databases linking data from different health-care settings of approximately 25% of the Dutch population.19-21 For the current study two PHARMO databases linked to Perined were selected: the GP Database, comprising data from electronic patient records registered by GPs, and the Out-patient Pharmacy Database, containing detailed drug information from both GP- and specialist-prescribed dispensings. Mandatory health insurance and required registration with a GP makes the GP Database representative of the general Dutch population.22,23 The Out-patient Pharmacy Database represents the Dutch population that has picked up prescription drugs or has registered with a pharmacy and has been shown to be representative of the general Dutch population in terms of age and gender. The linkage between PHARMO and Perined has been described in more detail elsewhere (including arrangements for data oversight), but was generally based on the birth date of the mother and child and their addresses.17 For the current database research with anonymous data, no ethics committee approval was required.
Study population
Women who gave birth between 2004 and 2020 were selected from the PPRN. No exclusion criteria were applied to increase the generalisability of the results. Women's medical details needed to be registered in the selected PHARMO databases from one year before the conception date (based on ultrasound or first day of the last menstrual period) until the delivery date as recorded in Perined.

Characteristics
Characteristics included age at delivery, neighbourhood socioeconomic status (SES), year of delivery, ethnicity, preconceptional use of medication for chronic conditions (see Supplementary Table 2 for included medication), parity, gestational age, care setting at the start of pregnancy and birth weight. Furthermore, women’s healthcare utilisation in primary care was assessed in the year before conception as well as during pregnancy, defined by the number of GP visits, GP prescriptions and incoming specialist letters. The type of electronic GP information system used for keeping the maternal medical file was also assessed, as multiple different systems are available for use in GP practices with varying options for registration of patient records in different reference tables.

GPs’ awareness
The concept of GPs’ awareness of pregnancy was quantified by using all available information from the women’s electronic patient records, considering that this is the information caregivers rely on in daily practice. It was defined at multiple levels of pregnancy indicators recorded in the GP information system: 1) Pregnancy confirmation: the presence of a specific coded diagnosis on confirmed pregnancy; 2) Pregnancy indicator: the presence of any record indicating that the women is pregnant in all digitally available GP records (for example an uncoded text note about pregnancy as recorded by the GPs assistant after a telephone consultation); 3) Pregnancy contra-indication: the presence of a recorded pregnancy contra-indication in this specific GP reference table that need to be linked actively and is intended for drug surveillance (i.e. without this additional data entry no popup will appear warning about contra-indicated medication, even when there is an entry for pregnancy as a diagnostic code). The timing of pregnancy confirmation was grouped by pregnancy trimester according to the first recorded occurrence. The occurrence of GPs providing formal individual preconception care was assessed by means of a recorded preconceptional GP consultation specifically set up and coded for preconception counselling. Exact underlying definitions and GP reference tables of the defined indicators are detailed in Supplementary Table 1.

Use of hazardous medication
Use of medication with potential safety risks was determined by means of GP prescriptions recorded or continuing during the pregnancy period. Medication was grouped according to the risk classification system for drugs in pregnancy of the Dutch Teratology Information Service Lareb. These safety profiles were used to define ‘hazardous medication’ (i.e. medication with pharmacological or teratogenic effects that requires monitoring or should be (temporarily) avoided) as well as ‘highly hazardous medication’ (i.e. medication with teratogenic effects that should be (temporarily) avoided). Prescriptions with a recorded pregnancy-driven indication were excluded (e.g. progesterone used to try to reduce the risk of preterm birth). Availability of a pregnancy confirmation or pregnancy indicator was assessed at the time (highly) hazardous medication was first prescribed. For those women with a pregnancy confirmation, the proportion that used (highly) hazardous medication before and after confirmation was assessed. Sensitivity analyses were performed in which use of (highly) hazardous
medication was defined by medication fills as recorded in the Out-patient Pharmacy Database, which includes both GP- and specialist-prescribed dispensings. Also, we performed separate analyses per categorised year of delivery (2004-2009, 2010-2014, 2015-2020).

**Statistical analysis**

All analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). Logistic regression models were used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) to estimate unadjusted associations between characteristics and pregnancy confirmation. Trends over time for defined GP-recorded pregnancy indicators were tested by Poisson regression \( (P < 0.05) \). The association between GP-recorded pregnancy indicators and use of hazardous medication was assessed by means of logistic regression analyses, providing ORs and 95% CIs adjusted for age, GP information system and all other characteristics that remained significant using backward selection \( (P < 0.05) \). Similarly, adjusted logistical models were created to assess the association between pregnancy confirmation and the drug-level use of highly hazardous medication.

**RESULTS**

**Study population and characteristics**

A total of 140,976 pregnancies among 96,182 women were selected from the PPRN between 2004 and 2020. During 48% of these pregnancies a pregnancy confirmation was identified in the GP records, indicating GPs’ (potential) awareness of pregnancy. Characteristics of included pregnancies are summarised in Table 1 and stratified by pregnancy confirmation. Particularly SES, year of delivery, ethnicity, preconceptional use of medication for chronic conditions, gestational age and women’s healthcare utilisation in primary care were associated with GP’s being aware of pregnancy. A total of seven different electronic systems were used in the included GP practices. The type of GP information system showed to be significantly associated with GPs’ awareness (data not presented).

**GPs’ awareness**

Figure 1 presents the GP-recorded pregnancy indicators reflecting GPs’ awareness of pregnancy over time. A strong increase was observed for the proportion of pregnancies with confirmation from 28% in 2004 to 63% in 2020 (48% overall). About 80% of these pregnancy confirmations happened first during the first trimester, then about 15% during the second and the remaining 5% in the third trimester. Using all available GP records (i.e. coded as well as based on search terms occurring in free text) as a pregnancy indicator, this proportion was 70% and increased from 50% in 2004 to 77% in 2020. Even though recording pregnancy as a contra-indication clearly increased during the second half of the study period, such a registration was observed for only 13% of pregnancies. Overall, only 1% of pregnancies was preceded by a GP consultation specifically set up and coded for preconception counselling.

**Use of hazardous medication**

During 22% (31,523 out of 140,976) of included pregnancies GPs prescribed hazardous medication. At the point in which such hazardous medication was prescribed for the first time, pregnancy was confirmed in the GP records for only 29% \( (N = 9,265) \). Any indicator was recorded for less than half of the women prescribed hazardous medication \( (N = 14,212; 45\%) \). For highly hazardous medication, which was prescribed in about 3% \( (N = 4,489) \) of pregnancies, these proportions were even lower: pregnancy was confirmed for only 13% and any indicator was available for 26%. Comparing GP
prescriptions of highly hazardous medication during pregnancy before and after pregnancy confirmation, only 11% of the women with such a prescription before confirmation also has such a prescription after confirmation.

GPs’ awareness and hazardous medication
Figure 2 shows the likelihood of (highly) hazardous medication being prescribed during pregnancy by the defined pregnancy indicators. Women without a pregnancy confirmation were 25% more likely to be prescribed hazardous medication during pregnancy compared to those with confirmation, with an adjusted OR of 1.25 (95% CI 1.21-1.29). No significant association between pregnancy confirmation and prescribed hazardous medication was found if confirmation occurred for the first time during the second (OR 95%CI: 1.01 0.96-1.07) or third (OR 95%CI: 1.04 0.94-1.14) trimester. For highly hazardous medication, the absence of a pregnancy confirmation was associated with a 59% higher odds of prescribing highly hazardous medication (OR 95%CI: 1.59 1.49-1.70). The absence of a recorded contra-indication for pregnancy significantly increased the prescription of hazardous medication (OR 95%CI: 1.12 1.07-1.18), particularly for highly hazardous medication including drugs actually contra-indicated during pregnancy (OR 95%CI: 1.41 1.26-1.59).

Taking a closer look at the type of medication, Figure 3 presents the highly hazardous medication that was significantly more often prescribed by GPs unaware of pregnancy compared to those aware. Absolute numbers per drug were generally below 10 per 10,000 pregnancies, however the top 3 relative differences were: isotretinoin (used to treat severe acne) which was prescribed about 30 times more often by GPs not aware of pregnancy, followed by methotrexate (used to treat inflammatory conditions and certain types of cancer) and mycophenolic acid (used to treat autoimmune conditions and to prevent organ rejection after transplant). In terms of absolute prescription rates, the top 3 consisted of doxycycline (used for bacterial infections such as acne), followed by misoprostol (used to prevent stomach ulcers, but also to induce abortion) and norethisterone (used for various menstrual problems).

Sensitivity analyses using medication dispensed in the pharmacy and by categorised year of delivery provided similar results for the analyses on GPs’ awareness and hazardous medication (Supplementary Figure 1 and 2).

DISCUSSION
Summary
Among 140,976 selected pregnancies, for only 48% a pregnancy confirmation was recorded in the GP records, indicating GPs’ (potential) awareness of pregnancy. A statistically significant increase was observed from 28% in 2004 to 63% in 2020. The large majority (80%) of these confirmations happened during the first trimester. In about 3% of all included pregnancies, the GP prescribed highly hazardous medication with teratogenic effects that should have (temporarily) been avoided, with pregnancy being GP-confirmed for only 13% at the first occurrence of such a prescription. Eleven percent of cases with a highly hazardous prescription before pregnancy confirmation repeated this prescription after the confirmation. Comparative analyses showed that women without a GP-recorded pregnancy confirmation were 59% more likely to be prescribed this highly hazardous medication. Even though this study demonstrated that the absence of a recorded pregnancy contra-indication in the GP system for automatic drug surveillance significantly increased the odds of prescribing highly hazardous
medication with 41%, such an active link was created in only 13% of pregnancies (increasing from 0% to 22% during the study period). When using all available coded and uncoded electronic records from the GP information system, a pregnancy indicator was available for 70% of pregnancies. Still, in 2020, 23% of the pregnancies were not registered in the GP information system. Only 1% had a GP consultation specifically set up for preconception counselling recorded in the 12 months preceding pregnancy.

Strengths and limitations
A major strength of this study was the use of over 15 years of routinely collected data from a unique and large population-based linked cohort, shown to be representative of the Dutch population. The timing of registered records relative to pregnancy could be accurately assessed based on information from the different databases. This study thereby provides a unique, contemporary perspective on GP involvement in pregnancy in real-world clinical practice. There are, however, several limitations. The qualitative concept of GPs’ awareness was quantified by using available electronic patient records from the women’s medical file, however should be regarded as ‘potential’ awareness. GPs may have been aware of pregnancy, but did not record this due to a variety of reasons (e.g. time constraints, deemed redundant, system difficulties or because no letter was even received from the midwife). It has been acknowledged, however, that GPs rely on the information registered in their systems for providing accurate patient care, for example in case of transfers to other caregivers. A common challenge in using administrative data is defining drug exposure or compliance. Prescription records can only approximate actual exposure and, particularly during pregnancy, prescriptions may not be filled or drugs may be discontinued. Although use of hazardous medication could therefore have been overestimated, it is not expected to have altered the conclusions in relation to GPs’ awareness, since sensitivity analyses using medication that was dispensed in the pharmacy provided similar results. Underestimated drug exposure is likely because specialist-prescribed and over-the-counter drugs were not included, however the intended focus of the current paper was on GPs’ prescription practices. Confounding by indication could not be ruled out in the definition of hazardous medication. Although we specifically excluded pregnancy-driven prescriptions where possible, some of the hazardous medication may still have been prescribed because of pregnancy. For example, as observed in the drug-level assessment, misoprostol may have been prescribed to induce abortion. However, since prescribing for these reasons would normally occur in secondary care, they are assumed to be prescribed for other indications in most of the cases. Unfortunately, data on the indication of use was only available for a small proportion of prescriptions. Absolute rates presented as part of the drug-level assessment should therefore be interpreted with caution and conclusions can be drawn from relative comparisons by GPs’ awareness status.

Comparison with existing literature
The study contributes valuable new evidence to the role of GPs in daily clinical practice during pregnancy. Although existing literature on the outcomes of interest is scarce, one previous Dutch study reported a recorded diagnosis for pregnancy in the GP records for 41% of births in 2007-2009, which is very similar to what we observed. Taking into account slight differences in study period and design, the findings of prescribed (highly) hazardous medication were in agreement with previous studies. To the authors’ knowledge, this is the first study to assess the association between GPs’ awareness of pregnancy and prescribing hazardous medication. Although no comparison information is available on the registration of pregnancy as a contra-indication in the GP information system, efforts have been
made to measure the quality of GP registrations by defining a set of quality indicators, such as the proportion with a recorded contra-indication. This was reported to vary among GP practices and thus they were instructed to critically review their daily habits for registering contra-indications. More generally, maintaining medical records has been acknowledged as a fundamental part of a doctor’s duties in providing patient care and despite this importance, it is often given low priority. Similar to this study, many other previous studies have concluded that delivery of preconception care is inadequate. A Dutch survey conducted among GPs and midwives reported that only 0.7% of GPs systematically invited patients for a formal preconception care consultation. Although this is similar to the 1% that we observed, 20% of those GPs indicated that they performed preconception care in a standardised manner, which is probably not captured by the strict definitions used for a preconceptional GP consultation in the current study. For example, it is likely that the GP may counsel women preconceptionally as part of a consultation (coded) for something else, e.g. the underlying condition. Although Dutch guidelines have clearly advocated standardised preconception care for some time, collaboration between GPs and other caregivers is advised. There seems to be a shift towards a more public, programmatical approach incorporated in the provided daily care that may explain the low occurrence of systematic preconceptional GP consultations observed in the current study. In comparison to other countries with similar health care systems, among which the United Kingdom, similar conclusions have been drawn on the need for shared, multidisciplinary pregnancy-related care programs in which preconception care should be offered.

Implications for research and/or practice
The finding that women without a GP-recorded pregnancy confirmation were significantly more likely to be prescribed hazardous medication indicates a potential awareness issue at the time these drugs are prescribed, placing women and their babies at avoidable risk of exposure to teratogens. Although pregnancy registration by GPs improved over the years, still inadequate use seems to be made of the available information systems for appropriate drug surveillance. The key challenge for improved registration lies with the shared responsibility, in which collaborative care is pivotal. The authors pose three main implications based on the study findings in combination with the existing evidence. First, caregivers should be supported and educated in maintaining accurate and readily available patient records for effective communication and information transfer to other involved caregivers. Specifically in pregnancy, this requires continuity of care by documenting medical records on a daily basis to prevent use of harmful medication due to delayed or incomplete record keeping. To achieve this, the second implication relates to the electronic information systems used to maintain records. There should be clear and standardised procedures for recording and communicating information so that healthcare providers know what is expected. The differences in GPs’ awareness observed between GP information systems suggest the need for further standardisation of systems. The increased availability of pregnancy indicators when using all available records from the GP information system implies difficulties in choosing the appropriate GP reference tables for registering pregnancy, obstructing GPs’ awareness. Further simplification would be helpful, for example by automatically establishing an active contra-indication in that specific GP reference table in case of pregnancy confirmation, blocking the prescription of certain high risk drugs and avoiding alert fatigue among caregivers. A financial impulse was provided by the Dutch government in 2012 and 2013 for improvement of coded registration in GP practices, which is also reflected in the increased coded pregnancy indicators in the second half of the study period. During the study period, also the conversion of GP records from handwritten to computerised took place. Third, public awareness about the potential risks of medication used during
pregnancy should be improved by means of population-wide education incorporating collaborative preconception care. In addition to caregivers acknowledging their duty here, this would ultimately increase women’s self-awareness recognising their own responsibility in timely informing caregivers about (planned or unplanned) pregnancy, so that appropriate action can be taken. When prescribing hazardous medication, raised awareness would make prescribers more actively inquire about pregnancy, even in case of repeat prescriptions. Interventions should be set up in such a way that women are informed about the potential pregnancy risks of the medicines they use as early as possible, so that the patient is alert if she considers to conceive. Whether interventions have the intended positive effects should be evaluated according to predefined targets. Pregnancy prevention programs for highly hazardous drugs should be continuously evaluated and set up as needed. Future qualitative research among GPs, midwives and pharmacists would be very useful to further estimate the scale of the posed awareness issue and associated aspects, such as the women’s lack of awareness of pregnancy, shortcomings of information systems and the barriers perceived in collaborative care.
### Table 1: Maternal and obstetric characteristics of included pregnancies, stratified by presence of a GP-recorded pregnancy confirmation

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Study cohort</th>
<th>GP-recorded pregnancy confirmation</th>
<th>No GP-recorded pregnancy confirmation</th>
<th>OR (95% CI) With vs. without GP-recorded pregnancy confirmation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 140,976</td>
<td>N = 67,496 (48%)</td>
<td>N = 73,480 (52%)</td>
<td></td>
</tr>
<tr>
<td><strong>Age at delivery (years)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤20</td>
<td>1,532 (1)</td>
<td>526 (1)</td>
<td>1,006 (1)</td>
<td>0.57 (0.51-0.64)</td>
</tr>
<tr>
<td>21-30</td>
<td>59,350 (42)</td>
<td>28,343 (42)</td>
<td>31,007 (42)</td>
<td>1 (reference)</td>
</tr>
<tr>
<td>31-40</td>
<td>76,629 (54)</td>
<td>37,043 (55)</td>
<td>39,586 (54)</td>
<td>1.02 (1.00-1.05)</td>
</tr>
<tr>
<td>≥41</td>
<td>3,465 (2)</td>
<td>1,584 (2)</td>
<td>1,881 (3)</td>
<td>0.92 (0.86-0.99)</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>31 ± 5</td>
<td>31 ± 4</td>
<td>31 ± 5</td>
<td>1.03 (1.02-1.04)</td>
</tr>
<tr>
<td><strong>SES</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>38,618 (27)</td>
<td>17,183 (25)</td>
<td>21,435 (29)</td>
<td>0.78 (0.76-0.80)</td>
</tr>
<tr>
<td>Normal</td>
<td>52,758 (37)</td>
<td>26,734 (40)</td>
<td>26,024 (35)</td>
<td>1 (reference)</td>
</tr>
<tr>
<td>High</td>
<td>49,210 (35)</td>
<td>23,449 (35)</td>
<td>25,761 (35)</td>
<td>0.89 (0.86-0.91)</td>
</tr>
<tr>
<td>Unknown</td>
<td>390 (&lt;0.5)</td>
<td>130 (&lt;0.5)</td>
<td>260 (&lt;0.5)</td>
<td>-</td>
</tr>
<tr>
<td><strong>Year of delivery</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2004-2009</td>
<td>19,005 (13)</td>
<td>6,606 (10)</td>
<td>12,399 (17)</td>
<td>1 (reference)</td>
</tr>
<tr>
<td>2010-2015</td>
<td>63,351 (45)</td>
<td>27,558 (41)</td>
<td>35,793 (49)</td>
<td>1.45 (1.40-1.49)</td>
</tr>
<tr>
<td>2016-2020</td>
<td>58,620 (42)</td>
<td>33,332 (49)</td>
<td>25,288 (34)</td>
<td>2.47 (2.39-2.56)</td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>122,630 (87)</td>
<td>59,233 (88)</td>
<td>63,397 (86)</td>
<td>1 (reference)</td>
</tr>
<tr>
<td>Non-caucasian</td>
<td>16,733 (12)</td>
<td>7,534 (11)</td>
<td>9,199 (13)</td>
<td>0.88 (0.85-0.91)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1,613 (1)</td>
<td>729 (1)</td>
<td>884 (1)</td>
<td>-</td>
</tr>
<tr>
<td><strong>Preconceptional use of medication for chronic conditions</strong></td>
<td>46,825 (33)</td>
<td>23,816 (35)</td>
<td>23,009 (31)</td>
<td>1.20 (1.17-1.22)</td>
</tr>
<tr>
<td><strong>Parity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>58,771 (42)</td>
<td>28,333 (42)</td>
<td>30,438 (41)</td>
<td>1 (reference)</td>
</tr>
<tr>
<td>1</td>
<td>54,431 (39)</td>
<td>25,850 (38)</td>
<td>28,581 (39)</td>
<td>0.97 (0.95-0.99)</td>
</tr>
<tr>
<td>2</td>
<td>19,543 (14)</td>
<td>9,368 (14)</td>
<td>10,175 (14)</td>
<td>0.99 (0.96-1.02)</td>
</tr>
<tr>
<td>≥3</td>
<td>7,731 (5)</td>
<td>3,736 (6)</td>
<td>3,995 (5)</td>
<td>1.00 (0.96-1.05)</td>
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<tr>
<td>Unknown</td>
<td>500 (&lt;0.5)</td>
<td>209 (&lt;0.5)</td>
<td>291 (&lt;0.5)</td>
<td>-</td>
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<tr>
<td><strong>Gestational age (weeks)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>≤24</td>
<td>10,064 (7)</td>
<td>2,854 (4)</td>
<td>7,210 (10)</td>
<td>0.40 (0.39-0.42)</td>
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<tr>
<td>25-&lt;28</td>
<td>352 (&lt;0.5)</td>
<td>172 (&lt;0.5)</td>
<td>180 (&lt;0.5)</td>
<td>0.97 (0.79-1.20)</td>
</tr>
<tr>
<td>28-&lt;33</td>
<td>1,480 (1)</td>
<td>693 (1)</td>
<td>787 (1)</td>
<td>0.90 (0.81-0.99)</td>
</tr>
<tr>
<td>33-&lt;37</td>
<td>7,765 (6)</td>
<td>3,689 (5)</td>
<td>4,076 (6)</td>
<td>0.92 (0.88-0.97)</td>
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<td>≥37</td>
<td>121,315 (86)</td>
<td>60,088 (89)</td>
<td>61,227 (83)</td>
<td>1 (reference)</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>38.0 ± 5.3</td>
<td>38.5 ± 4.3</td>
<td>37.5 ± 6.0</td>
<td>1.22 (1.21-1.23)</td>
</tr>
</tbody>
</table>

*Note: OR = Odds Ratio, CI = Confidence Interval.
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Study cohort</th>
<th>GP-recorded pregnancy confirmation</th>
<th>No GP-recorded pregnancy confirmation</th>
<th>OR (95% CI) With vs. without GP-recorded pregnancy confirmation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 140,976</td>
<td>N = 67,496 (48%)</td>
<td>N = 73,480 (52%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td>Care setting at start pregnancy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary care</td>
<td>120,592 (86)</td>
<td>57,685 (85)</td>
<td>62,907 (86)</td>
<td>1 (reference)</td>
</tr>
<tr>
<td>Secondary care</td>
<td>20,109 (14)</td>
<td>9,694 (14)</td>
<td>10,415 (14)</td>
<td>1.02 (0.99-1.05)</td>
</tr>
<tr>
<td>Unknown</td>
<td>275 (&lt;0.5)</td>
<td>117 (&lt;0.5)</td>
<td>158 (&lt;0.5)</td>
<td>-</td>
</tr>
<tr>
<td>Birth weight (grams)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>3,384 ± 653</td>
<td>3,392 ± 641</td>
<td>3,377 ± 665</td>
<td>1.02 (1.01-1.03)*</td>
</tr>
<tr>
<td>Healthcare utilisation in primary care</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year before conception (mean ± SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of GP visits</td>
<td>1.2 ± 2.4</td>
<td>1.4 ± 2.5</td>
<td>1.0 ± 2.2</td>
<td>1.09 (1.08-1.09)</td>
</tr>
<tr>
<td>Number of GP prescriptions</td>
<td>3.9 ± 4.7</td>
<td>4.2 ± 4.8</td>
<td>3.7 ± 4.7</td>
<td>1.02 (1.02-1.02)</td>
</tr>
<tr>
<td>Number of incoming specialist letters</td>
<td>1.7 ± 2.2</td>
<td>1.8 ± 2.3</td>
<td>1.5 ± 2.1</td>
<td>1.07 (1.07-1.08)</td>
</tr>
<tr>
<td>During pregnancy (mean ± SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of GP visits</td>
<td>1.0 ± 1.9</td>
<td>1.3 ± 2.1</td>
<td>0.8 ± 1.7</td>
<td>1.17 (1.16-1.18)</td>
</tr>
<tr>
<td>Number of GP prescriptions</td>
<td>2.8 ± 3.7</td>
<td>3.1 ± 3.7</td>
<td>2.5 ± 3.6</td>
<td>1.05 (1.04-1.05)</td>
</tr>
<tr>
<td>Number of incoming specialist letters</td>
<td>1.8 ± 2.1</td>
<td>2.3 ± 2.2</td>
<td>1.4 ± 1.9</td>
<td>1.23 (1.23-1.24)</td>
</tr>
</tbody>
</table>

CI = confidence interval; OR = odds ratio; SD = standard deviation; SES = neighbourhood socioeconomic status; *Based on both GP- and specialist-prescribed medication dispensed in the out-patient pharmacy in the year before conception (see Supplementary Table 2 for included medication); †OR for 5 weeks change; ‡OR for 500 grams change.
Figure 1 Selected GP-recorded pregnancy indicators reflecting GPs’ awareness of pregnancy over time
Hazardous medication

Pregnancy confirmation

Pregnancy confirmation during 1st trimester

Pregnancy confirmation during 2nd* trimester

Pregnancy confirmation during 3rd* trimester

Pregnancy indicator

Pregnancy contra-indication

Preconceptional GP consultation

Highly hazardous medication

Pregnancy confirmation

Pregnancy indicator

Pregnancy contra-indication

Preconceptional GP consultation

*First recorded, i.e. without recorded pregnancy confirmation in the prior trimester(s)

**Figure 2** Likelihood of (highly) hazardous medication being prescribed during pregnancy by selected GP-recorded pregnancy indicators reflecting GPs’ awareness
Figure 3 GP prescriptions of highly hazardous medication during pregnancy, stratified by presence of a GP-recorded pregnancy confirmation.
ADDITIONAL INFORMATION

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Ethical approval
For the current database research with anonymous data, no ethical approval was required.

Competing interests
None of the authors has any conflict of interest to disclose.

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