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Methods of mapping adverse events of medicine use during pregnancy

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Abstract

Introduction The current system of verifying and quantifying adverse reactions to drug use during pregnancy is disparate. Pharmacovigilance methods play an important part in protecting pregnant women from the possible harmful effects of the use of drugs during their pregnancies. The main aim of this study was to identify methods used for assessment of the relationship between drug use and adverse events during pregnancy. A secondary aim was to determine the quality of the methods for which this is useful.
Method In MEDLINE (Pubmed) articles about methods for assessment of the relation between drug use during pregnancy and adverse events were selected and studied following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Advantages and disadvantages were retrieved from the included articles. We also looked at the quality of some of these methods using a method described by Murad et al.
Results The Pubmed search obtained 151 titles, of which 16 articles were finally included. The found methods for mapping adverse events of medicine use during pregnancy were case-control studies, cohort studies, case reports and case series, data-linkage, the use of real-world data and prescription event monitoring. Advantages and disadvantages of each method retrieved from the articles are summarized. The quality assessment of studies was not reliable as there were low numbers of studies included for each method for which quality assessment was useful.
Conclusion The methods used for mapping adverse events of medicine use during pregnancy found in this study have their own advantages and disadvantages. The best method to use depends on the settings and circumstances of the pharmacovigilance method. The use of real-world evidence generation seems to become a valuable method for evidence generation of the association between adverse events and medicine use during pregnancy in pregnancy pharmacovigilance.

Keywords: methods; drugs; pregnancy; adverse events; pharmacovigilance

Drug use during pregnancy may also result in drug exposure to the unborn child. However, data on safety of drug use for the unborn child is often poor or lacking[1]. In the past, events as a result of these poor or lacking data, have highlighted its need.

For instance Thalidomide, a drug for morning sickness during pregnancy in the late 1950's, resulted in phocomelia, malformations of the arms and legs, in approximately 10,000 children. Pediatrician Dr. Lenz was the first doctor to recognize the connection between Thalidomide and pediatric limb malformations. Then, a gynecologist, Mc Bride, published an article concerning this subject in the Lancet. This resulted in a dispute of the question whether thalidomide did or did not cause malformations, which was going on for months. After an increasing number of well documented case reports in which the mother had definitely taken thalidomide in early pregnancy, it was possible to delineate the spectrum of malformations to the drug[2,3]. Currently, Thalidomide has other indications than morning sickness during pregnancy, including HIV/AIDS, multiple myeloma and leprosy (not

during pregnancy)[4]. To prevent teratogenicity, a comprehensive program (Thalidomide Risk Evaluation and Mitigation Strategies (REMS) program) has been established in order to; control access to the drug (including registration of dispensing pharmacies, prescribing physicians, and patients), mandatory informed consent and education procedures, and limitations of the quantity of drug dispensed. Also, clinical, and in some patients electrophysiologic monitoring for the detrimental side effect neuropathy is indicated with thalidomide therapy[5]. According to the FDA pregnancy risk categories, which were established in 1979, the drug Thalidomide has been classified under the risk category X. This category means that studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits[6].

Another example is diethylstilbestrol (DES) use from the 1940s till the 1970s for prevention of miscarriages, resulting in an increased risk of clear-cell adenocarcinoma and vaginal adenosis, fertility problems and genital tract anomalies in the daughters of women who used DES during pregnancy. These problems became only apparent after 15 to 20 years, resulting in late discovery of this teratology[7] (abnormal development as caused by environmental agents, such as drugs, viruses, chemicals, and radiation[8]). In this example, also observations by clinicians were published as case reports[7].

However, sometimes drug use cannot be avoided during pregnancy, for instance in mothers with epilepsy, because seizures can be harmful for both mother and child as it can result in preterm labor, preeclampsia, hemorrhage and other maternal disorders including maternal death. But antiepileptic drugs may be associated with increased risk of major congenital malformation[9]. In autoimmune disorders like HIV/AIDS, depression, inflammatory bowel disease or asthma, drug use may also be unavoidable[10].

Besides essential drug therapy during pregnancy which could, when omitted, be harmful for mother and child, there is also a concerning unnecessary administration of drugs to pregnant women. The latter especially applies to over the counter drugs (OCTs), for instance nonsteroidal anti-inflammatory drugs (NSAIDs)[11]. NSAIDs may, for instance, be harmful by prolonging the duration of labor and the length of gestation and causing early closure of the ductus arteriosus[12,13].

So, there is a need of more thorough and reliable information about drug safety during pregnancy. However, teratogenic data often relies on animal data and is generally only obtained in the post-marketing phase. Due to this lack of data, many drugs are not indicated, or contraindicated during pregnancy[6]. A study by Adam et al. even showed that for 97.7% of drugs approved by the FDA between 2000 and 2010, the teratogenic risk was undetermined[14].

Attention should be paid to drugs which are essentially used during pregnancy, like antiepileptics, or unnecessarily used, like OCTs[7,8,9], but also to drugs with a similar mechanism of action or chemical structure as drugs known to be harmful during pregnancy, like retinoids and related drugs which are vitamin A analogues and associated with congenital malformations[15][16], and drugs which have a new mode of action or chemical structure.

The complex embryonic and foetal development may result in stillbirths, miscarriages or minor or major congenital malformations due to medicine use during pregnancy[17]. The presence and kind of adverse event as a result of drug use during pregnancy is also dependent on the pregnancy period in which the drug was taken by the mother. Before the 20th day after fertilization, drugs administered to pregnant women typically have an all-or-nothing effect, which means killing the embryo or not affecting it at all, and teratogenesis is unlikely. During the organogenesis, which is between 20 and 56 days after fertilization, teratogenesis is most likely to occur as a result of drug use by the mother[18]. Teratogenesis may occur as a direct or indirect effect of the drug, and the drug may act as a co-factor or may sensitize the embryo to some harmful effect of some other substance[19]. An indirect effect

may be caused by drugs affecting the maternal cardiovascular system, resulting in inadequate supply of nutrients to the fetus, which may adversely affect fetal growth and induce teratogenesis[20]. Exposure to drugs by the embryo in this stage may cause e.g. spontaneous abortion or malformations. After organogenesis, in the second and third trimester of pregnancy, teratogenesis is unlikely, but medicines may alter growth and function of fetal organs and tissues[18].

Both a study in Canada and a study in Ireland showed that congenital anomalies, the major cause of child and neonatal mortality, represented approximately 1% of infant mortality. However, in developing countries this percentage is higher as these countries are usually not able to afford essential medicines and accessing healthcare is difficult in these countries, resulting in untreated pregnancy complications. For instance, a study in the developing country India found that congenital anomalies accounted for 10-15% of infant deaths and 8-18% of perinatal mortality[17].

Major birth defects are conditions presented at birth which cause structural changes in one or more parts of the body and which require medical treatment. Major malformations are anomalies that create significant medical problems for the patient or that require specific surgical or medical management[21]. For instance, genetic disorders like Down's syndrome, may be caused by abnormal cell division after fertilization resulting in chromosomal abnormality, or by a defective gene inherited from (one of) the parents, but these genetic disorders are not the result of medicine use by the mother during pregnancy. Also, other disorders, like mouth or facial defects such as cleft lip and/or palate, heart defects, musculoskeletal defects, stomach or intestinal defects and eye defects may occur that can be either genetical or non genetical in nature. These disorders may also result from adverse drug events. Other examples of adverse events that may be the result from the use of certain medicines during pregnancy, are for instance a low birth weight, increased risk of premature birth[22], behavioral problems such as attention deficit hyperactivity disorder which has been linked with antidepressant use during pregnancy[23], or developmental malformations which have for example been associated with antiepileptic drug use during pregnancy[24].

A relatively high percentage of women use drugs during pregnancy. For instance in the Netherlands, 86% of all pregnant women[25], which is comparable to other countries. For example in the United States, approximately half of all pregnant women used prescribed drugs during pregnancy[26].

Pharmacovigilance is defined by the WHO as "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug related problem. Its aims are to enhance patient care and patient safety and to support public health programs by providing reliable, balanced information for the effective assessment of the benefit-risk profile of medicines and vaccines."[27]. The major aim of pharmacovigilance is signal detection. As defined by the WHO, a signal is "reported information on a possible causal relationship between an adverse event and a drug, the relationship being previously unknown or incompletely documented. Usually more than a single case report is required to generate a signal, depending on the seriousness of the event and quality of the information".[28] There are five types of adverse drug reaction (ADR) as shown in Table 1 (type A till E). The most common ADRs in pharmacovigilance include type A and type B, and the less common ADRs include type C, D and E reactions[29]. ADRs are a subset of adverse drug events (ADEs). ADEs are defined by harm caused by appropriate or inappropriate use of a drug (also include e.g. provider error, incorrect dosages and non-adherence), and ADRs as being directly caused by a drug under appropriate use (i.e. at normal doses). So, an ADR is an ADE with a causal link to the drug [30].

Table 1 Types of adverse drug reactions[29]

Type	Type of effect	Characteristics	Example
A	Augmented	- Dose dependent - Related to the pharmacological effects of the drug	Hyperglycemia due to insulin
B	Bizarre	- Unpredictable - Dose dependent - Rare, fatal	Anaphylaxis due to penicillin
C	Chronic	- Continuing reactions, persist for a relatively long time	Neuropathy due to anagesics
D	Delayed	- After years of treatment	Antipsychotic tardive dyskinesia
E	End of use	- Withdrawal effect	(Too rapid) glucocorticosteroid withdrawal → adrenocortical insufficiency

There are several methods used for detection of possible signals. In the post-marketing phase of drugs, observational studies are preferred, including; case-control studies, cohort studies, case reports and case series.

Case-control studies can be used to ascertain information on differences in suspected exposures, for instance exposure to drugs during pregnancy, and outcomes, such as birth defects, between cases, individuals with the specific outcome, and controls[31]. Advantages of a case-control study are that they are efficient for rare diseases or diseases with a long latency period between exposure and disease manifestation, and, for studies performed in the same center, once the infra-structure is established, multiple studies can be conducted[32]. A disadvantage of case-control studies is that these studies are subject to selection bias, as the controls might not be representative of the cases. Another disadvantage is that information of exposure is subject to observation bias, as different observers may assess subjective criteria differently[31]. Also, reporting bias may occur as a result of potential underreporting, which may result in some foundational adverse events not appearing at all in the literature, and other foundational adverse events being linked to only a sub-set of the actual number of diseases impacted during pregnancy[33]. Existing registries or reporting systems such as birth defect registries can be used for identification of cases in case-control studies, for instance, the congenital anomaly register EUROCAT. For the identification of exposure, medication history of pharmacists, interviews or questionnaires can be used[34,35].

Cohort studies can be used for information about the relation of exposure to a medicinal product and outcome over time[36]. In these studies, cohorts of pregnant women are created that can be followed longitudinally to study the outcome of the pregnancy. An advantage of cohort studies is that exposure can be precisely defined in most cases. A disadvantage is that ascertainment of the outcome can be difficult, since interviews or questionnaires may be needed to obtain information. This may result in difficulty in the comparison between observed and expected outcomes[36]. Another disadvantage is that in case of rare events[31], on which many of the methods used in pharmacovigilance are focused on[37], the use of a prospective cohort studies is less useful since the number of included patients will then probably be too low resulting in an underpowered study[38]. For the collection of data, for instance record-linkage of data sources, pregnancy registries or Teratology Information Services (TIS) can be used[35].

Case reports and case series can provide valuable information on the effects of exposure of medicinal products as a first indication for malformations. However, case reports and case series can only be applied to highlight a potential association between drug and malformation, as these descriptive studies have a low level of evidence compared to the other methods. Additional studies are usually needed for substantiation and confirmation of the association. Information can be provided from TIS. TIS in Europe, Israel and Latin America collaborate in the European Network of Teratology Information Services (ENTIS). The network of TIS in America is called the Organization of Teratology Information Specialists (OTIS).[39,35].

There are clear rules and regulations for pharmacovigilance in the post-marketing phase. The

"Exposure to Medicinal Products during Pregnancy: Need for Post-authorisation Data" guideline, introduced by the European Medicines Agency (EMA) in 2005, provides criteria for selecting products (including medicines) for which active surveillance in pregnancy is necessary[11]. The "Risk Assessment of Medicinal Products on Human Reproduction and Lactation" guideline, published by the EMA in 2008, describes how clinical and non-clinical data should be integrated in pharmacovigilance studies. Also, in 2009, the EMA introduced the guideline "Risk Assessment of Medicinal Products on Human Reproduction and Lactation" in order to address the way the European Pharmacovigilance Legislation of 2009 should be implemented[35]. This guideline consists of chapters which fall into two categories; modules covering major pharmacovigilance processes (such as data collection from spontaneous reports), and product- or population specific considerations (for instance biological medicinal products, or the pediatric population)[40].

So, there are several methods suitable for identification of adverse events associated with drug use during pregnancy. We do not know which methods exactly are used and what the quality is of these methods, therefore the aim of this essay is to identify which methods can be used for assessment of the relationship between drug use and adverse events. A secondary is to assess the quality of these methods from the perspective of observational research.

Methods

The review process was according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Search strategy

A systemic search was performed using the database MEDLINE (Pubmed). There was no year limit applied. The search strategy for MEDLINE was: Methods[MeSH Subheading] AND (teratology OR pharmacovigilance) AND pregnancy. A filter applied to the search was NOT (Animals NOT Humans), in order to exclude animal-only studies. The selected articles were also screened for relevant references to include. References from the chapter 'congenital malformations' of the book 'evidence-based pharmacovigilance'[35] were also screened for possible inclusion.

Study selection

The studies were firstly selected based on abstract. Subsequently, of those selected, the full text was screened. Selected articles met the following inclusion criteria: described methods for the assessment of adverse events that are possibly or likely associated with drug use during pregnancy. Articles were excluded if: the inclusion criteria did not apply, the background or reporting was insufficient, it was a review article, the article was incomplete, or the data was already reported in another article.

Assessment of articles' methodological quality

The methodological quality of the included studies was assessed using the method described by Murad et al.[41]. For each article, 8 items were scored with leading explanatory questions. Added scores were ranked as "low", "moderate", or "good". The method described by Murad et al. has been developed to rank observational studies. Case reports and case series can be useful to highlight a potential association between drug and malformation, but they generally have less quality compared to the other methods[35]. Therefore, case reports and series were not assessed for their quality by this method.

Data collection

For included studies, data were extracted following a standardized approach. When available, data were extracted on: study design, number of pregnancies, drug(s) used, disease area, number of live born children, number of adverse events, type of adverse events, causality method and method of data collection.

Synthesis of results

The methods and adverse events were abstracted from the articles exactly as written. Also, advantages and disadvantages were retrieved from the included articles. Lastly, the average quality of the methods for which the quality was assessed, was determined by the method of Murad et al.[41].

Results

Search results

The search strategy obtained 151 titles; another 6 articles were identified through references. The selection process is shown in Figure 1, and table 1 provides an overview of the finally included articles. From the included articles, 3 were cases reports, 3 were case-control studies, 3 were cohort studies, 5 were large data resources on morbidity and drug use, 1 was prescription event monitoring, and in 1 article real-world data was used.

Figure 1 Selection of studies according to the PRISMA statement.

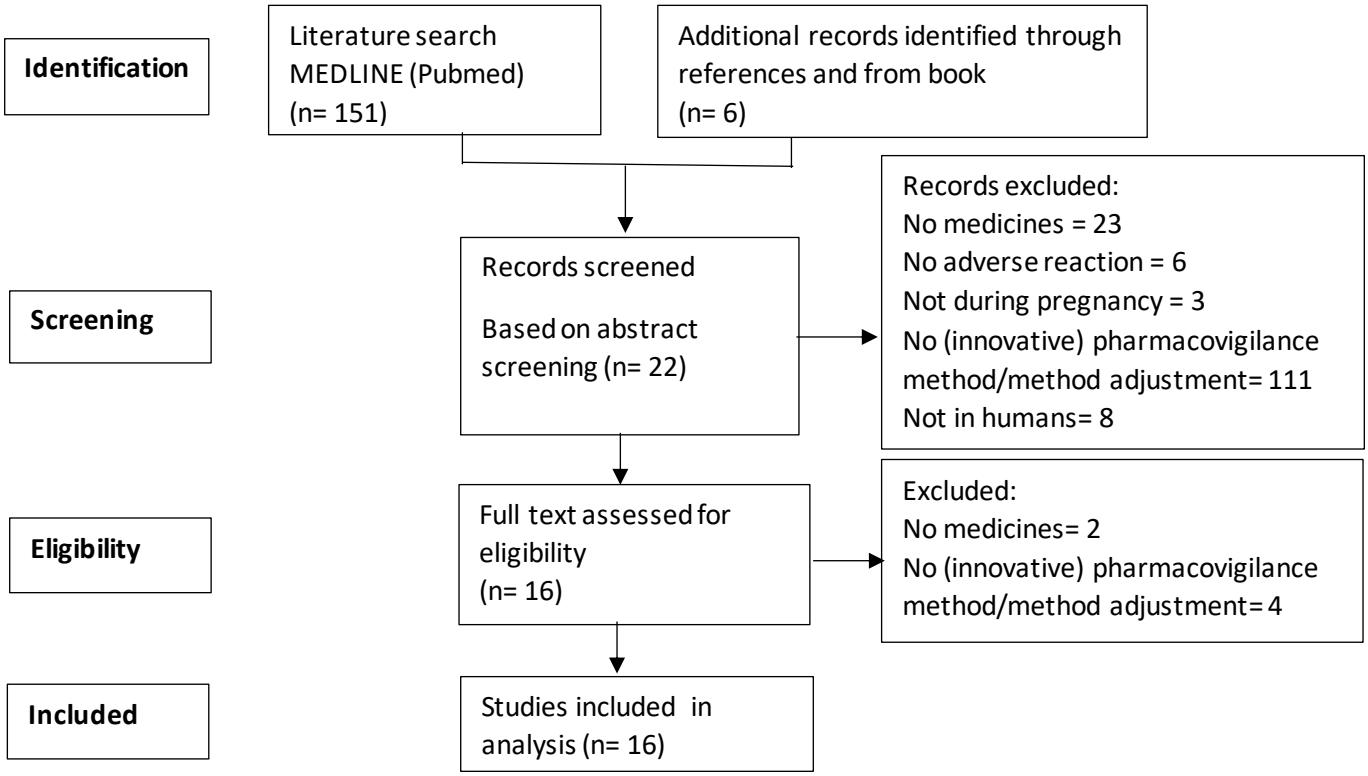

Table 2 Overview of included articles reporting adverse events of drugs used during pregnancy

First Author [reference]	Year	Study Design	Number of Pregnancies	Medicine(s)	Disease area	Number of live-born children	% (/OR/RR) with AE	Type of AE(s)	Method of Data Collection
Case reports and case series									
Mauro[44]	2014	Case reports	2	Aripiprazole (ARI)	Depression, anxiety	2 (DEGRA centre), 7 (Pubmed search)	Both newborns did not present adverse drug events (DEGRA centre), 2 case reports had perinatal complications (Pubmed search)	Malformations or perinatal complications	MEDLINE and PubMed databases were searched using the following keywords: (aripiprazole) AND (major malformations OR perinatal complications OR pregnancy). Also, two cases of women treated with ARI during their pregnancy at the DEGRA Center were reported.
Pellegrino[45]	2018	Case series (TIS) and literature review	75 pregnancies (27 mono- and 48 multidrug therapy), (control; 187)	Antiglaucoma medications	Glaucoma	66 (22 mono- and 44 multidrug therapy (control: 174)	Low birth weight; 7% in mono- and 6% in multidrug therapy (8% in control). Neonatal respiratory complication; 4% in both (0.5% in control). Major malforma-tions; 0 in mono- and 6% in multidrug therapy (0.5% in control).	Low birth weight, respiratory complications, major malformations.	"Telefono Rosso" is an Italian TIS that provides counseling about risk factors during the preconception period, pregnancy and lactation via phone interviews.
Hazell[46]	2013	Retrospective analysis of spontaneous reporting. Three datasets were created; patient reports, healthcare professional reports and all reports combined	5180 patient reports, 20.949 health care reports (HCR)	Diverse	Diverse	ND	HCR compared with patient reports ; n= 931. Approxima tely 10 % (n=47); serous ADR.	Diverse	Data were analyzed from all reports submitted directly to the Yellow Card Scheme (YCS) between October 2005 and September 2007.
Large data resources on morbidity and drug use (including data linkage)									
Colvin[47]	2010	Linkage of database and registry	106.074	Medicines in categories D or X of the Australian ADEC pregnancy risk category	Diverse	47 medicines dispensed at least once during pregnancy; 23 with a registered birth defect	Higher risk of adverse events; medroxy-progeste-rone-acetate (OR: 1.8), follitropin alfa (OR: 2.5), carbama-zepine (OR: 3.1) and enalapril maleate (OR: 8.1).	Diverse	The Pharmaceutical Benefits Scheme is a national claims database that has been linked with population-based data to extract linkages for women with a pregnancy event in Western Australia from 2002 to 2005. Population rates of registered birth defects per 1000 births were calculated for each medicine.

Colvin[48]	2009	Population-based linked datasets	132.781 pregnancies	Subsidized prescription medicines	Diverse	106.074	Dispensed medicines were linked to 28% of pregnancy events.	Diverse	Pregnancy events were identified in the Hospital Morbidity Data System from 2002 to 2005 (N = 98.265 women) and linked to the midwives' notification system (MNS), the registry of births and deaths, the Western Australian birth defects registry and the pharmaceutical benefit scheme.
Dellicour[49]	2013	Probabilistic record linkage (databases)	685	Artimisinin-based combination therapy	Malaria	94.6% of the 536 eligible for record linkage	1.6% major congenital malformations	Major congenital malformations	Data (2004-2008) from paper-based registers from outpatient clinics, antenatal care services (ANC) and the delivery unit from the St Joseph dispensary in Mlomp, south-western Senegal, were entered into databases.
Hurault-Delarue[50]	2016	A newly developed method: 1. conversion of prescription data into exposure variable (using ATC-DDD), 2. Construction of individual trajectories of exposure, 3. Clustering of trajectory of exposure (using the R package Kml)	54.918	Psychotropic drugs	Anxiety, schizophrenia, depression and other mood disorders	n/a	This method of exposure measure-ment aids for accurate subse-quent measure-ment of adverse events. Exposure to psycho-tropic drugs was 6.7% (subdivi-ded in different clusters of exposure; moderate constant exposure etc.)	n/a	Obtaining prescription data from women using psychotropic drugs during pregnancy in Haute-Garonne (France) between 2004 and 2010, included in the EFEMERIS database.
Cavadino[51]	2019	Double false discovery rate	n/a	Diverse	Diverse	15.058 malformed fetuses	Double FDR; 50% 16 signals (of which 6 high-risk) (Single FDR; 50% 8 medica-tion signals (of which 3 high-risk))	Diverse	Data on 15.058 malformed fetuses with first trimester medication exposures from 1995–2011 were available from EUROmediCAT, a network of European CA registries.
Case-control studies									
Gelder[52]	2015	Case-control	12.821	Antihypertenw sive medication.	Specific maternal hypertensive disorders and/or prenatal exposure to antihyperten sive medication	12.821	5568	Birth defects	Obtaining data from the Slone Birth Defects Study, 1998-2010
Lumsden[53]	2020	Retrospective case-control study	97	Cardiac medications	Cardiac disease in pregnancy (e.g. rheumatic	97	Cases vs. controls; cardiac (56% vs. 0.4%) and neonatal	Cardiac and neonatal adverse events	Data of pregnant women admitted to a national referral hospital in western Kenya between 2011-2016.

					heart disease)		(61% vs. 27%)		
Pels[54]	2015	Retrospective case control study	128 (64 cases (with FCM treatment), 64 controls (without FCM treatment)	Intravenous ferric carboxymalto-se (FCM)	Anemia	74 live-born children in cases and 74 in controls	Major adverse outcomes in cases; 5% maternal only, 8% fetal only and 3% maternal and fetal. Minor adverse outcomes in cases; 36%.	Major adverse outcomes; delivery before 34 weeks of gestation, death of fetus, , atrioventricular septal defect, respiratory problems, pneumonia and skin abnormalities	Pregnancy data (2010-2012) were obtained from the electronic patient charts of the Department of Obstetrics and Gynecology of the Academic Medical Centre in Amsterdam, Netherland.
Cohort studies									
Maschi[55]	2008	Prospective, controlled cohort study	1400	Antidepres-sant drugs	Depression, anxiety	200 cases, 1200 controls	Cases; 14 with adverse event (7%), (controls; 50 (4%))	Cases; Jaundice (n = 5), agitation (n = 3) and respiratory distress (n = 2) were the most common symptoms.	Neonatal adverse events and Special Care Unit admission rate was assessed through an interview with the mother in a Drug and Health Information Centre in Milan, Italy.
Watts[56]	2011	Prospective corhort study	1404	Nucleoside and protease inhibitor antiretroviral (ARV) therapy	HIV	1404	60	Birth defects (including heart defects, central nervous system defects and limb reduction/addit ion)	Obtaining data from the Phase III PACTG 316 study.
Williams[57]	2016	Prospective cohort study, using a trigger-based design	2680	Antiretroviral drugs	HIV	ND	Zidovudine ; associated with increased metabolic case (RR= 0.69). Didanosi-ne plus stavudine; neurodeve lopmental (RR=1.69) and language (RR= 4.84) cases.	Metabolic abnormality, neurodevelopm ental impairment, language impairment, impaired growth, neurologic.	Data of HIV-infected pregnant women using antiretroviral drugs during pregnancy from the Surveillance Monitoring of Ani-retroviral Therapy Toxicities Study cohort study conducted at 22 US sites.
Prescription event monitoring									
Mosha[58]	2014	Pilot pharmacovigi-lance system using the health and demographic surveillance platform; HDSS (Health and Demographic Surveillance System)	1089	Any new drug used during pregnancy	Diverse	994	Iron and folic acid were associated with an decreased risk of miscarry-age/stillbir ths (OR 0.1; 0.08-0.3). Antimala-rial and antibiotics exposure (recomme nded pregnancy doses); no significant associa-tion with adverse pregnancy outcomes.	Stillbirths, miscarriage	Using the platform of the Rufiji Health and Demographic Surveillance System (HDSS) to obtain information about pregnant women from Rufiji (Coastal region, Eastern Tanzania), using questionnaires to interview these pregnant women.

Real-world data (number of sources associated with outcomes in a heterogenous patient population in real-world settings, such as patient surveys and cohort studies)									
Lupattelli[59]	2018	Using real-world safety data (these include, among others, pregnancy cohort studies and registries, research consortia, health registries, administrative databases and direct-to-patient research initiatives)	n/a	Psychotropic drugs	Anxiety, schizophre-nia, depression and other mood disorders (e.g. bipolar disorder)	n/a	n/a	Immediate perinatal outcomes such as congenital anomalies, foetal death, and poor neonatal adaptation. And longer-term developmental outcomes such as cognition, neuromotor and behavioural efects, e.g. attention-defcit hyperactive disorder.	From real-world data via observational, pharmaco-epidemiological investigations

PS; prospective study, RS; retrospective study, TIS; teratology information service, OR; odds ratio, RR; relative risk, ADR; adverse drug reaction, CA; congenital anomalies.

Table 3 Assessment of the quality of the methods

First author [reference]	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Assessment
Colvin[48] (linked datasets)	Yes	Yes	Yes	No	No	No	Yes	Yes	Moderate
Van Gelder[52] (case-control)	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Good
Dellicour[49] (probabilistic record linkage (databases))	Yes	Yes	Yes	No	No	No	Yes	Yes	Moderate
Pels[55] (case-control)	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Good
Maschi[54] (cohort study)	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Good
Lumsden[53] (case-control)	Yes	Yes	Yes	No	No	No	Yes	Yes	Moderate
Williams[57] (cohort study)	Yes	Yes	Yes	No	No	No	Yes	Yes	Moderate

Questions: Q1: Does the patient(s) represent(s) the whole experience of the investigator (center) or is the selection method unclear to the extent that other patients with similar presentation may not have been reported?; Q2: Was the exposure adequately ascertained?; Q3: Was the outcome adequately ascertained?; Q4: Were other alternative causes that may explain the observation ruled out?; Q5: Was there a challenge/rechallenge phenomenon?; Q6: Was there a dose -response effect?; Q7: Was follow-up long enough for outcomes to occur?' Q8: Is the case(s) described with sufficient details to allow other investigators to replicate the research or to allow practitioners make inferences related to their own practice? Score : : <=3 = low; >3-<6 = moderate; >=6 = good. (Based on the method described by Murad et al.; . Murad MH, Sultan S, Haffar S, et al: Methodological quality and synthesis of case series and case reports. BMJ Evid Based Med 23:60-63, 2018).
Y; yes, N; no.

Assessed Methodological Quality of Included Studies when applicable

In terms of methodological quality, 3 were rated as good, and ..5% (n=) as moderate an ..% (n=) as low, as shown in Table 2.

Table 4 Advantages and disadvantages of the method included in this study and their average quality

Method	Advantages and disadvantages	Average quality (if applicable)*
Case reports and case series	Advantage: - Useful for hypothesis generation[44] - It turns patient observations into useable data (the observations can possibly be replicated by others)[46] - It is good for formative research that is exploratory in nature, even if it must be completed with remote communication (e.g. by (interviews conducted over the) phone, email or another form of remote communication)[45] Disadvantage: - The potential of selective reporting or underreporting[60] - It can usually not be generalized to the wider population, as the findings can only apply to groups in similar circumstances with the same experiences (e.g. due to missing information about patient compliance and surgical treatment)[45] - Unreliable; it relies on history which might result in errors regarding the study results, e.g. recall bias[59] - It is difficult to draw a definite cause/effect from case studies, further research is necessary for ascertainment of this[46]	-
Data linkage (databases)	Advantage: - Automated databases can minimize the cost and reduce the amount of time involved in obtaining information on the effects of marketed medicines[49] - The databases can be sufficiently large to study relatively infrequently used medicines[47] - Since medicine exposure is determined from pre-recorded automated data, there is no opportunity for recall bias[48] - Record linkage to a variety of data sources provides the opportunity to control for a wide range of potential confounders[48] Disadvantages: - No information about whether the medicine was consumed (under-ascertainment of medicine exposure), and whether it was consumed as directed[47] - No over the counter drug information if based on dispensing data[47]	Moderate
Automated signal detection tools (e.g. double-false discovery rate) (databases)	Advantages: - Improves detection of potential teratogens in comparison to the single FDR[51] - Low risk of false positives[51] Disadvantages: - Relatively high possible type I error rate[51]	-
Real-world data (including cohort studies, registries and databases)	Advantages: - It provides meaningful clinical information about human drug exposure during pregnancy in an actionable and clinically meaningful way, e.g. integrate these data into drug labelling for e.g. long-term side effects[59]	-

	- Ability to focus on various longer-term developmental outcomes in the offspring, such as cognition, neuromotor and behavioral effects[59] - Limits bias due to exposure or outcome misclassification, e.g. by ascertaining psychotropic drug exposure in pregnancy via multiple sources (direct-to-patient studies can provide valuable, granular data on women's mental health, behaviours and drug exposures at multiple time points during gestation, which are often lacking in registry-based and administrative data studies)[59] - These strategies, coupled to methods to address the impact of 'unmeasured' confounding (e.g., sibling-designs) can enable to get closer to the 'true' psychotropic drug effects on maternal and child health[59] - This may be essential for clinical guidance on treatment options and evidence-based counselling to perinatal women with severe psychiatric disorders[59] Disadvantages: - Possible confounding, bias and chance[59]	
Prescription event monitoring (such as the health and demographic surveillance system (HDSS) platform)	Advantage: - Feasible, reliable and manageable in resource-limited setting[58] - Unaffected by the kind of selection and exclusion criteria, thereby eliminating selection bias[60] Disadvantage: - Operational costs may be high in resource-limited countries (e.g. for skilled medical personnel)[57] - the proportion of adverse effects that go unreported to doctors is unknown[59]	-
Cohort studies	Advantage: - Ability to assess causality, as data is gathered by sequence of events[54] - Ability to examine multiple outcomes for a given exposure[54] - Suitable for investigating rare exposures[56] - Ability to calculate incidence and relative risk in exposed and unexposed over time[56] Disadvantage: - Large number of subject are required for rare exposures[54] - Susceptible to selection bias[55] - Susceptible to loss of follow-ups or withdrawals[55] - A prospective cohort may be expensive and long time of follow-up[55] - A retrospective cohort is susceptible to recall and information bias[61]	Good/moderate
Case-control studies	Advantage: - Generally quick, cheap and easy to perform - Case-control studies are particularly suitable for studying risk factors associated with rare diseases or conditions - Not prone to loss of follow-up - Efficient for rare diseases or conditions - Case-control studies can be performed as initial studies to establish potential associations before undertaking larger and more expensive study[62] Disadvantage: - The recruitment of controls is typically prone to selection bias - Information on exposure is prone to observation or recall bias[62]	Good

	- It is generally not possible to calculate the incidence - Not suitable when the exposure of the risk factor (e.g. drug exposure during pregnancy) is rare[62]	

*Only based on small numbers (see table 3).

Summary of Findings

The methods found in this study to be used in pharmacovigilance for mapping adverse events of medicine use during pregnancy, are case series and case reports, case-control studies, cohort studies, large data resources on morbidity and drug use (including data linkage), prescription event monitoring and the use of real-world data. These methods all have distinct advantages and disadvantages (table 3).

Cohort studies and data linkage (of databases) were assessed as, on average, moderate and moderate/good, respectively, in the assessment of the quality of the methods, and case-control studies were assessed as good, on average (table 2). However, as the number of studies involved in this assessment of method quality is low, this assessment might, for instance, possibly also be the result of chance.

Discussion

There are several steps in pharmacovigilance. Usually, first case reports or case series are analyzed in order to determine whether confirmation is necessary by e.g. case-control studies or the use of large databases. However, in pregnancy, fast confirmation is desirable as consequences of a false-positive or false-negative signal could be severe. In this study, methods used during pregnancy were analyzed, and if necessary also the quality of the methodology was assessed.

The methods found to be used for pharmacovigilance of medicine use during pregnancy are case-control studies, cohort studies, case studies and case reports, large data resources on morbidity and drug use (including data-linkage), the use of real-world data, and prescription event monitoring.

These methods indeed seem to be effective methods to study the relationship between the use of medicines and adverse effects during pregnancy, with their own advantages and disadvantages. But the suitability of these methods are dependent on the settings and the circumstances of the study.

Case-control studies are suitable for cases of medicine use during pregnancy for which the outcome, such as birth defects, is rare. As it is generally easy, quick and cheap, it can also be useful in establishing potential associations before undertaking larger and more expensive study. However, attention should be paid on possible selection bias. The recruitment of controls in case-control studies is prone to selection bias, as controls are often recruited through convenient sampling, for example from a hospital clinic or a general practice[62]. In the study by Lumsden et al., only women hospitalized at a tertiary care facility were included, which could have resulted in selection bias. This may have contributed to overestimation of adverse events[53]. However, this selection bias could be overcome by selecting the controls at random[62]. Besides that, information on exposure is prone to observation bias, as different doctors might assess adverse drug events during pregnancy differently. For example, in the study by Lumsden et al., the record keeping from paper medical charts was inconsistent, which could have resulted in missing data and thus in a possible underestimation of outcomes. Also, it is not possible to calculate the incidence, as there is no follow-up period[62]. Case-control studies are also prone to recall bias, for instance in the study by van Gelder et al., the use of standardized interviews of the Slone Birth Defects Study, conducted 6 months after birth, may have resulted in recall bias[52].

Cohort studies have as advantage, for instance, to be suitable for rare exposures and the examination of multiple outcomes (e.g. multiple birth defects). However, disadvantages of cohort studies are the often large number of subjects required and long follow-up time. So, the large

amount of subjects and long time of follow-up was a strength in the study by Williams et al.[57]. Another limitation is the susceptibility to different types of biases, which was also the case in the study by Williams et al., as older children typically had a longer follow-up, but they accounted for this by controlling for birth cohort and conducting time-to-event-analysis[57]. In the cohort study by Williams et al., a trigger-based design is used[57]. A trigger-based design consists of a list of previously tested triggers, including medicines, laboratory findings and clinical outcomes, that act as clues to identify adverse drug reactions[63]. For each domain (e.g. metabolic, growth or neurological outcomes), a study "trigger" was established (for instance, a metabolic trigger). Also, trigger thresholds were chosen to determine which participants to investigate further, and a panel determined whether each study participant who met a trigger also had an adverse event in the study by Williams et al.. This trigger-based method was shown to be generally more efficient for estimating adverse events than without the trigger-based design[57].

Some of the advantages of case reports and case series are their usefulness for hypothesis generation and turning patient observations into useable data. Also, it is useful for exploratory research, even if it is completed with remote communication, e.g. by interviews conducted over the phone as was the case in the study by Pellegrino et al.[45] Disadvantages are the general under-reporting and selective reporting in these studies. For instance, in the study by Hazell et al., they mentioned, besides underreporting, possible selective reporting due to media coverage of problems with controversial or commonly used drugs[46]. The study by Hazell et al., showed that patient reporting may provide a positive complementary contribution to that of healthcare professionals in the identification of signals[46].

Prescription event monitoring is a method to record all patients exposed to selected drugs. The patients or their doctors can then be approached by means of a questionnaire to record any or selected events[60]. For instance in the study by Mosha et al., they used a platform of the Rufiji Health and Demographic Surveillance System (HDSS) to obtain information about pregnant women from Rufiji (Coastal region, Eastern Tanzania), using questionnaires to interview these pregnant women.[58] An advantage of this method is that this method is unaffected by selection and exclusion criteria that characterize clinical trials. This way, selection bias is prevented. Another advantage is that it is feasible, reliable and manageable in resource-limited settings. The study by Mosha et al., for instance, showed that HDSS proved to be a useful platform to establish a reliable pharmacovigilance system in resource-limited countries[58]. A disadvantage of prescription event monitoring is that the proportion of adverse events which go unreported to doctors is unknown[60].

Large data resources on morbidity and drug use found to be used in pregnancy in this study are databases and registries. Databases and/or registries can be linked using a data linkage method, and the (double) false discovery rate (FDR) can be used to correct for multiple comparison. In data linkage, two or more sets of administrative or survey data about the same person or entity, from different organizations are linked together in order to create a new, richer dataset. It also integrating processes to remove duplicates or mis-matches within the combined data[64]. One of the advantages is that databases can be sufficiently large to study relatively infrequently used medicines, for instance category D and X medicines in the study by Colvin et al. (2010)[47]. Also, recall bias and potential confounders can be prevented with data linkage. Recall bias is prevented since medicine exposure is determined from pre-recorded automated data. Disadvantages are a lack of information about whether the medicine was consumed and whether this was as directed. For instance, in the study by Colvin et al. (2009) was mentioned that there was an under-ascertainment of medicine exposure, due to exclusion of medicines dispensed with a price below which the Commonwealth will subsidise it (approximately 13.6% of medicines dispensed between 2003 and 2005)[48]. Probabilistic record linkage is based on combinations of non-unique characteristics of individuals, for instance name, gender and data of birth, and is prone to errors. Patterns of agreement and disagreement between

identifying items are translated into quantitative scores, which then predicts whether the two records should be linked[65]. A study by Dellicour et al., showed the usefulness of probabilistic record linkage as a method to assess the safety of antimalarials in early pregnancy to assess increased risk of overall birth defects, and stillbirths[49]. The FDR, an automated signal detection tool, is the proportion of false positive results (e.g. 10% for an FDR of 10%). The double false discovery rate takes grouping of Anatomical Therapeutic Chemical (ATC) medications or grouping of congenital anomalies into account. It appeared to improve the detection of potential teratogens compared to single FDR, while maintaining a low risk of false positives in a study by Cavadino et al.[51].

Real-world data (RWD) is data derived from multiple, really diverse sources of available safety information associated with outcomes in a heterogenous patient population in real-world settings, including cohort studies, registries and databases. RWD can be analyzed to produce real-world evidence (RWE), which is evidence from RWD on the usage and/or benefits and risks of a medication or a medical product. It supports the clinical interpretation of how products act in more diverse patient populations and may have additional therapeutic benefits or uses beyond those originally studied in clinical trials. The increase in electronic health records within clinical practice, and the surge in technology applications that record health information, increased the availability of information to track the use of medication products in the real world[66]. A number of databases have been established to collate RWD, e.g. the Premier Healthcare Database. These global databases store data of a large number of patients, including medication and procedure, physician and patient survey data, laboratory results and outcomes, costs, and demographic and socioeconomic status. This information can be analyzed by health care professionals to generate RWE for research hypotheses that cannot be addressed by clinical trials. However, disadvantages include the possible confounding and bias, for instance due to heterogeneity of results, possible inclusion of poor-quality data and publication bias. Currently, only few guidelines review RWD and few use RWE for clinical practice recommendation[66]. The study by Lupatelli et al. showed, for instance, the importance and usefulness of the use of real-world safety data on psychotropics in pregnancy and their incorporation into labelling for clinical guidance in treatment options and evidence-based counselling to perinatal women with severe psychiatric disorders. In the study by Lupatelli et al., they expect that by valuing RWD, and making these a larger part of the regulatory decision-making process, we move toward a modern, improved pregnancy pharmacovigilance[59].

Determination of which is the best method to use for mapping adverse events as a result of medicine use during pregnancy is hard, but from the assessment of quality of the studies, case-control studies seem to have the highest quality. However, not all methods were assessed this way, and the amount of studies included in this analysis were small. So the results from the assessment of the quality of the method could, for instance, also be the result of chance. Also, the best method depends on the settings and circumstances of the pharmacovigilance study[24].

Conclusion

The methods used for pharmacovigilance of medicine use during pregnancy found in this study are case-control studies, cohort studies, case reports and case series, data-linkage, the use of real-world data and prescription event monitoring, each with their own advantages and disadvantages. From our study results, it was not possible to determine which is the method to use, but this also depends on the settings and circumstances of the pharmacovigilance method. In modern pregnancy pharmacovigilance, real-world evidence generation seems to become a valuable method for evidence generation of the association between adverse events and medicine use during pregnancy.

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