The limitations of some European healthcare databases for monitoring the effectiveness of Pregnancy Prevention Programmes as risk minimisation measures.

Concise title – Healthcare data to evaluate pregnancy prevention programmes


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Abstract

Purpose
Pregnancy prevention programmes (PPPs) exist for some medicines known to be highly teratogenic. It is increasingly recognised that the impact of these risk minimisation measures require periodic evaluation. This study aimed to assess the extent to which some of the data needed to monitor the effectiveness of PPPs may be present in European healthcare databases.

Methods
An inventory was completed for databases contributing to EUROmediCAT capturing pregnancy and prescription data in Denmark, Norway, the Netherlands, Italy (Tuscany/Emilia Romagna), Wales and the rest of the UK, to determine the extent of data collected that could be used to evaluate the impact of PPPs.

Results
Data availability varied between databases. All databases could be used to identify the frequency and duration of prescriptions to women of childbearing age from primary care, but there were specific issues with availability of data from secondary care and private care. To estimate the frequency of exposed pregnancies, all databases could be linked to pregnancy data, but the accuracy of timing of the start of pregnancy was variable, and data on pregnancies ending in induced abortions often not available. Data availability on contraception to estimate compliance with contraception requirements was variable and no data were available on pregnancy tests.

Conclusion
Current electronic healthcare databases do not contain all the data necessary to fully monitor the effectiveness of PPP implementation, and thus special data collection measures need to be instituted.
1.0 Introduction

Risk minimisation measures aim to reduce the occurrence or severity of adverse drug reactions and improve the benefit-risk profile.\[1\] These measures range from routine requirements such as providing a patient information leaflet and summary of product characteristics, to special education programmes or controlled access programmes.\[2, 3\] Increasingly, the need to monitor the effectiveness or impact of risk minimisation measures in limiting adverse drug reactions is being discussed at a European level.\[2, 3\]

Pregnancy prevention programmes (PPPs) are special risk minimisation measures, implemented when there is sufficient evidence to demonstrate that a product is highly teratogenic when used during pregnancy.\[4-6\] PPPs aim to allow women of childbearing potential to use these highly teratogenic products, when alternative treatments have failed, whilst ensuring they are not pregnant when they start treatment and do not become pregnant during treatment and within an appropriate time period after stopping treatment.\[7\] The precise components of PPPs vary depending on the product but commonly include: a requirement that the medicine should not be used as first line treatment, a requirement for women of childbearing potential to undergo pregnancy testing at specific time intervals before, during and following treatment, a requirement for the use of two methods of contraception, restrictions on the quantity of a product that can be issued in a single prescription, limits on the time-window that a prescription can be dispensed following the date of issue, and education material for the patient, prescriber and pharmacist.\[8, 9\] Products with a PPP include probably the best known of all teratogenic medicines, thalidomide, as well as more commonly used medicines, such as the dermatological acne medicines acitretin and isotretinoin.\[10\] Despite the implementation of PPPs, there is still evidence of women becoming pregnant whilst on treatment and of non-compliance.\[11-13\] However, monitoring of the effectiveness of PPPs remains ad hoc.

We aim here to assess the extent to which some of the data needed to monitor the effectiveness of PPPs may be present in some European electronic healthcare databases; focusing specifically on the ability to monitor the frequency of prescribing to women of
childbearing age, compliance with PPP requirements concerning pregnancy testing and contraception, and the ability to identify exposed pregnancies and their outcomes.
2.0 Methods

An inventory was completed for a sample of European databases that were contributing to the EUROmediCAT study,\[^{14}\] a Seventh Framework Programme study funded by the European Union that aimed to make more systematic use of electronic healthcare databases in combination with EUROCAT\[^{15}\] congenital anomalies data. The databases covered Denmark,\[^{16-18}\] the Northern Netherlands,\[^{19, 20}\] Norway,\[^{21-23}\] two regions of Italy (Tuscany\[^{24, 25}\] and Emilia Romagna\[^{26}\]), Wales\[^{27, 28}\] and the Clinical Practice Research Datalink (CPRD)\[^{29, 30}\] capturing a sample of the rest of the UK. A summary of the databases can be found in Table 1 and has been reported elsewhere.\[^{14}\] For each database, the inventory requested information on the population covered and the source of the information captured, the extent and availability of prescription data, data relating to contraception and pregnancy, patient characteristics and pregnancy outcomes. The inventory was completed based on the data available within the databases between 2004 and 2012. For the EUROmediCAT study, the Danish databases were restricted to women who had a pregnancy during the study period, but data on all individuals are available subject to data access approvals and charges and this paper therefore reports on the full Danish databases.
3.0 Results

The seven databases were all population-based and captured data from either an entire country/region or a sample of a country’s population (Table 1). For the remainder of this paper, for ease of reading, the databases will be referred to by the country or region they cover.

3.1 Data to allow estimation of frequency of prescriptions to women of childbearing age and duration of treatment.

All databases had data to allow identification of the timing of prescriptions issued (Wales/rest of the UK) or dispensed (Denmark, Italy, Norway and the Netherlands). However, there were limited data on private prescriptions and prescriptions issued in secondary care (Table 2), and secondary care prescriptions may be particularly important for medications with a PPP where prescribers are often restricted to specialists. The duration of prescriptions could be estimated based on defined daily dose (DDD) data in the Italian and Norwegian databases, whilst in the UK, data was available on the prescribed daily dose (PDD) and in the Netherlands on the number of days prescribed (Table 2). The nature of DDD data means that it may not correspond directly to actual daily intake resulting in the estimates of prescription duration being less accurate than those with data on prescribed daily dose.

In the UK, prescriptions issued by a specialist in secondary care were only likely to be captured if the GP chose to enter the information into the patient’s computer record following receipt of a letter from the specialist. For many products the specialist will initiate the prescribing and all subsequent prescribing will be carried out by the GP, however, for some products with a PPP such as isotretinoin, the PPP may state that all prescribing should only be carried out by a consultant-led team and issued from a hospital-based pharmacy.\[31, 32\]

In non-UK databases, prescribing data were based on prescriptions actually dispensed by a pharmacist. In Denmark, Norway and the Netherlands, all prescriptions with the exception of those issued to in-patients during a hospital stay were captured. In the Italian regions,
only prescriptions reimbursed by the Italian National Health Service were captured, this also
excluded private prescriptions and those issued during an in-patient hospital stay. In Emilia
Romagna, secondary care prescriptions and those dispensed at a hospital pharmacy for
home use have been captured at an individual patient level from 2009, and are considered
to be reliable from 2011.

No data on the indication for prescribing were available in the Italian or Dutch databases. In
Norway, up until March 2008, only broad categories relating to indication were available
before the introduction of more granular International Classification of Diseases (ICD) codes.
Indication for prescribing was available in some cases in the UK and Wales databases while
in Denmark, the Italian regions and also Wales this could sometimes be inferred from
hospital discharge diagnoses or diagnostic codes (usually ICD 10 codes) relating to hospital
out-clinic patient appointments.

3.2 Data to allow identification of exposed pregnancies and pregnancy outcome
Identification of exposed pregnancies usually requires linkage of data on pregnancies to
data on prescriptions, except in the UK where primary care databases may contain all the
relevant information (Table 2).

All databases captured pregnancies that ended in a live delivery and all databases except
the Netherlands captured data on stillbirths. Databases that could combine information on
prescribing and the approximate start date of a pregnancy would therefore be able to
identify a breakthrough pregnancy during treatment that ended in a live delivery (Table 3).
The accuracy by which the timing of exposure could be determined was dependent on the
information available on the start date of the pregnancy and this varied between databases:
in the Norwegian and Wales databases the date of the first day of the last menstrual period
was captured, in the Italian and Danish databases the pregnancy start date could be
extrapolated from information on gestational age at delivery, in the CPRD, information on
the last menstrual period was captured for ~40% and for the reminder an algorithm could
be used to estimate the start date based on other records, including those relating to
gestational age and estimated date of delivery, in the Netherlands no information was
available and all pregnancies are assigned a default duration of 280 days.
Estimation of timing of exposure in relation to pregnancy is also dependent on the data on the timing of medication intake (see 3.1) and neither date issued nor date dispensed necessarily accurately reflects the time the prescription was self-administered, or whether it was definitely taken at all.

Given the known teratogenic potential of products with a PPP, some women may decide to undergo a termination of pregnancy when they discover they have been unintentionally exposed during their pregnancy.\textsuperscript{[33]} Databases that do not capture induced terminations are therefore likely to underestimate the incidence of breakthrough pregnancies among women using products with a PPP. Data on pregnancies that ended in an induced termination or spontaneous abortion were captured and available in the CPRD and Danish databases but in the other databases this information was either not captured or restricted. In the Emilia Romagna database there was no information on spontaneous abortions and it was not possible to link induced terminations to prescription data. In Tuscany, it was possible to link prescription data to records of pregnancies that ended in a termination, for any reason, provided the woman did not deny consent during her hospital stay. Less than 1\% of terminations had a record of denied consent but only 55\% of induced terminations and 44\% of spontaneous abortions could be linked to the health discharge record and therefore had the potential to be linked to the prescription registry. In Wales, the data on induced terminations and spontaneous abortions at <24 weeks gestation are considered by the NHS Wales Informatics Service to be too sensitive to be used for research, and thus are not available in primary and secondary care records. In the Norwegian database, spontaneous abortions were captured from 12 gestational weeks (although these data are more reliable from 16 weeks) and induced terminations were captured only if they followed the diagnosis of a congenital anomaly.

All databases (except the CPRD in the UK) could link to EUROCAT congenital anomaly registers to identify diagnosed congenital anomalies\textsuperscript{[34]} (including livebirths, stillbirths and terminations of pregnancy for fetal anomaly), although in Denmark only a region capturing ~8\% of the population can be linked. In the CPRD, congenital anomalies may be recorded by the GP in the coded data and for pregnancies ending in a live birth it is possible to identify
these by linking the mother’s medical record to the medical record of the child;[30] the level of detail on the congenital anomaly, however, may not be as accurate/exhaustive or complete as that of the congenital anomaly registries. For pregnancies ending in an induced termination, identification of congenital anomalies is more difficult in the CPRD; an algorithm can be developed to identify pregnancy losses that appear to have ended in a termination for medical reasons but determining the precise reason and exact congenital anomaly is often not possible, especially now access to the anonymised free text comments is no longer available.

3.3. Data to allow evaluation of compliance with PPP provisions on pregnancy tests and contraception among women of childbearing age/women with exposed pregnancies.

No data were available on contraception within the Italian databases, as contraception is not reimbursed by the Italian National Health Service (Table 2). No databases provided data on barrier contraceptives, including condoms; although this will result in an underestimation of contraceptive use, a PPP usually recommends that the main form of contraception should be hormonal and will not sanction the use of only one barrier method. As a result you would expect to still capture women receiving other non-barrier methods of contraception. In all regions, other than Italy, data were available on the issue/prescribing of oral hormonal contraceptives, intrauterine devices, contraceptive implants and depot contraceptives. In Norway, data on intrauterine devices without hormones (e.g. ordinary copper devices) were not captured within the prescription database. In Wales and the rest of the UK, in normal circumstances, women have the option of going to family planning clinics for their contraception so not all contraceptives will be recorded in the databases. It is possible, however, that visiting a family planning clinic may be less likely for women who are under a PPP. When evaluating longer-lasting contraception methods, such as intrauterine devices which are effective for up to five years, not all women will have sufficient follow-up in the databases to determine whether they had received this method of contraception in the years prior to receipt of the PPP related prescription. Data on whether a woman did not require contraceptives because she had undergone a hysterectomy, oophorectomy, sterilisation or her husband/partner had undergone a vasectomy were more likely to be
captured in the databases in Denmark, Norway (from 2008), Wales and the rest of the United Kingdom than the other regions. In addition, none of the databases collected information on sexual activity and whether women were actually ‘at risk’ of becoming pregnant.

Data on whether a woman had undergone a supervised pregnancy test, as required by a PPP, was not routinely captured in any of the data sources.

3.4. Data to allow evaluation of factors that may influence compliance to PPPs to inform a more targeted approach to improve PPP compliance.

The age of a woman at time of prescription was available in all databases which would also allow age specific rates of exposure to be calculated (Online supplement Table S1). All databases captured an indicator of socioeconomic status and co-prescribing, with several of the databases also containing information on comorbidities. Data on lifestyle factors, such as smoking status, alcohol and body mass index were largely available in the UK/Wales databases but were absent from many of the other databases. In Norway and Denmark, data on smoking status were only available for pregnant women and not all women of childbearing age as this was captured within the Medical Birth Registry, but not the Patient Registry.
Discussion

This study opportunistically accessed seven European population-based electronic healthcare databases, to assess their strengths and limitations for routine monitoring of the effectiveness of PPPs. The study found a number of limitations in terms of absence of data on; prescriptions from secondary care, which are particularly relevant for products with a PPP; data on and induced terminations and spontaneous abortions; compliance with contraception and pregnancy testing requirements; information on the indication for prescription to assess appropriateness of use, plus difficulties determining the exact timing of exposure during or before pregnancy. It was found that no single database or system of linked databases contained all the relevant data, but individual countries/databases could assess some specific aspects of PPP implementation.

In terms of the strengths of these data sources, the population-based nature provides a denominator population which allows the prevalence of prescribing to women of childbearing age to be calculated and thus the numbers of women “at risk”, whilst the longitudinal nature provides the ability to evaluate trends over time. The prescription data are recorded independently by the prescriber or dispensing pharmacist, preventing recall bias and it is possible to determine duration of treatment. No data, however, are available on whether the product was actually taken or the date when taken. Depending on the nature of prescribing of the product under evaluation, some data sources may be more useful given their ability to capture data on prescribing in both primary and secondary care; however in these databases, data were typically less likely to be available on contraceptive prescribing, indication for prescribing and user characteristics, than those capturing data from primary care alone. In the databases limited to primary care prescribing, there will be some situations where women receive prescriptions from their GP that are normally issued in secondary care or where they have them entered into their electronic medical record following issue by a specialist; however, there is a question surrounding whether this sample of women will be a fully representative subgroup of the population of all female users.
Our study did not look at the ability to determine the appropriateness of prescribing as a major element of risk minimisation. For products such as isotretinoin, future work could investigate whether it is possible to determine whether women are appropriately prescribed the product as a second-line therapy and whether records of previous prescribing of first-line therapies is evident.

For a full evaluation of PPP effectiveness, other elements may also be needed that are not captured within electronic healthcare data, for example information on sexual activity, healthcare professional or patient knowledge of teratogenic risk and PPP requirements, and the different factors women may consider when deciding whether or not to accept the risks associated with the product. Qualitative studies, including focus groups, questionnaires and interviews, can provide a useful means of obtaining information to help understand the difficulties clinicians and patients encounter in implementing PPPs and the way the risk-benefit ratio is perceived and assessed. In addition, a recent EUROmediCAT study has highlighted the potential to purchase isotretinoin, one of the medicines requiring a PPP, from the internet bypassing a PPP altogether.\(^35\) None of the databases included in this study would capture prescriptions purchased over the internet.

To date, many of the studies reporting on the effectiveness of a PPP in Europe have focussed on isotretinoin and have used data collected via surveys/questionnaires,\(^{36-38}\) a medical birth register\(^{39}\) or one of the European Network of Teratology Information Services (ENTIS)\(^{33,40}\). These methods of data collection have the benefit of being able to obtain information directly from the patient or her prescriber that is not readily available or reliably recorded in electronic healthcare databases. However, for studies based on voluntary participation, it is not possible to calculate the prevalence of prescribing and there is always the possibility that women who opt to take part in the research are not a representative sample of the entire population of interest. Two studies, both based in the Netherlands, have used data from electronic healthcare databases to evaluate the effectiveness of a PPP in terms of contraceptive use.\(^{41,42}\) These studies evaluated isotretinoin using data from pharmacy prescription databases and both studies found evidence of non-compliance with fewer than 60% of women filling prescriptions for contraception. Another study in the Netherlands, also using electronic healthcare data, looked at isotretinoin exposure during
pregnancy and found that exposed pregnancies do still occur despite the PPP.\cite{43} A French study has evaluated compliance with the acitretin PPP using data from the French national insurance database (SNIIRAM) and the hospital discharge database. This study focused on pregnancy testing and pregnancy occurrence and using data on reimbursed serum βHCG and urine laboratory pregnancy tests, found that pregnancy tests were only carried out in 12% of women starting treatment.\cite{12}

Our study has demonstrated that the electronic healthcare databases evaluated do not contain all the data necessary to fully monitor the effectiveness of PPP implementation, and thus special data collection measures need to be instituted that would likely benefit from including a qualitative data collection component. The potential for creating special prescribing data that can be linked with healthcare databases could also be explored. This is relevant also to other teratogenic medications, where measures fall short of a full PPP, such as sodium valproate,\cite{44} where specific information on the frequency of prescribing, the number of exposed pregnancies and any attempts made to reduce the risk of an unplanned exposed pregnancy would be very valuable as part of ongoing post-marketing surveillance.

The online purchasing of medicines bypassing the PPP is an additional concern which should be fully investigated and monitored.\cite{35}
Table 1 Summary of the databases contributing to the medicine utilisation component of EUROmedICAT

<table>
<thead>
<tr>
<th>Country/Region</th>
<th>Italy - Emilia Romagna</th>
<th>Italy - Tuscany</th>
<th>Norway</th>
<th>Wales</th>
<th>United Kingdom(^a)</th>
<th>Denmark</th>
<th>Netherlands</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Database for live &amp; stillbirth pregnancy identification</strong></td>
<td>Certificate of Delivery Assistance (CeDAP) Hospital Discharges Registry</td>
<td>Certificate of Delivery Assistance (CeDAP) Hospital Discharges Registry</td>
<td>Medical Birth Registry of Norway</td>
<td>National Community Child Health Database (NCCHD)</td>
<td>Clinical Practice Research Datalink (CPRD)(^b)</td>
<td>Danish National Birth Registry</td>
<td>IADB.nl Database</td>
</tr>
<tr>
<td><strong>Database for pregnancy loss identification</strong></td>
<td></td>
<td></td>
<td></td>
<td>Patient Episode Database for Wales (PEDW) CARIS for TOPFAs(^c)</td>
<td>Clinical Practice Research Datalink</td>
<td>Danish National Patient Registry</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Database for medicine use data</strong></td>
<td>Emilia-Romagna Prescription Database (ERPD)</td>
<td>Tuscany Prescription Database (TPD)</td>
<td>Norwegian Prescription Database</td>
<td>The General Practice (GP) Dataset</td>
<td>Clinical Practice Research Datalink</td>
<td>Danish Prescription Registry</td>
<td>IADB.nl Database</td>
</tr>
<tr>
<td><strong>Source for medicine use data</strong></td>
<td>Pharmacy dispensing(^d)</td>
<td>Pharmacy dispensing and Healthcare Facilities Dispensing (except inpatient)(^e)</td>
<td>Pharmacy dispensing</td>
<td>GP practice prescribing(^f)</td>
<td>GP practice prescribing(^f)</td>
<td>Pharmacy dispensing</td>
<td>Pharmacy dispensing</td>
</tr>
<tr>
<td>Involves database record linkage</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Population base</td>
<td>4,200,000</td>
<td>3,700,000</td>
<td>4,800,000</td>
<td>2,000,000(^g)</td>
<td>5,000,000(^h)</td>
<td>5,000,000(^h)</td>
<td>500,000</td>
</tr>
<tr>
<td>Coverage</td>
<td>Regional</td>
<td>Regional</td>
<td>National</td>
<td>~70% sample of GP practices in Wales(^i)</td>
<td>~8% sample of the UK population</td>
<td>National</td>
<td>Regional</td>
</tr>
</tbody>
</table>

\(^a\) For the EUROmedICAT study patients registered at a practice in Wales were excluded to avoid duplication with the database in Wales
\(^b\) Previously the General Practice Research Database (GPRD)
\(^c\) Congenital anomaly and Information Service for Terminations of pregnancy for a fetal anomaly
\(^d\) Only products reimbursed by the Italian National Health Service and excluding those dispensed to inpatients
\(^e\) Including nurse prescribers working within the GP practice
\(^f\) Secure Anonymised Information Linkage (SAIL) databank
\(^g\) The Child Health Database and Patient Episode Database capture the whole population of Wales (3 million), whereas the General Practice Dataset currently contains ~2 million records
\(^h\) The size of the population captured by the CPRD has grown steadily over time and was approximately 5.0 million in May 2012
\(^i\) For the EUROmedICAT study, the data available in the database was restricted to women who had a pregnancy and was not available for the entire population

In 2017 capturing 60% of the population
<table>
<thead>
<tr>
<th>Data available on</th>
<th>Emilia Romagna</th>
<th>Tuscany</th>
<th>Norway</th>
<th>Wales</th>
<th>United Kingdom</th>
<th>Denmark</th>
<th>The Netherlands</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Practice prescribing</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Specialist/outpatient prescribing</td>
<td>Yes*</td>
<td>Yes**</td>
<td>Yes</td>
<td>Occasionally</td>
<td>Occasionally</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----------------------------------</td>
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<td>-------</td>
<td>-----</td>
<td>-------------</td>
<td>-------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Private prescriptions</td>
<td>Yes**</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inpatient hospital prescribing</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Date prescription was issued/dispensed</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quantity issued/dispensed</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Majority</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily dose/number to take per day</td>
<td>DDD**</td>
<td>DDD**</td>
<td>DDD**</td>
<td>No***</td>
<td>Majority</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prescription duration/days supplied</td>
<td>Can be estimated</td>
<td>Can be estimated</td>
<td>Can be estimated</td>
<td>No</td>
<td>Majority</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brand/generic</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indication for prescribing</td>
<td>No</td>
<td>Sometimes</td>
<td>Sometimes</td>
<td>Some</td>
<td>Majority</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral contraception (OC)</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yesh</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration issued/dispensed</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intra-uterine device (IUD)</td>
<td>No</td>
<td>No</td>
<td>Yes**</td>
<td>Yes**</td>
<td>Yes**</td>
<td></td>
<td></td>
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<tr>
<td>Date fitted</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes**</td>
<td>Yes**</td>
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<td></td>
</tr>
<tr>
<td>Date removed</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes**</td>
<td>Sometimes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Implanon/Nexplanon/Etonogestrel</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
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</tr>
<tr>
<td>Date inserted</td>
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<td>No</td>
<td>No</td>
<td>Yes**</td>
<td>Yes**</td>
<td></td>
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</tr>
<tr>
<td>Date removed</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes**</td>
<td>Sometimes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Noristerat/Norethisterone enantate</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Date injected</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes**</td>
<td>Yes**</td>
<td></td>
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</tr>
<tr>
<td>Depo-Provera</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes**</td>
<td>Yes**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Date injected</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes**</td>
<td>Yes**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Record of general contraception advice</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Occasionally</td>
<td>Occasionally</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hysterectomy</td>
<td>No</td>
<td>Sometimes</td>
<td>Yes**</td>
<td>Yes</td>
<td>Majority</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oophorectomy</td>
<td>No</td>
<td>Sometimes</td>
<td>Yesi</td>
<td>Yes</td>
<td>Majority</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sterilisation</td>
<td>No</td>
<td>No</td>
<td>Yesi</td>
<td>Yes</td>
<td>Majority</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Husband/partner vasectomy</td>
<td>No</td>
<td>No</td>
<td>Yesi</td>
<td>Sometimes</td>
<td>Sometimes</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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11 Excluding those administered during a hospital in-patient stay and those not reimbursed
12 When prescribing information is passed on to the GP
13 Excluding those dispensed at a hospital pharmacy
14 Defined daily dose
15 Can sometimes be inferred from tablet strength
16 Inferred from hospital discharge data only
17 Only broad diagnoses categories were available until the introduction of ICD codes in 2008, after which more specific diagnoses started to be recorded
18 Excluding those from family planning and genitourinary medicine clinics
19 Excluding those without hormones (e.g. copper devices)
20 Available in the Norwegian Patient Registry from 2008, although this registry was not included as part of the EUROMEDICAT study
References


Compliance with ethical standards

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Conflicts of interest
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