Systematic overview of data sources for drug safety in pregnancy research

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An overview of pregnancy exposure registries

Pregnancy exposure registries are essentially prospective observational studies that follow women up from the time of enrolment in the registry until a short period after pregnancy outcome. They are created with the aim of detecting major teratogenicity, that is, where a large proportion (e.g. 30-40%) of those pregnancies exposed to a particular drug are adversely affected.[1] Pregnancy exposure registries can be set up either by pharmaceutical companies, academic groups or research groups, they can be international or country specific and they can focus on a single drug, a drug class or a disease. The European Medicines Agency (EMA) and the Food and Drug Administration in the USA (FDA) recommend pharmaceutical companies consider developing a pregnancy exposure registry for products that may be used during pregnancy to treat new or chronic conditions and for products frequently used by women of childbearing age where the likelihood of inadvertent exposure during pregnancy is high.[2, 3]

Pregnancy exposure registry methods

The precise methodology used varies slightly between registries but in general, women can enrol either directly themselves or via one of their healthcare providers (GP, midwife, epilepsy nurse etc.). Enrolment should ideally be before any prenatal screening has taken place and before the pregnancy outcome is known in order to avoid selection bias towards more severe outcomes. At the time of enrolment, informed consent is obtained and information is collected on some or all of the following: general demographics, use and timing of prescription and over-the-counter medicines, disease status (e.g. number / type of epilepsy seizures), potential confounding factors including smoking status, alcohol consumption and folic acid exposure. Given our knowledge of the different stages of foetal development, pregnancy registries have tended to focus their analysis on pregnancies where drug exposure occurred during the first trimester of pregnancy as this

is the time period of greatest susceptibility in terms of the risk of major congenital malformations.[a]

Follow up information on the pregnancy outcome and the presence or absence of a congenital malformation is collected, shortly after the expected date of delivery, by a GP or patient questionnaire or telephone call. Live births, stillbirths, induced terminations and spontaneous abortions are captured by registries although the number of spontaneous pregnancy losses captured may be relatively low depending on the week's gestation at which women enrol. The primary endpoint of a pregnancy registry is an estimate of the overall risk of all major congenital malformations[5] with the aim of providing data based on exposures in humans that is clinically relevant and can be used to inform healthcare professionals and patients.[6] In addition to collecting information on congenital malformations, some registries have chosen to extend the length of infant follow-up in order to evaluate any evidence of an association between maternal drug exposure and developmental delay in the offspring.[5]

To reduce the likelihood of selection bias, analysis of data collected by pregnancy exposure registries tends to focus on those pregnancies that were prospectively enrolled before any prenatal screening or knowledge of the pregnancy outcome has occurred. Pregnancies reported to registries retrospectively, following the diagnosis of a major congenital malformation, are still reviewed and analysed because they may help to identify multiple cases of the same defect type, which would require further investigation.[6]

In addition to the main aim of identifying major teratogenicity, pregnancy exposure registries can also act as hypothesis-generating studies by detecting adverse pregnancy outcomes that may warrant further investigation. To do this many pregnancy registries have adopted the 'rule of 3' where review is thought warranted if the

[a] Major congenital malformations are broadly defined as abnormalities present at birth that are of surgical, medical or cosmetic importance

registry observes 3 or more reports to be of a particular defect following the same exposure. The 'rule of 3' is based on the rationale that in a registry with fewer than 600 exposures, the likelihood of observing 3 of the same specific birth defect when it normally occurs with a rate of less than 1/700 is unlikely to be by chance alone.[7]

Limitations of pregnancy exposure registries

Although pregnancy registries have several strengths over other surveillance methods it is widely recognised that they also have a number of limitations.

Enrolment

Low levels of enrolment are commonly found to hinder pregnancy exposure registries. The European Committee for Medical Products for Human Use considers 1000 exposures to be representative of widespread market exposure,[8] yet the pharmaceutical company GlaxoSmithKline has sponsored five international registries, none of which managed to enrol 1000 pregnancies with informative outcomes during their first ten years of data collection.[9] Attempts to raise awareness and encourage enrolment are often hampered by the lack of knowledge regarding the safety of the product being monitored, making it difficult to decide on how to communicate the message and the need to ensure any promotional material does not appear to encourage use of the product or give a false impression of safety.[6, 10]

The voluntary nature of enrolment can result in selection bias if women opting to enrol differ from those who do not, in terms of factors associated with the underlying risk of the outcome being studied.[11] For example, women choosing to enrol into a registry may be more health conscious and more likely to follow advice in relation to the potential benefits of pre-conceptional folic acid, smoking cessation and reducing alcohol intake during pregnancy than those who do not. In addition to selection bias resulting from enrolment by the women themselves, registries may also suffer from referral bias with healthcare professionals being more or less likely to enrol women with a particular

disease severity or those exposed to a particular type of treatment. To our knowledge, thus far no reports have been published comparing the population characteristics and disease severity for individuals enrolled in a pregnancy registry with those from a representative sample of individuals who would be eligible to enrol.

Loss to follow-up

Pregnancy exposure registries often suffer from loss to follow-up. This has been reported to be as low as 8.1% in the UK Epilepsy and Pregnancy Register[12] and as high as 35.8% in the Buproprion Pregnancy Registry.[13] In 2004, in an attempt to reduce loss to follow-up, three pregnancy registries trialled the introduction of a stipend for healthcare professionals who reported follow-up pregnancy outcome data to the registry. Analysis of loss to follow-up rates before and after this introduction found the incentive of a stipend, to reimburse healthcare professionals for the time taken to report follow-up pregnancy outcome data, did not significantly reduce the proportion of pregnancies lost to follow-up.[14]

Statistical power

A combination of low enrolment, loss to follow-up and a low frequency of the exposure and outcome of interest limits the statistical power and validity of pregnancy exposure registries. At best, pregnancy registries are often only powered to detect major teratogens and evaluate the risk of all major congenital malformations combined. There may, however, be instances where a registry generates a signal relating to an increased risk of a particular defect type.[15] In these instances, although data from other pregnancy registries monitoring the same exposure can be analysed in an attempt to confirm of refute the possible association, it is likely that they too will lack statistical power and therefore additional data sources will be required to investigate this further.

Information on potential confounders

When sample sizes are small, the inclusion of too many confounding variables can make any statistical models of risk assessment unstable but as more individuals are enrolled the number of confounding variables considered can potentially be increased.[16] Pregnancy exposure registries, however, require primary data collection, which can be both costly and time consuming. This can often mean that less information on potential confounding variables is requested so as not to dissuade pregnant women and healthcare professionals from choosing to enrol.[17] For the identification of a high-risk teratogen a lack of this information, although restrictive, is unlikely to dramatically alter the risk estimates.[1]

Comparator group

The selection of a suitable comparator group when evaluating data from pregnancy exposure registries is challenging, especially when there is a possibility that the medical condition that the treatment is for may itself be associated with the outcome of interest (e.g. diabetes, epilepsy).[11] There are many possible comparator groups that can be used and the most appropriate will depend on the question being asked and the exposure and outcome of interest. Some analyses carried out by registries involve making comparisons with population-based birth defect surveillance systems such as the Metropolitan Atlanta Congenital Defects Program (MACDP),[7] some make comparisons with other monotherapy exposures that have been collected via the registry, some registries enrol women who have the disease but were not treated during pregnancy,[12] some enrol their own unexposed comparator group such as family or friends of the exposed woman[18] and some make multiple comparisons using a combination of the comparator groups mentioned. It could be argued however, that given the aim, to identify major teratogenicity, no formal comparator group is needed and instead comparison with background prevalence

should be sufficient.[1, 19] The FDA on their website[b] list a number of international product specific and USA based disease registries. A list of these and other pregnancy registries is provided in Table 1.

b

http://www.fda.gov/scienceresearch/specialtopics/womenshealthresearch/ucm134848.htm

Table 1 An overview of pregnancy registries with contact details as identified at 1 June 2012

Registry	Drug / Disease	Date range	Number of pregnancies reported	Mean number of exposures per year	Further information
Disease specific					
UK Epilepsy and Pregnancy Register	Epilepsy All anticonvulsants	1996 – is ongoing	7,120 by April 2009	~565	http://www.epilepsyandpregnancy.co.uk/
Irish Epilepsy and Pregnancy Register	Epilepsy All anticonvulsants	2001 – 2007 2007 – formally joined with the UK Epilepsy and Pregnancy Register			http://www.epilepsypregnancyregister.ie/about%20the%20register.html
Australian Epilepsy Pregnancy Register	All anticonvulsants	1999 – is ongoing	1,436 by 2009	~150	http://www.neuroscience.org.au/apr/
North American Antiepileptic Drug Pregnancy Registry	Epilepsy All anticonvulsants	1997 – is ongoing	8,500 by April 2012	~550	http://www2.massgeneral.org/aed/
Antiretroviral Pregnancy Register	HIV/AIDs All antiretrovirals	1989 – is ongoing	16,142 by July 2011 14,198 with outcome data	~717 ~630	http://www.apregistry.com/
National Transplantation Pregnancy Registry	Including: Mycophenolate (Myfortic and Cellcept) Belatacept (Nulojix)	1991 – is ongoing	>3,300	~165	http://www.tju.edu/NTPR/
The UK Transplant Pregnancy Registry		Mar 1997 – is ongoing			
Adenovirus vaccine Pregnancy Registry		Dec 2011 – is ongoing			adenovirus@incresearch.com
Cancer and Childbirth Pregnancy Registry					www.cancerandpregnancy.com
Product specific					
EURAP – European and	All anticonvulsants	1999 – is ongoing	17,454 by June 2012	~1300	http://www.eurapinternational.org/

International registry of antiepileptic drugs in pregnancy					
National Pregnancy Registry for Atypical Antipsychotics	Abilify (aripiprazole) Clozaril (clozapine) Geodon (ziprasidone) Invega (paliperidone) Risperdal (risperidone) Seroquel (quetiapine) Zyprexa (olanzapine) Saphris (asenapine) Latuda (lurasidone)	Nov 2008 – is ongoing			http://www.womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/ http://clinicaltrials.gov/ct2/show/NCT01246765?term=pregnancy+registry&rank=14
Laronidase	Mucopolysaccharidosis I Hurler's Syndrome Scheie's Syndrome Hurler-Scheie Syndrome	April 2003 – is ongoing	>1000 by Dec 2011	~120	https://www.lsdregistry.net/mpsiregistry/
Benlysta Pregnancy Registry	Systemic lupus erythematosus (SLE)	Nov 2011 – is ongoing			http://pregnancyregistry.gsk.com/benlysta.html
Exenatide Pregnancy Registry	Type 2 Diabetes	Dec 2007 – is ongoing			http://www.exenatidepregnancyregistry.com/ http://clinicaltrials.gov/ct2/show/NCT00579150
Cymbalta Pregnancy Registry	Major depressive disorder Generalized anxiety disorder Diabetic Peripheral Neuropathic Pain Fibromyalgia	July 2009 – is ongoing			http://www.cymbaltapregnancyregistry.com/ http://clinicaltrials.gov/ct2/show/study/NCT01074151
Fabry Registry	Fabry Disease Agalsidase beta				https://www.lsdregistry.net/fabryregistry/
The Gilenya Pregnancy Registry	Multiple sclerosis Fingolimod	Oct 2011 – is ongoing			http://clinicaltrials.gov/ct2/show/NCT01285479

The Herceptin Pregnancy Registry	Breast cancer Trastuzumab	Dec 2008 – is ongoing			http://www.herceptinpregnancyregistry.com/ http://clinicaltrials.gov/ct2/show/NCT00833963
The Pregnancy Registry for JANUVIA and JANUMET	Type 2 Diabetes				http://www.merckpregnancyregistries.com/januvia.html
UCB Keppra Pregnancy Registry	Epilepsy Levetiracetam (Keppra)	Dec 2004 – is still ongoing			http://www.kendle.com/LS_Pregnancy_Registries.php http://clinicaltrials.gov/ct2/show/NCT00345475
Merck Pregnancy Registry Program – Maxalt	Migraine headaches Maxalt (rizatriptan)				http://www.merckpregnancyregistries.com/maxalt.html
Pompe Disease Registry	Myozyme (alglucosidase alfa)	Sept 2004			https://www.lsdregistry.net/pomperegistry/
Neoral Pregnancy Registry for Psoriasis and Rheumatoid Arthritis					
Nplate (romiplostim) Pregnancy Exposure Registry	Thrombocytopenic Purpura				http://www.amgenpregnancy.com/en-us/patient/the-program.aspx
Nuvigil Pregnancy Registry	Excessive sleepiness associated with obstructive sleep apnea, hypopnea syndrome, narcolepsy, shift work sleep disorder				http://www.nuvigilpregnancyregistry.com/
Amgen's Pregnancy Surveillance Program	Available for all of Amgen's medications	Is ongoing			http://www.amgenpregnancy.com/en-us/patient/pregnancy-exposure-registries/pregnancy-exposure-registries-for-other-amgen-products.aspx
PROMACTA Pregnancy Registry	Thrombocytopenia	Mar 2010 – is ongoing			http://clinicaltrials.gov/ct2/show/NCT01064336

Provigil Pregnancy Registry	Excessive sleepiness associated with obstructive sleep apnea, hypopnea syndrome, narcolepsy, shift work sleep disorder	Is ongoing			http://provigilpregnancyregistry.com/
Ribavirin Pregnancy Registry	Hepatitis C	2003 – is ongoing	391 by Feb 2011	~50	http://www.ribavirinpregnancyregistry.com/
Savella Pregnancy Registry	Fibromyalgia	Nov 2009 – is ongoing			http://www.savellapregnancyregistry.com/
Singular Merck Pregnancy Registry	Asthma Singular (montelukast)				http://www.merckpregnancyregistries.com/singulair.html
Tysabri Pregnancy Registry	Multiple Sclerosis	Jan 2007 – is ongoing			http://clinicaltrials.gov/ct2/show/NCT00472992
VIBATIV Pregnancy Registry	Antibacerial skin infection	Nov 2009 – is ongoing			http://www.vibativ.com/SafetyInPregnancy.aspx http://clinicaltrials.gov/ct2/show/NCT01130324
EXPECT Xolair Pregnancy Registry	Asthma	Is ongoing			http://www.xolairpregnancyregistry.com/
The ellaOne Pregnancy Registry	Emergency contraception				http://www.hra-pregnancy-registry.com/en/
Vaccine specific					
Merck Gardasil Pregnancy Registry	Human papillomavirus	Is ongoing			http://www.merckpregnancyregistries.com/gardasil.html
Menactra vaccine Pregnancy Registry	Meningococcal vaccine	Is ongoing			http://www.sanofipasteurpregnancyregistry.com/?fa=menactra
ADACEL vaccine Pregnancy Registry	booster immunization for the prevention of tetanus, diphtheria, and pertussis	Is ongoing			http://www.sanofipasteurpregnancyregistry.com/?fa=adacel
The pregnancy registry	VARIVAX	1995 – is ongoing			http://www.merckpregnancyregistries.com/variva

for Varicella Zoster Virus containing vaccines	PROQUAD ZOSTAVAX	2006 – is ongoing 2006 – is ongoing			x.html
Cervarix Pregnancy Registry	Cervarix™ Human Papillomavirus Bivalent (Types 16 and 18) Vaccine	Is ongoing			http://pregnancyregistry.gsk.com/Cervarix.html
Twinrix Pregnancy Registry	Twinrix® Hepatitis A & Hepatitis B (Recombinant) Vaccine	Is ongoing			http://pregnancyregistry.gsk.com/twinrix.html
Boostrix Pregnancy Registry	Boostrix® Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine, Adsorbed	Is ongoing			http://pregnancyregistry.gsk.com/boostrix.html
Varilrix Pregnancy Registry	Varicella Vaccine	Is ongoing			http://pregnancyregistry.gsk.com/Varilrix.html
Priorix Pregnancy Registry	Measles, mumps and rubella vaccine	Is ongoing			http://pregnancyregistry.gsk.com/Priorix.html
Fluorix Pregnancy Registry	Influenza virus vaccine	Is ongoing			http://pregnancyregistry.gsk.com/fluarix.html
Flulaval Pregnancy Registry	Influenza virus vaccine	Is ongoing			http://pregnancyregistry.gsk.com/flulaval.html
Varivax Pregnancy Registry	Prevention of chickenpox	1995 – is ongoing			
Closed registries					
Acyclovir Pregnancy	Herpes Simplex	01/06/1984	597	~40	http://pregnancyregistry.gsk.com/acyclovir.html

Registry		Stopped enrolment in 30/04/1999			
Amevive Pregnancy Registry	Chronic plaque psoriasis Ameviv	March 2004 – March 2012			http://clinicaltrials.gov/ct2/show/NCT00342862
Avonex Pregnancy Registry	Rheumatoid arthritis Ankylosing spondylitis Psoriatic arthritis Psoriasis Relapsing multiple sclerosis	February 2004 – September 2011			http://clinicaltrials.gov/ct2/show/NCT00168714
Betaseron Pregnancy Registry	Relapsing forms of multiple sclerosis	Stopped enrolment 31/07/2011			http://www.betaseronpregnancyregistry.com/index.html
Buproprion Pregnancy Registry	Depression	31/09/1997 Stopped enrolment 01/11/2007	1,597	~150	http://pregnancyregistry.gsk.com/documents/bup_report_final_2008.pdf
Fluoxetine Pregnancy Registry	Depression Fluoxetine	01/07/1989 – Closed 09/04/1999	796	~120	Closed
Lamotrigine Pregnancy Registry	Lamotrigine regardless of indication	31/09/1992 – Stopped enrolment 03/06/2009	3,416 2,444 with known outcomes	~200 ~150	http://pregnancyregistry.gsk.com/lamotrigine.html
Raptiva Pregnancy Registry	Chronic moderate to severe plaque psoriasis	Jan 2005 – Sept 2009			http://clinicaltrials.gov/ct2/show/NCT00097240
Rebif Pregnancy Registry	Multiple Sclerosis	Dec 2002 – Feb 2008	34	~7	http://clinicaltrials.gov/ct2/show/NCT00338741
Sumatriptan and Naratripan Pregnancy Registry	Migraine Sumatriptan and Naratriptan	01/01/1996 Stopped enrolment 31/01/2012	809 sumatriptan 92 naratriptan	~50 ~ 6	http://pregnancyregistry.gsk.com/sumatriptan.html
Valacyclovir Pregnancy Registry		01/01/1995 Stopped enrolment 30/04/1999	22	~5	http://pregnancyregistry.gsk.com/acyclovir.html

Other					
OTIS* – Autoimmune Disease in Pregnancy study	Tocilizumab Leflunomide Etanercept Adalimumab Abatacept				http://www.otispregnancy.org/
Motherisk Pregnancy Registry Program	Including: Lamisil Meridia (Sibutamine) Singulair (Montelukast)				http://www.motherisk.org/women/currentStudies.jsp
Hepatitis B Vaccine in Pregnancy Motherisk Program	Twinrix Engerix-B Recombivax HB Comvax				http://www.motherisk.org/women/index.jsp

* OTIS = Organization of Teratology Information Specialists

Literature search to identify alternative data sources to pregnancy exposure registries

Pregnancy exposure registries have been successful in both providing reassurance that certain products are not major teratogens[20] and in generating signals of potential teratogenicity that require further investigation.[15] Their limitations, however, along with the acceptance that a single data source is unlikely to be sufficient to provide all the answers, have led researchers to identify alternative and complementary sources of data for evaluating safety of prenatal drug exposures.

One alternative type of data source that is becoming the focus of much research is that of electronic healthcare databases. Electronic databases are increasingly being used to manage medical insurance claims and patient medical records and this has resulted in an ever-growing volume of healthcare data being available for pharmacoepidemiology research. The initial signal that suggested a possible association between first trimester exposure to paroxetine (a selective serotonin reuptake inhibitor (SSRI)) and an increased risk of major congenital malformations and cardiovascular defects resulted from a study based on electronically recorded healthcare claims data from the United States.[21] Given that there was no pregnancy exposure registry set up for paroxetine this potential association could have otherwise gone undetected. Following the initial study a number of other studies were conducted using a range of different data sources and epidemiological study designs in order to try to confirm or refute the association.[22-26] The findings of these studies ultimately resulted in changes being made to the product label.[27]

Additional sources of information on drug exposures during pregnancy and associated pregnancy outcomes have the ability to complement pregnancy exposure registries in a number of ways. This document reports on a literature review carried out to identify additional data sources that are currently being used to monitor the safety of medicine

use during pregnancy. This review builds on a review that was published in January 2008.[9]

Methods

A review of the literature was conducted to identify papers (excluding conference abstracts) reporting on the safety of medicine use during pregnancy that had used a data source which had systematic data collection. In PubMed papers were identified based on the following search: ((‘Pregnancy’[Mesh] OR ‘Congenital Abnormalities’[Mesh] OR ‘Teratogens’[Mesh]) AND (‘Product Surveillance, Postmarketing’[Mesh])), whilst in Embase papers were identified based on ((‘Pregnancy’ OR ‘Pregnancy outcome’ OR Pregnancy termination’ OR ‘Congenital disorder’ OR ‘Congenital malformation’ OR ‘Birth defects’ OR ‘Teratogenic agent’ OR ‘Teratogenicity’) AND (‘Postmarketing surveillance’ OR ‘Drug surveillance program)) and were restricted to papers reporting on studies in Humans. All papers were restricted to those published in English between 1 January 2000 and 30 November 2011. In addition to searching the literature, individuals who are specialists in the field of drug safety in pregnancy were consulted to ensure any additional data sources were captured.

Results

The literature searches identified 236 articles through PubMed and a further 381 articles via Embase. Of these 505 were excluded following review of the title and abstract and a further 30 were excluded following review of the full text (Figure 1).

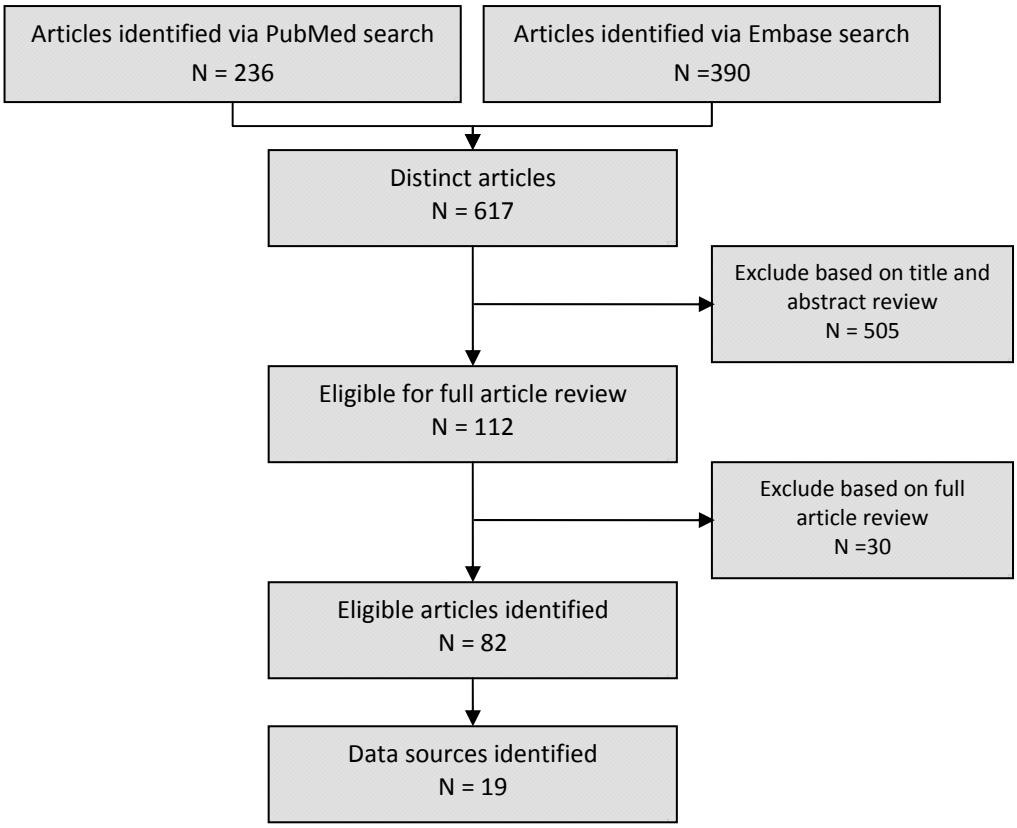

Figure 1 Identification of articles in the literature

Table 2 summarises the rationale for excluding the papers identified and excluded at this stage. A total of 82 articles were included. Overall the studies reported on used data from 19 different data sources. A further 6 data sources were identified and included as a result of our knowledge of the sources available and by contacting specialists in the field. Table 3 provides an overview of each of the 25 data sources identified. Where the papers identified via the literature search did not have sufficient information to complete all the fields in the table, additional papers reporting on those sources where identified. Where information was still missing, the authors of the papers were contacted.

Table 2 Summary of the rationale for those articles excluded

Reason for exclusion	Number of articles excluded
Pregnancy exposure registries	23
Teratology information centres	17
Field studies with one-off manual data collection	16
Meta-analyses	7
Spontaneous/case reports	11
Environmental or occupational exposures	19
Alcohol or illicit drug use exposures	6
Overview of teratogenicity in general or pregnancy exposure registries	47
Comments or letters to the editor	97
Review papers	154[c]
Other (e.g. product surveillance in general - not specifically pregnancy, reviews of medical conditions during pregnancy)	138[b]

[c] These categories are large but they mainly come from the Embase search where the search strategy is not as refined as in PubMed and this results in a large number of unrelated publications being identified

Table 3 Summary of the data sources identified to evaluate the safety of medicine use during pregnancy
Key: Dark text represents those variables captured by the data source and light text represents those variables that are not available.

Name of data source	Time period of data collection	Population covered	Source of exposure information	Types of pregnancy outcome captured	Source of outcome information	Additional risk information (all capture maternal age)
Population-based record linkage surveillance systems						
Swedish Medical Birth Register[22, 28]	Medical birth register since 1973, including drug use since July 1994 Prescribed drug register since 2005	**Country** Sweden **Population-based –** Yes ~98% of all deliveries **Sample size** ~110,000 births per year	Maternal self reporting at first antenatal interview and copies of antenatal care records are reviewed Prescribed drug register of filled prescriptions since 2005	• Live births • Stillbirths • Spontaneous losses • Elective terminations	Identified from the Register of Birth Defects and the Patient Register – data recorded by a paediatrician **Opportunity for medical record review** - Yes	• Smoking status • Alcohol consumption • Body mass index • Socioeconomic status • Maternal diagnoses • Co-prescribing • Folic acid - if reported • Over-the-counter medicines - if reported • Reproductive history
Norwegian Medical Birth	Medical birth	**Country** Norway	Recorded during	• Live births • Stillbirths	Recorded by physicians and	• Smoking status – since 1998

Register[29, 30]	registry of Norway since 1967, including drug use since 1998 Norwegian Prescription database since 2004	**Population-based –** Yes Compulsory reporting of all births and late abortions from 12 weeks gestation **Sample size** ~60,000 births per year	antenatal visits to GP, midwife and obstetrician. Potential to use prescribed drug register of filled prescriptions since 2004	• Spontaneous losses • Elective terminations - from 12 weeks gestation	midwives **Opportunity for medical record review** – Yes	• Alcohol consumption • Body mass index • Socioeconomic status • Maternal diagnoses • Co-prescribing • Folic acid - Since 1998 • Over-the-counter medicines - if the GP is aware • Reproductive history
Finnish linked national health registers[31, 32]	Medical birth register since 1987 Register on induced abortions since 1977 Register of reimbursem	**Country** Finland **Population-based –** Yes Compulsory reporting of all deliveries and elective terminations **Sample size**	Information on reimbursed purchases of prescription medicines from the Register of Reimburseme nt Drugs	• Live births • Stillbirths • Spontaneous losses • Elective terminations Will have spontaneous losses treated in hospital and primary care	Identified from the register of congenital malformations – data recorded by hospital personnel. **Opportunity for medical record review** - Yes	• Smoking status • Alcohol consumption • Body mass index • Socioeconomic status • Maternal diagnoses - chronic • Co-prescribing • Folic acid – high dose only

	ent drugs since 1994	~58,000 deliveries and ~ 10,500 elective terminations per year		from 2011		• Over-the-counter medicines • Reproductive history
Danish National Patient Registry[33-35]	Danish National Patient Registry since 1996 Prescription data from 1995 but only available since 2003	**Country** Denmark **Population-based –** Yes Compulsory reporting of all births **Sample size** ~50,000 deliveries per year	Filled prescription data from the Registry of Medicinal Product Statistics since 2003 Previously would have been self reported via maternal interview	• Live births • Stillbirths • Spontaneous losses • Elective terminations	Routinely recorded inpatient and outpatient data recorded by paediatrician **Opportunity for medical record review** - Yes	• Smoking status • Alcohol consumption • Body mass index • Socioeconomic status • Maternal diagnoses - hospital diagnoses only • Co-prescribing • Folic acid – high dose only • Over-the-counter medicines • Reproductive history
The North Jutland Pharmaco-Epidemiologi	Prescription database since 1991	**Country** Denmark **Population-**	Dispensed prescription data used to secure	• Live births • Stillbirths • Spontaneous losses	County hospital Discharge Register – discharge	• Smoking status • Alcohol consumption • Body mass index

cal Prescription Database with linked registries[36]	Danish National Patient Registry since 1996	**based –** Yes County of North Jutland - compulsory reporting of all births **Sample size** ~6,000 deliveries a year	reimburseme nt from the Health Service to the pharmacies	• Elective terminations	diagnoses recorded by paediatrician **Opportunity for medical record review** - Yes	• Socioeconomic status • Maternal diagnoses - hospital diagnoses only • Co-prescribing • Folic acid – high dose only • Over-the-counter medicines • Reproductive history
Saskatchewa n population registries[37, 38]	Hospital date fro 1970 Prescription data from 1975	**Country** Canada **Population-based –** Yes Covers >90% of the Canadian province **Sample size** ~11,400 deliveries per year	Dispensed prescriptions on the Outpatient Prescription Drug Database	• Live births • Stillbirths • Spontaneous losses • Elective terminations	Identified from the Hospital Services Database – data recorded electronically by physician **Opportunity for medical record review** - Yes	• Smoking status • Alcohol consumption • Body mass index • Socioeconomic status • Maternal diagnoses • Co-prescribing • Folic acid • Over-the-counter medicines • Reproductive history

Taiwan National Health Insurance Research Dataset linked to the Birth Certificate Registry[39]	Since 1996	**Country** Taiwan **Population-based –** Yes ~98% of the Taiwan population **Sample size** ~200,000 births per year	Dispensed prescription data recorded in the National Health Insurance Research Dataset	• Live births • Stillbirths • Spontaneous losses • Elective terminations	Identified from medical claims recorded in the National Health Insurance Research Dataset **Opportunity for medical record review** - No	• Smoking status • Alcohol consumption • Body mass index • Socioeconomic status - maternal education only • Maternal diagnoses • Co-prescribing • Folic acid • Over-the-counter medicines • Reproductive history
Western Australia population-based Data Linkage System[40, 41]	Since 2002 Birth defect registry since 1980	**Country** Australia **Population-based –** Yes All pregnancies in Western Australia **Sample size** ~ 40,000	Dispensed prescriptions. Covers those issued in community and private hospitals and from 2004 public hospitals that are subsidised	• Live births • Stillbirths • Spontaneous losses • Elective terminations Looking into linking elective terminations with the birth	Notifications received from paediatricians, obstetricians, cytogenetics, ultrasound, genetic counselling departments to the Birth Defects	• Smoking status • Alcohol consumption • Body mass index • Socioeconomic status • Maternal diagnoses • Co-prescribing • Folic acid • Over-the-counter

		pregnancies a year	~80% of all prescriptions	defect registry	Registry of western Australia.	medicines • Reproductive history
Region Emilia-Romagna (RER) Database[42]	Since 2000	**Country** Italy **Population-based –** Yes ~99% of pregnancies in Region Emilia-Romagna **Sample size** ~ 33,000 pregnancies a year	Reimbursed prescription data (~70% of medicines can be reimbursed)	• Live births • Stillbirths • Spontaneous losses • Elective terminations	Hospital assistance at birth records, hospital discharge records and links to Congenital anomaly register **Opportunity for medical record review** –No	• Smoking status • Alcohol consumption • Body mass index • Socioeconomic status • Maternal diagnoses • Co-prescribing • Folic acid • Over-the-counter medicines • Reproductive history
<u>Healthcare databases</u> **Medical record databases**						
General Practice Research Database[43, 44]	Since 1987	**Country** United Kingdom **Population-based –** Yes ~8% sample of	Prescriptions issued by GPs and recorded in medical records	• Live births • Stillbirths • Spontaneous losses • Elective terminations	Diagnoses recorded in medical records by GPs **Opportunity**	• Smoking status • Alcohol consumption • Body mass index • Socioeconomic status

		the UK population **Sample size** ~80,000 pregnancies per year			**for medical record review** - Yes	• Maternal diagnoses • Co-prescribing • Folic acid – high dose only • Over-the-counter medicines • Reproductive history
The Health Improvement Network (THIN)[45, 46]	Since 2003	**Country** United Kingdom **Population based –** Yes ~6% sample of the UK population **Sample size** ~60,000 pregnancies per year	Prescriptions issued by GPs and recorded in medical records	• Live births • Stillbirths • Spontaneous losses • Elective terminations	Diagnoses recorded in medical records by GPs **Opportunity for medical record review** - Yes	• Smoking status • Alcohol consumption • Body mass index • Socioeconomic status • Maternal diagnoses • Co-prescribing • Folic acid – high dose only • Over-the-counter medicines • Reproductive history
Administrative claims databases						
Tennessee	Since 1985	**Country**	Pharmacy	• Live births	Identified from	• Smoking status

Medicaid[47, 48]		United States **Population-based –** No - generally low income adults **Sample size** ~36,000 deliveries per year	claims data for dispensed prescriptions	• Stillbirths • Spontaneous losses • Elective terminations	Medicaid inpatient, emergency department physician visit, hospital, discharge diagnoses records Also link to birth and foetal death certificates **Opportunity for medical record review** - Yes	• Alcohol consumption • Body mass index • Socioeconomic status • Maternal diagnoses - chronic • Co-prescribing • Folic acid • Over-the-counter medicines • Reproductive history
Kaiser Permanente[4] [9, 50]	Since ~1995	**Country** United States **Population-based – No** Under-represents those at the extremes of household	Pharmacy claims data for dispensed prescriptions	• Live births • Stillbirths • Spontaneous losses • Elective terminations	Medical claims records **Opportunity for medical record review** - Yes	• Smoking status • Alcohol consumption • Body mass index • Socioeconomic status - maternal education only • Maternal

		income **Sample size** ~30,000 deliveries per year				diagnoses • Co-prescribing • Folic acid • Over-the-counter medicines • Reproductive history
United Healthcare[21, 51, 52]	Since 1990	**Country** United States **Population-based –** No ~2% of US population. 90% are employer groups, some individuals from Medicaid population **Sample size** ~32,000 deliveries per year**.** ~ 75% of infants remain in the health plan	Electronically recorded dispensed prescription data	• Live births • Stillbirths • Spontaneous losses • Elective terminations	Medical claims records from inpatient, hospital, outpatient, emergency department, surgery centre and physician's office **Opportunity for medical record review** - Yes	• Smoking status • Alcohol consumption • Body mass index • Socioeconomic status • Maternal diagnoses • Co-prescribing • Folic acid • Over-the-counter medicines • Reproductive history
Régie de	Since 1980	**Country**	Dispensed	• Live births	Diagnoses	• Smoking status

l'assurance maladie du Québec (RAMQ)[53, 54]	– recipients of social welfare Since 1997 – workers and their families not covered under private drug insurance	Canada **Population-based –** No Drug information for only recipients of social welfare and those who do not have private healthcare **Sample size** ~20,000 pregnancies per year	prescription data	• Stillbirths • Spontaneous losses • Elective terminations	recorded in the administrative databases of RAMQ and MED-ECHO **Opportunity for medical record review** - No	• Alcohol consumption • Body mass index • Socioeconomic status • Maternal diagnoses • Co-prescribing • Folic acid • Over-the-counter medicines • Reproductive history
Clalit Data Warehouse[55, 56]	Since 1998	**Country** Israel **Population based -** No Members of the Southern district of Clalit Health Services - ~70% of women 15-49 years	Dispensed prescription data	• Live births • Stillbirths • Spontaneous losses • Elective terminations	Medical diagnoses during hospitalisation drawn directly from hospital records **Opportunity for medical record review**	• Smoking status • Alcohol consumption • Body mass index • Socioeconomic status • Maternal diagnoses • Co-prescribing • Folic acid - some • Over-the-counter

		Sample size ~9,500 births per year			-Yes	medicines • Reproductive history
Purpose built surveillance systems						
Slone Epidemiology Unit Birth Defects Study[23, 57]	Since 1976	**Country** United States and previously Canada **Population based -** Yes **Sample size** To date >40,000 women have been interviewed	Self-reporting via maternal telephone questionnaire (face to face interview up until 1998)	• Live births • Stillbirths • Spontaneous losses • Elective terminations	Recorded by a paediatrician **Opportunity for medical record review** -Yes, with mothers permission	• Smoking status • Alcohol consumption • Body mass index • Socioeconomic status • Maternal diagnoses • Co-prescribing • Folic acid • Over-the-counter medicines • Reproductive history Opportunity to add additional interview questions relevant to a particular study.

National Birth Defects Prevention Study[58, 59]	Since 1997	**Country** United States **Population based -** Yes **Sample size** ~10% of annual US birth cohort	Self reporting of exposure by maternal assisted telephone interview between 6 weeks and 2 years after the expected date of delivery	• Live births • Stillbirths • Spontaneous losses • Elective terminations The capture of stillbirths and elective terminations varies by state Controls are live births only	Medical record extraction **Opportunity for medical record review -** Yes	• Smoking status • Alcohol consumption • Body mass index • Socioeconomic status • Maternal diagnoses • Co-prescribing • Folic acid • Over-the-counter medicines • Reproductive history Opportunity to add additional interview questions relevant to a particular study
The Latin-American Collaborative Study of Congenital Malformations (ECLAMC)[60, 61]	Since 1967	**Country** 9 countries in South America **Population based -** Yes **Sample size**	Self reported by the mother and collected by a trained paediatrician during the puerperium	• Live births • Stillbirths • Spontaneous losses • Elective terminations	Identified from registered malformations diagnosed at birth **Opportunity for medical**	• Smoking status • Alcohol consumption • Body mass index • Socioeconomic status • Maternal diagnoses

		~150 - 200,000 births per year			**record review -** No	• Co-prescribing • Folic acid • Over-the-counter medicines • Reproductive history Collects data on 50 possible risk factors
Spanish Collaborative Study of Congenital Malformations (ECEMC)[62, 63]	Since 1976	**Country** Spain **Population based -** Yes **Sample size** ~87,000 births per year ~1,100-1,300 case-control pairs per year	Maternal interviews with paediatricians within the first 3 days following delivery.	• Live births • Stillbirths • Spontaneous losses • Elective terminations	Diagnosed by paediatricians within the first 3 days of life. **Opportunity for medical record review -** No	• Smoking status • Alcohol consumption • Body mass index • Socioeconomic status • Maternal diagnoses • Co-prescribing • Folic acid • Over-the-counter medicines • Reproductive history >300 data points of information collected.

Hungarian Case-control of Congenital Abnormalities Study[64]	1980-1996 Appears to be no longer recruiting - Emailed Professor Czeizel but did not get a response	**Country** Hungary **Population based -** Yes **Sample size** In 1996 ~22,843 cases and 38,151 controls	Review of antenatal log book and medical records recorded by obstetrician, additional data requested by maternal questionnaire	• Live births • Stillbirths • Spontaneous losses • Elective termination - following a prenatal malformation diagnosis	Cases reported by a physician or paediatrician during first 3 months after birth or termination. **Opportunity for medical record review -** Yes, discharge summaries	• Smoking status • Alcohol consumption • Body mass index • Socioeconomic status - employment status only • Maternal diagnoses • Co-prescribing • Folic acid • Over-the-counter medicines • Reproductive history
European Concerted Action on Congenital Anomalies and Twins (EUROCAT)[65-67]	Since 1979	**Country** 20 European countries **Population based -** Yes **Sample size** ~1.7 million births per year	Varies by register – hospital records, GP records, pharmacy records, maternal interview Not all registers	• Live births • Stillbirths • Spontaneous losses • Elective terminations	Largely reported by a physician to a local or national congenital anomaly register **Opportunity for medical record review**	• Smoking status • Alcohol consumption • Body mass index • Socioeconomic status • Co-morbidities • Co-prescribing • Folic acid • Over-the-counter medicines • Reproductive

			capture drug exposure data		-varies by registry	history **All vary by register**
<u>New data sources undergoing evaluation</u>						
Secure Anonymised Information Linkage Databank (SAIL)[68]	General practice data since 1992 Hospital admissions from 2004	**Country** Wales **Population based –** Yes **Sample size** ~44,000 pregnancies per year	Prescriptions issued by a GP	• Live births • Stillbirths • Spontaneous losses • Elective terminations	Diagnoses recorded by a GP or paediatrician **Opportunity for medical record review** - Yes	• Smoking status • Alcohol consumption • Body mass index • Socioeconomic status • Maternal diagnoses • Co-prescribing • Folic acid – high dose only • Over-the-counter medicines • Reproductive history
German Pharmaco-epidemiological Research Database[69]	Assessment of a mother-baby link in 2010	**Country** Germany **Population based –** No German	Dispensation data of reimbursed drugs	• Live births • Stillbirths • Spontaneous losses • Elective terminations	Under investigation but have access to hospital data and ambulatory	• Smoking status • Alcohol consumption • Body mass index • Socioeconomic status

		statutory health insurances **Sample size** ~83,000 live births per year		Work is ongoing into the capture of pregnancy losses	physician visits **Opportunity for medical record review** - No	• Maternal diagnoses • Co-prescribing • Folic acid • Over-the-counter medicines • Reproductive history
Evaluation chez la Femme des Medicaments et de leurs RISque (EFEMERIS Database)[70]	Since 2004	**Country** France **Population based -** No Pregnant women in the Haute-Garonne department registered under general state coverage (~80% of the population **Sample size** ~13,500 pregnancies per year	Dispensed prescription data recorded to be sent to the French Health Insurance System Caisse Primaire d'Assurance Maladie (CPAM)	• Live births • Stillbirths • Spontaneous losses • Elective terminations	Recorded by physician during compulsory medical examinations at 8 days, 9 months and 3 years Prenatal diagnoses resulting in a termination are recorded by the antenatal diagnostic centre **Opportunity**	• Smoking status • Alcohol consumption • Body mass index • Socioeconomic status • Maternal diagnoses • Co-prescribing • Folic acid • Over-the-counter medicines • Reproductive history

					for medical record review - No	

Discussion of alternative data sources

The review of the literature identified a large number of data sources being used for drug safety in pregnancy research. Based on the population captured and the type of data collected they can be grouped into three broad categories: population-based surveillance registers that rely on linked data sets, healthcare databases and purpose-built data sources such as case-control surveillance systems. Below, the key strengths and limitations of each type of data source are summarised.

Population-based surveillance registers

A key strength of population-based surveillance registers, such as those of the Nordic countries, is the mandatory reporting of all live- and stillbirths within a country or region. This results in the capture of exposure and outcome data from a representative sample of women and reduces concerns about the generalisability of study findings. One limitation, however, is that not all of these registers capture spontaneous pregnancy losses and induced terminations of pregnancy.

In the past, almost all data collected on first trimester drug exposure in these registers would have been based on maternal self-reporting during antenatal visits. Today, however, many have access to linked prescription data and the independent recording by the prescriber has the advantage of removing the possibility of recall bias. Capturing prescription data only does, however, mean over-the-counter exposures are not covered and there is a lack of information on whether the woman actually took the medicine and the precise timing of exposure. Studies using population based surveillance registers often identify congenital malformations from birth defect registers. As malformations are reported to these registers by physicians, midwives or paediatricians, the recording and reliability of the data is thought to be good.

Population-based surveillance registers have similar restrictions to pregnancy registries in terms of the volume of information that can be feasibly collected on covariates of interest, owing to the time available during an antenatal care interview with a midwife. Whilst they all tend to

collect data on maternal chronic diseases and co-prescribing, data on lifestyle factors such as alcohol intake, smoking status and body-mass-index is not always available.

Healthcare databases

Two main types of healthcare database were identified from the review of the literature; those that contain patient medical records and those that are based on administrative claims for reimbursement of medical treatment and prescriptions. Medical record databases such as the GPRD and The Health Improvement Network (THIN) capture data on a representative sample of the UK population in terms of age, sex and morbidity.[71] The representative nature of the population captured by claims databases, however, varies by the type of insurance policy. The population of Kaiser Permanente, for example, has been found to be reasonably representative of the geographical areas that it covers, although the extremes of household income are thought to be under-represented. Tennessee Medicaid, however, is a US government-funded scheme and generally captures more mothers from populations with lower socio-economic status.[72]

Electronic medical record data has the advantage of exposure information being recorded prospectively by the prescriber before the pregnancy outcome is known.[71] Claims data from dispensing sources also has the added advantage that exposure classification is based on dispensed, rather than prescribed, prescriptions however, uncertainty remains as to whether the medication was actually used.[73] Neither source captures information on over-the-counter exposures including standard dose (400µg) folic acid.

Identification of congenital malformations within healthcare databases is based on the presence of medical codes relating to either a diagnosis of or treatment for a congenital malformation. The level of detail and completeness of the information available in these codes varies considerably. In primary care medical records, diagnoses made in a hospital setting will only be recorded in the database if the patient's GP

chooses to enter the information received from a specialist. Medical codes recorded for the purpose of administrative claims may lack detail and accuracy as they are recorded purely for the purpose of creating an invoice for payment and therefore for the purposes of the database it is the procedure, rather than the diagnosis, that is of the greatest importance. Primary care medical record databases have the advantage of capturing all types of pregnancy outcome including spontaneous abortions and induced terminations of pregnancy, which are not commonly available within administrative claims databases.

Within healthcare databases medical information is routinely recorded preventing the need for active follow-up as is required by pregnancy registries. Medical record databases have the benefit that an individual can only be lost to follow-up if they change GP practice or the GP practice stops contributing data to the database. This enables individuals to be followed for many years without any additional effort and makes it possible to identify malformations diagnosed later in life. Administrative claims databases, however, often have less follow-up time as individuals may change insurer when they move jobs or when they become pregnant, which can reduce the availability of exposure and outcome data for research purposes.

Electronic medical records such as the GPRD contain information on smoking, alcohol and body mass index (BMI) although this information is not always complete and available for every patient.[74] Information on lifestyle factors is less likely to be recorded in claims databases,[73] owing to the purpose and nature of the database, although there are exceptions such as Tennessee Medicaid, which contains data on smoking status.

One recognised advantage of healthcare databases is the large number of individuals and pregnancies that they capture. Contrary to some belief, however, small sample sizes can still be a limitation and the ability to identify an association in these databases is dependent on the prevalence of the disease being studied and the frequency of prescribing.[9]

Data sources that capture a representative sample of the population, rather than only those with a particular disease or exposure enable the identification of multiple internal comparator groups that will have been recruited in the same way as those exposed to the product of interest.[9] Depending on the exposure(s) of interest, these data sources may still be limited in terms of the number of individuals that are eligible for inclusion in any particular control group.

Case-control surveillance systems

Case-control surveillance systems are purpose-built data sources where cases and controls are recruited with the aim of the data being analysed using the case-control study design. The efficiency and statistical power resulting from the case-control study design are key strengths in enabling these data sources to be used to detect increases in risk for rare outcomes and malformation types.

One of the main limitations of case-control surveillance systems is the fact that exposure data is collected by maternal self reporting after the pregnancy outcome is known. This has the potential to introduce recall bias if there is differential reporting of exposure between women who had a pregnancy outcome with a congenital malformation and those who did not. In some circumstances attempts can be made to control for this by selecting malformed controls for the risk assessment studies; either those with chromosomal defects or those with a malformation other than the one(s) of interest and thought not to be associated with the exposure under study.

Systems that rely on maternal self-reporting do, however, have the advantage that they are able to collect data on all types of exposures including those issued in a hospital, bought over-the-counter or even borrowed from a friend or relative. A further strength is that there is the ability to extend or adapt the interview questionnaire to include questions on any potential confounding variables that may be associated with the particular exposures and outcomes of interest.[57]

Case-control surveillance systems either recruit cases of congenital malformations directly from hospitals or birth defect registries where they have been reported and diagnosed by a paediatrician and often have the benefit of access to patient medical records with the mother's consent. Although some systems do capture stillbirths and induced terminations of pregnancy[66] no system captures spontaneous pregnancy losses.

Purpose-built case-control surveillance systems have a number of strengths for drug safety in pregnancy research but unfortunately they are expensive and often trade-offs have to be made in terms of the amount and level of detail of information collected and the time and cost required for data collection. There is also a need to limit the amount of information requested to minimise the burden on participants in order to maximise recruitment.

Other data sources

In addition to the data sources with systematic data collection outlined in Table 2.2, the review of the literature identified a number of publications by Teratology Information Services (TIS).[75-79] The TIS recruit women who have voluntarily contacted them in search of information on the safety of a medicine they have used during pregnancy. Women who consent participate in a short telephone interview and are given a diary to record any further exposures. They are then contacted shortly after the expected date of delivery to obtain information on the pregnancy outcome. The voluntary nature of enrolment of women in these studies means they are subject to potential selection and self-referral biases and often the number of exposures captured for a particular product is small. The TIS are, however, valuable signal generating tools and they have the strength that information on a large number of potential confounding variables can be collected.

The International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR) was one source that was identified that did not fit into a single data source category.[80,81] The ICBDSR is affiliated with the World Health Organisation and aims to bring together a range of data sources

being used for birth defect research including congenital anomaly registries, case-control surveillance systems and national birth registers. A number of the data sources listed in Table 2.2 also contribute data and are members of the ICBDSR.[82]

Conclusion

In addition to pregnancy exposure registries, a large number of other data sources is being used to monitor the safety of medicine use during pregnancy. A number of data sources were identified that are currently undergoing review to determine their suitability to be used in this kind of research.[68, 69, 70]

Not all data sources will be capable of capturing all exposures. Partly this will be because some sources do not capture exposures in hospitals or over-the-counter medicine use but it will also result from differences in prescribing practices and the availability of products in different countries.[11] It is because of these geographical variations that relatively small surveillance systems[70] can be incredibly valuable as a means of monitoring *in utero* drug exposure and its effects.

Few data sources were identified that monitor exposure and pregnancy outcomes in less developed countries. The patient characteristics and medicines available to pregnant women in these countries are likely to differ considerably from other geographical areas and the findings from studies in more developed countries may therefore not be generalisable. In recent years attempts have been made to develop a pregnancy exposure registry evaluating the safety of anti-malarial drugs in malaria-endemic countries[83] but it is likely to be a long time before the healthcare systems of many of these countries have an automated system that can be utilised for drug safety in pregnancy research.

Given that the data sources identified in this review have different strengths and limitations, a combined approach using a range of data sources could enhance considerably the extent of information available to women and healthcare professionals. This needs to be balanced, however,

against the reliability and accuracy of information in each of the information sources contributing, which, to date, has not been established fully for each of these data sources.

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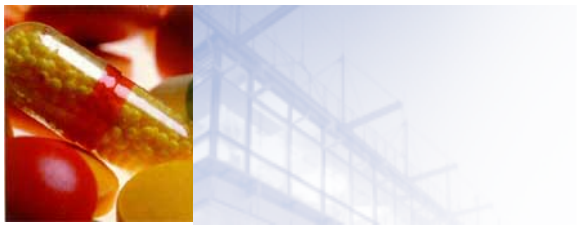

Further information

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