Risk management of teratogenic medicines: A systematic review

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Abstract

Aim: To systematically identify studies of implementing risk management measures when prescribing teratogenic medicines for women of childbearing age and studies reporting risk perceptions of teratogenic medications.

Methods: MEDLINE, CINAHL, Scopus, EMBASE, and International Pharmaceutical Abstracts were searched. Studies were included in the risk management section if they reported any of the following risk management measures: teratogenic counseling, contraceptive counseling, pregnancy testing before starting treatment, pregnancy testing during treatment, use of contraception before starting treatment, and use of contraception during treatment. Studies were included in the perceptions section if they reported perceived teratogenic risk as numerical value.

Results: Fifty-five studies were included in the risk management section and seven studies were included in the perceptions sections. Prevalence of risk management measures varied as follows: teratogenic counseling (9.5%–99.3%), contraceptive counseling (6.1%–98%), pregnancy testing before starting treatment (0%–95.1%), pregnancy testing during treatment (12.7%–100%), contraception use before starting treatment (15.7%–94%), and contraception use during treatment (1.7%–100%). A proper estimation of the teratogenic risk was reported for thalidomide (by general practitioners and obstetric/gynecologists), for etretinate (by pregnant women), and for misoprostol (by pregnant and nonpregnant women). An under-estimation was reported for warfarin and retinoids (by general practitioners and obstetric/gynecologists). And over-estimation was reported for thalidomide, valproate, lithium, isotretinoin, phenytoin, warfarin and etretinate by different populations.

Conclusion: Considerable variation in the implementation of risk management measures when prescribing teratogenic medicines to women of childbearing age is reported in the literature. A common tendency to over-estimate the risk of teratogenic medications was evident.

Keywords
contraception, perception, pregnancy prevention, risk management, teratogenic
1 | INTRODUCTION

A teratogen is a substance that can adversely affect the development of an embryo or a foetus if administered under specific conditions of dose, route of administration, gestational age, and genotype (Bánhidy, Lowry, & Czeizel, 2005). A wide range of substances have been recognized as teratogens, including some medications (Holmes, 2011; Twining’s Textbook of Fetal Abnormalities, A. M. Coady & S. Bower, 2014). There is a need to ensure that potential teratogens are used as safely as possible by women of childbearing age, because the use of teratogenic medications is likely to be inevitable in many cases due to the unavailability of equally effective alternative treatment options (Honein, Moore, & Erickson, 2004; E. B. Schwarz, Parisi, Handler, et al., 2012).

To minimize foetal harm when prescribing potential teratogens, risk management programmes have also been developed for certain medications, with the manufacturer of isotretinoin launching the first pregnancy prevention programme aimed at preventing foetal exposure in 1988 (Honein et al., 2004; Mayall & Banerjee, 2014). Subsequently, the use of teratogenic medications has been increasingly controlled through the development of risk minimisation activities and programmes (Mayall & Banerjee, 2014). Elements to ensure safe use of teratogenic medications include certification of prescribers and dispensers, patient counseling regarding contraception use and monitoring patient contraception behaviors through regular pregnancy testing and use of contraception (FDA, n.d.; Mayall & Banerjee, 2014).

The development and implementation of teratogenic risk management programmes should also take into consideration patients’ experience of using a medication (Bwire, Freeman, & Houn, 2011). The value of recognizing patients’ experience of medication-taking as part of ensuring medications are used effectively and deliver intended outcomes is one of the principles of medicines optimisation, a model for informing pharmacy practice based on the aim of improving outcomes of medication use. The four guiding principles of medicines optimisation are: aim to understand the patient experience; evidence-based choice of medicines; ensure medicines use is as safe as possible and make medicines optimisation part of routine practice (Royal Pharmaceutical Society, 2013). Medicines optimisation is a patient-centred approach for achieving optimal use of medications by providing personalized care for each patient (Cutler, Fattah, Shaw, & Cutts, 2011). Conceptualized in terms of medicines optimisation, with the patient at the centre of healthcare, patients’ views, opinions, and perceptions of taking a teratogenic medicine, and understanding of teratogenic risk, are therefore important factors when investigating the effectiveness of any risk management programme (Collins & Bonneh-Barkay, 2016; Widnes & Schjott, 2017). Moreover, because a key actor in ensuring evidence-based choice of medications are healthcare providers, these stakeholders’ perceptions of teratogenic risk will play a part in understanding patients’ experience of using the medication (Bwire et al., 2011). In fact, evidence from the literature suggests that the patient-physician relationship and teratogenic risk communication have a significant impact on patients’ medication utilization (Widnes & Schjott, 2017). In this context, over-estimation of teratogenic risk may result in poor adherence to treatment during pregnancy, anxiety or pregnancy termination, while under-estimation of teratogenic risk can result in foetal exposure to the harmful effects of a teratogenic medication (Gils, Pottegard, Ennis, & Damkier, 2016; Sanz, Gomez-Lopez, & Martinez-Quintas, 2001; E. B. Schwarz, Maselli, Norton, & Gonzales, 2005).

A growing body of literature has investigated the implementation of pregnancy prevention measures while prescribing teratogenic medications to women of childbearing age (Brandenburg et al., 2017; Hayward et al., 2016; Leverenz et al., 2019; Paton et al., 2018; Uuskula et al., 2018). Additionally, research has focused on the perceived risk of teratogenic medications of various populations (Ceulemans et al., 2019; Gils et al., 2016; Petersen, McCrea, Lupattelli, & Nordeng, 2015). Yet to date, what is lacking is a systematic synthesis of data from a medicines optimisation perspective that explores teratogenic medication safety by systematically reviewing publications on the implementation of risk management (pregnancy prevention) measures when prescribing teratogens to women of childbearing age in combination with a review of patients’ experience of using teratogenic medications in terms of reported perceptions of teratogenic risk.

2 | METHODS

The protocol for this systematic review was registered with PROSPERO (International Prospective Register of Systematic Reviews) registration number CRD42019142944 (Shrouk, Steinke, & Willis, 2019). The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement has guided the write-up of this review paper (Moher, Liberati, Tetzlaff, Altman, & Group, 2009).

2.1 | Information sources

Five electronic databases were systematically searched (MEDLINE, Cumulative Index to Nursing and Allied
Health Literature (CINAHL), Scopus, Embase, and International Pharmaceutical Abstracts (IPA)). The search strategy was based on Medical Subject Headings (MeSH) and free text keywords in each database. Search terms included: pregnancy prevent*, risk manag*, teratogen*, risk perception and perceiv*. No limits were applied to publication dates. Papers not written in English and conference abstracts were excluded. Reference lists of included articles were manually screened to identify additional papers for inclusion in the review. The full search strategy is available in Appendix A.

2.2 Inclusion/exclusion criteria

1. Risk management: the review aimed to establish the implementation of risk management for teratogenic medications used by women of childbearing age. Therefore, papers were included in the review if they reported the use of at least one teratogenic medication by females of childbearing age and the implementation of at least one risk minimisation measure consistent with the Food and Drug Administration (FDA) Risk Evaluation and Mitigation Strategies (REMS) drug safety programme designed to address safety concerns. Most of the included medicines were established teratogens. However, some included medicines were considered potential teratogens like deferoxamine and deferiprone, cyclophosphamide, and mood stabilizers. Safety of teratogenic medications use was further monitored against Elements to Assure Safe Use (ETASU), see Table 1 (Arnold, 2019; Dabrowska, 2018).

Papers focused on the following were excluded from the review: pregnancy rates while using a teratogenic medication, pregnancy outcomes after exposure to a teratogenic medication, emergency contraception, contraception due to a medical condition (medical conditions that require contraception regardless of the use of drugs), abortion or pregnancy termination, side effects of contraceptives, venous thromboembolism, teratogenic risk of contraceptives, prescription patterns during pregnancy and need for contraceptive due to HIV infection.

2. Perceptions of teratogenic risk: to address the aim of reviewing publications reporting how teratogenic risk of medications is perceived, papers included in the review were those reporting perceived teratogenic risk as numerical value. Studies reporting the perception of risk of non-teratogenic medications were excluded from the review.

2.3 Study selection

All papers identified through the database search and through manual search of reference lists were checked to remove any duplicates. Following this, study selection was carried out through three phases. First, all titles were screened against the inclusion and exclusion criteria. Second, abstracts from articles selected in the first phase were screened against the same criteria. Third, full texts of articles retrieved from the second phase were reviewed to check for eligibility for inclusion in the review.

2.4 Data extraction

Data were extracted by the three authors and synthesized into summary tables presenting information about study characteristics, methods and outcomes of interest. For the part covering perceptions of teratogenic risk, the authors aimed to examine whether the results of the included studies indicated a true (proper) estimation of the teratogenic risk or not. If not, the perceived estimations of the teratogenic risk were examined to see if they were higher than the true risk (over-estimated) or lower than the true risk (under-estimated). Therefore, the numeric value of the perceived teratogenic risk extracted from the results section of each paper and presented as a percentage was compared to the true value of the teratogenic risk that was extracted either from the methods or the results section. The true value of the teratogenic risk was described in the included studies as the risk of
causing “congenital malformations” or “birth defects” and was also presented as a percentage to allow comparison with the perceived risk. No description of specific outcomes was included and the risk was described in general terms. The values were based on the available literature on the risk of the included medicines. The authors followed the method shown in Figure 1 to assign the perceived teratogenic risk of every medication included in the review into one of three categories: properly-estimated, over-estimated, or under-estimated.

2.5 | Quality assessment

The critical appraisal tool developed by Hawker et al. (Hawker, Payne, Kerr, Hardey, & Powell, 2002) was used to assess the quality of included papers. The tool includes nine questions to assess the abstract and title, introduction and aims, method and data, sampling, data analysis, ethics and bias, results, transferability or generalisability, and implication and usefulness. Each question has four options: good, fair, poor or very poor, scored from 1 (very poor) to 4 (good). This scoring method therefore allows for a total score to be calculated ranging from 9 to 36 for each paper. Based on the total score for each paper, four quality categories were applied to each paper as follows: high quality (score of 30–36), medium quality (score of 24–29), and low quality (score of 9–24).

Results of the quality assessment were not used as inclusion/exclusion criteria.

2.6 | Data analysis

Extracted data were presented in summary tables. In addition, the following analyses were carried out:

1. Risk management: For each risk minimisation measure reported, prevalence of implementing that measure was calculated as the proportion of a study population reported to be using a measure. This was calculated as follows:

   \[
   \text{Prevalence of risk minimisation measure implementation/100 patients} = \frac{\text{total number of patients implementing the measure}}{\text{total number of patients using the teratogenic medication}} \times 100
   \]

2. Perceptions of teratogenic risk: The perceived teratogenic risk for each medication was assigned into one of three categories: properly-estimated, over-estimated, or under-estimated (as shown previously in Figure 1). Categorized results were presented in tabular form.

3 | RESULTS

3.1 | Risk management

A total of 55 studies were included in the review as shown in Figure 2. Characteristics of the included studies are shown in Table 2 and summarized in Appendix B. Table 3 presents a summary of the risk minimisation measures reported by studies of prescribing teratogenic medications for women of child bearing age. No studies reported on all aspects of risk management included in the current review.

Prevalence of teratogenic counseling ranged from 9.5% (Mulryan et al., 2018) to 99.3% (Brandenburg et al., 2017), contraceptive counseling from 6.1% (E. B. Schwarz et al., 2005) to 98% (Brandenburg et al., 2017), pregnancy
testing before starting treatment from 0% (Chave et al., 2001; Mulryan et al., 2018) to 95.1% (Cheetham et al., 2006), pregnancy testing during treatment from 12.7% (Raguideau et al., 2015) to 100% (Hayward et al., 2016), contraception use before starting treatment from 15.7% (Uuskula et al., 2018) to 94% (Brandenburg et al., 2017), and contraception use during treatment from 1.7% (Tsur et al., 2008) to 100% (Ozyurt & Kaptanoglu, 2015).

3.2 Perceptions of teratogenic risk

A total of 6,000 articles were initially screened. Of those, 141 were removed because of duplication, 5,725 were excluded based on title screening, 68 were excluded based on abstract screening, and 59 were excluded based on full text screening leaving a total of seven articles to be included in the review (see Figure 3). Characteristics of the seven included papers are shown in Table 4.

Two studies out of seven (28.6%) included multiple countries (Lupattelli, Picinardi, Einarson, & Nordeng, 2014; Petersen et al., 2015), and the rest were from Denmark (n = 1; 14.3%) (Gils et al., 2016), Norway (n = 1; 14.3%) (Nordeng, Ystrom, & Einarson, 2010), France (n = 1; 14.3%) (Damase-Michel, Pichereau, Pathak, Lacroix, & Montastruc, 2008), Spain (n = 1; 14.3%) (Sanz et al., 2001), and Brazil (n = 1; 14.3%) (Pons Eda, Pizzol Tda, & Knauth, 2014). All studies had a cross sectional design and were published after the year 2000. Four studies out of seven (57.1%) utilized online questionnaires for data collection (Gils et al., 2016; Lupattelli et al., 2014; Nordeng et al., 2010; Petersen et al., 2015), two studies used questionnaires filled during a continuous educational course (Damase-Michel et al., 2008; Sanz et al., 2001), and one study collected data within prenatal services in primary care (Pons Eda et al., 2014). Data were collected using questionnaires in all studies. A numeric scale was used to measure the perception of teratogenic risk in five studies out of seven (71.4%) (Gils et al., 2016; Lupattelli et al., 2014; Nordeng et al., 2010; Petersen et al., 2015; Pons Eda et al., 2014) and a visual analogue scale was used in two studies (28.6%) (Damase-Michel et al., 2008; Sanz et al., 2001). Five studies (71.4%) (Gils et al., 2016; Lupattelli et al., 2014; Nordeng et al., 2010; Petersen et al., 2015; Pons Eda et al., 2014) were of high quality and two (28.6%) were of medium quality (Damase-Michel et al., 2008; Sanz et al., 2001).

A proper estimation of the teratogenic risk was reported for thalidomide (by general practitioners and obstetric/gynecologists) (Gils et al., 2016), for etretinate (by pregnant women) (Sanz et al., 2001), and for
| Study                          | Country: setting                                                                 | Age     | Time             | Data source | Teratogenic medication | Risk management programme or pregnancy risk classification system                                                                 | Quality assessment score |
|-------------------------------|----------------------------------------------------------------------------------|---------|------------------|-------------|------------------------|------------------------------------------------------------------------------------------------------------------------------------------|-------------------------|
| Algoblan, Bakhsh, and Alharithy (2019) | Saudi Arabia: outpatient clinics including private clinics and governmental hospitals | 33 to 40 | 6/2017–11/2017 | Patient survey | Isotretinoin           | NS                                                                           | 28                      |
| Atturu and Odelola (2015)     | United Kingdom: Adult Psychiatric service                                        | 18 to 45 | 2005–2012        | Medical records | Valproate              | Bipolar disorder: The management of bipolar disorder in adults, children and adolescents, in primary and secondary care (NICE) 2006 | 29                      |
| Banas et al. (2014)           | Poland: NS                                                                       | NS      | NS               | Patient survey | Leflunomide            | Services for patients with epilepsy: report of a CSAG Committee chaired by Professor Alison Kitson                                         | 26                      |
| Bell et al. (2002)            | United Kingdom: General practices and outpatient department of hospital consultants (neurologists, pediatricians and pediatric neurologists), in addition to mailed questionnaire | 14 to 55 | 2000             | Patient survey | Anti-epileptic drugs   | Anti-epileptic drugs (phenobarbital, primidone, phenytoin, fosphenytoin, ethosuximide, carbamazepine, valproate, and topiramate) | 28                      |
| Bhakta, Bainbridge, and Borgelt (2015) | United States: Outpatient Neurology Clinics in a hospital                           | 15 to 44 | 7/2011–6/2012    | Medical records | Anti-epileptic drugs   | NS                                                                           | 25                      |
| Bosak, Cyranka, and Slowik (2019) | Poland: A university epilepsy clinic                                             | 16 to 49 | 8/2017–8/2018    | Patient survey and medical records | Anti-epileptic drugs | NS                                                                           | 28                      |
| Study                          | Country: setting                                                                 | Age     | Time               | Data source | Teratogenic medication | Risk management programme or pregnancy risk classification system | Quality assessment score (out of 36) |
|-------------------------------|---------------------------------------------------------------------------------|---------|--------------------|-------------|------------------------|---------------------------------------------------------------|-----------------------------------|
| Boucher and Beaulac-Baillargeon (2006) | Canada: Telephone interview                                                    | ≥14     | 11/2003–7/2004    | Patient survey | Isotretinoin           | NS                                                            | 30                                 |
| Brandenburg et al. (2017)     | United States: Mandatory and voluntary surveys of the REMS program             | NS      | 6/2012–6/2013     | Patient survey | Thalidomide and lenalidomide | REMS for thalidomide and lenalidomide                      | 29                                 |
| Brinker, Kornegay, and Nourjah (2005) | United States: A novel pharmacy compliance survey and an ongoing, voluntary survey | 15 to 45 | 10/2002–4/2003    | Patient survey | Isotretinoin           | System to Manage Accutane-Related Teratogenicity (SMART) program | 33                                 |
| Castaneda et al. (2008)       | United States: REMS                                                            | females of child bearing potential | 12/2005–12/2007 | Patient survey | Lenalidomide           | RevAssist®                                                   | 29                                 |
| Chang et al. (2018)           | Uganda: Uganda Heart Institute (UHI)                                           | 15 to 59 | NS                 | Patient survey | Warfarin               | NS                                                            | 35                                 |
| Chave, Finlay, and Knight (2001) | United Kingdom: Dermatologists                                                  | NS      | 36,434             | Physician questionnaire | Thalidomide         | NS                                                            | 25                                 |
| Cheetham et al. (2006)        | United States: Kaiser Permanente (a national, nonprofit, managed care organization) | NS      | 2000–2004          | Medical records | Isotretinoin           | Kaiser Permanente Southern California isotretinoin risk management program | 28                                 |
| Crijns, van Rein, Gispen-de Wied, Straus, and de Jong-van den Berg (2012) | Netherlands: IADB (a database, containing information of prescribed medication in public pharmacies in the Netherlands) | 15 to 49 | 1999–2006          | Medical records | Isotretinoin           | NS                                                            | 27                                 |
| Entezari-Maleki et al. (2012)  | Iran: Institutional community pharmacy service affiliated with the college of pharmacy, Tehran University of Medical Sciences | NS      | 7/2007–1/2008      | Patient survey and medical records | Isotretinoin       | NS                                                            | 33                                 |

(Continues)
| Study                        | Country: setting                                                                 | Age  | Time               | Data source       | Teratogenic medication                                                                 | Risk management programme or pregnancy risk classification system | Quality assessment score |
|------------------------------|----------------------------------------------------------------------------------|------|--------------------|-------------------|----------------------------------------------------------------------------------------|---------------------------------------------------------------|-------------------------|
| Ferguson et al. (2016)       | United States: Academic and community practices, lupus support groups and conferences, and websites and other forms of publicity | ≤45  | 2003–2010          | Patient survey    | Azathioprine, mycophenolate, methotrexate, cyclosporine, leflunomide, cyclophosphamide, rituximab, abatacept, or belimumab | NS                                                               | 31                      |
| Force et al. (2012)          | United States: Family medicine clinics                                           | 18 to 44 | NS                | Medical records | Angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers or statin       | FDA                                                             | 28                      |
| Fritsche, Ables, and Bendyk (2011) | United States: Family medicine clinic                                            | 15 to 44 | 10/2002–11/2008   | Medical records | Category D or X* (paroxetine, methotrexate or warfarin; selected longer-term tetracyclines (minocycline or tetracycline); a benzodiazepine (defined as any medication containing either “azepam” or “azolam”) and any statin (defined as any medication containing “astatin”) | FDA                                                             | 29                      |
| Gotlib et al. (2016)         | United States: A tertiary medical centre                                          | 15 to 49 | 1/2013–7/2014     | Medical records | Valproic acid                                                                         | American Psychiatry Association, American Congress of Obstetrics and Gynecologists, National Institute for Health and Care Excellence and American Academy of | 29                      |
| Study                          | Country: setting                                                                 | Age  | Time            | Data source                  | Teratogenic medication                                      | Risk management programme or pregnancy risk classification system                                                                 | Quality assessment score (out of 36) |
|-------------------------------|---------------------------------------------------------------------------------|------|-----------------|------------------------------|-------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------|--------------------------------------|
| Goyal et al. (2015)           | United States: National Hospital Ambulatory Medical Care Survey (NHAMCS)         | 14-40| 2005–2009       | Patient survey               | Category D or X<sup>a</sup>                                 | FDA                                                                             | 35                                   |
| Hayward et al. (2016)         | United States: Children’s Hospital                                              | 12-21| 7/2011–6/2015   | Medical records              | Cyclophosphamide                                            | NS                                                                              | 31                                   |
| Hogan, Strand, and Lane (1988)| Canada: Dermatology clinic and general practitioner clinic                      | NS   | 4/1983–3/1985   | Patient survey and medical records | Isotretinoin                                             | NS                                                                              | 24                                   |
| James, Barnes, Lelliott, Taylor, and Paton (2007) | United Kingdom: A mental health trust                                            | 18-45| 2006            | Medical records              | Lithium, carbamazepine or valproate                      | NS                                                                              | 26                                   |
| Landis et al. (2012)          | United States: The National Ambulatory Medical Care Survey (NAMCS)               | 12-55| 1993–2008       | Patient log                  | Isotretinoin and oral contraceptives                       | iPledge                                                                         | 31                                   |
| Langan, Perry, and Oto (2013) | United Kingdom: Secondary care psychiatric contacts                               | 16-50| 2002–2005       | Medical records              | Valproate, carbamazepine, lamotrigine and topiramate       | NS                                                                              | 31                                   |
| Lelubre et al. (2018)         | Belgium: Questionnaires delivered online by email                                | NS   | 12/2014–10/2015 | Patient survey               | Isotretinoin                                               | Pregnancy Prevention Program for isotretinoin                                                                                 | 29                                   |
| Leverenz et al. (2019)        | United States: Rheumatology Clinic, Dermatology Clinics and an online community of people living with inflammatory arthritis | ≤40  | 2015–2017       | Patient survey               | Methotrexate, anti-TNF (infliximab, adalimumab, etanercept, golimumab, or certolizumab) and novel medications (abatacept, apremilast, rituximab, tocilizumab, tofacitinib, secukinumab, and ustekinumab) | NS                                                                              | 30                                   |
| Study                          | Country: setting                                                                 | Age   | Time             | Data source | Teratogenic medication                                                                 | Risk management programme or pregnancy risk classification system | Quality assessment score (out of 36) |
|-------------------------------|----------------------------------------------------------------------------------|-------|------------------|-------------|----------------------------------------------------------------------------------------|-----------------------------------------------------------------|--------------------------------------|
| Mager et al. (2018)           | United States: Life plans completed as part of Toledo-Lucas County Healthy Start | 13 to 44 | 4/2016–10/2016   | Reproductive life plan                                                                   | Category C, D or X<sup>a</sup>                                   | FDA                                                                | 25                                   |
| Martin, Foreman, Travis, Casson, and Coleman (2008) | United Kingdom: Hypertension Clinic in a University Hospital                      | 16 to 45 | 1/2004–10/2006   | Medical records                                                                          | Angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) | NS                                                                 | 22                                   |
| Mitchell, Van Bennekom, and Louik (1995) | United States: Telephone or mailed survey                                        | 12 to 59 | 1/1989–12/1993   | Patient survey                                                                          | Isotretinoin                                                     | Pregnancy Prevention Program for isotretinoin                     | 25                                   |
| Mody et al. (2015)            | United States: Family medicine at an academic institution                        | 18 to 45 | 4/2011–4/2012   | Medical records                                                                          | Category D or X<sup>a</sup>                                    | Review of the category D and X medications in 2012 by a counselor for California Teratogen Information Specialists | 32                                   |
| Mody et al. (2015)            | United States: An academic outpatient family medicine clinic                     | 18 to 45 | 4/2012–4/2013   | Patient survey and medical records                                                       | Category D or X<sup>a</sup>                                    | FDA                                                                | 33                                   |
| Mulryan, McIntyre, McDonald, Feeney, and Hallahan (2018) | Ireland: Irish mental health service                                             | 18 to 49 | 42,370           | Medical records                                                                          | Valproate                                                       | NS                                                                 | 28                                   |
| Ozyurt and Kaptanoglu (2015)  | Turkey: Dermatology clinic in a Hospital                                         | 14 to 35 | 1/2012 for 18 months | Patient survey                                                                          | Isotretinoin                                                    | NS                                                                 | 24                                   |
| Paton et al. (2018)           | United Kingdom: Mental health provider organizations                              | ≤ 50   |                  | Medical records                                                                          | Valproate                                                       | NICE guideline for bipolar disorder (NICE 2014)                  | 25                                   |
| Pinheiro et al. (2013)        | United States: IMS Health, Vector One<sup>c</sup>: Data Extract Tool (DET)       | 13 to 45 | 3/2004–2/2008   | Medical records                                                                          | Isotretinoin                                                    | iPledge                                                            | 28                                   |
| Study                          | Country: setting                                                                 | Age       | Time              | Data source   | Teratogenic medication | Risk management programme or pregnancy risk classification system | Quality assessment score (out of 36) |
|-------------------------------|----------------------------------------------------------------------------------|-----------|-------------------|---------------|------------------------|-----------------------------------------------------------------|-------------------------------------|
| Raguideau et al. (2015)       | France: The French national health insurance database (SNIIRAM), The complementary Universal Health Insurance (CMUc), and The French hospital discharge database (PMSI) | 15 to 49  | 1/2006–12/2013    | Medical records | Acitretin              | NS                                                               | 27                                  |
| Rao, Glynn, Werler, Van Bennekom, and Mitchell (2000) | United States: Telephone or mailed survey                                           | NS        | 1990–1993         | Patient survey  | Isotretinoin           | NS                                                               | 28                                  |
| Ruiter, Teichert, Straus, Stricker, and Visser (2012) | Netherlands: The Dutch Foundation for Pharmaceutical Statistics (SFK)         | 15 to 45  | 1/2005–12/2009    | Medical records | Category D or X\(^a\) and coumarin anticoagulants, phenprocoumon and acenocoumarol | Swedish Catalogue of Approved Drugs (FASS), Australian Drug Evaluation Committee (ADEC) and US Food and Drug Administration (FDA) | 26                                  |
| Schwarz et al. (2005)         | United States: The National Ambulatory Medical Care Survey (NAMCS), an annual survey of nonfederal employed, office-based physicians | 14 to 44  | 1998–2000         | Medical records | Category D or X\(^a\) | FDA                                                             | 27                                  |
| Schwarz, Postlethwaite, Hung, and Armstrong (2007) | United States: Kaiser Permanente (a health maintenance organization)          | 15 to 44  | 2001              | Medical records | Category D or X\(^a\) | FDA                                                             | 30                                  |

(Continues)
| Study                | Country: setting                                                                 | Age | Time            | Data source         | Teratogenic medication                                                                 | Risk management programme or pregnancy risk classification system | Quality assessment score |
|---------------------|---------------------------------------------------------------------------------|-----|-----------------|---------------------|----------------------------------------------------------------------------------------|--------------------------------------------------------------------|--------------------------|
| Schwarz et al. (2010) | United States: Pharmacy Benefits Management Database (PBM)                  | 18 to 45 | 10/2006–9/2008 | Medical records     | Category D or X²                                                                   | FDA                                                               | 35                       |
| Schwarz et al. (2012) | United States: Academic general internal medicine practice                    | 18 to 50 | 10/2008–4/2010 | Medical records     | Potential teratogens                                                             | NS                                                                | 33                       |
| Schwarz et al. (2013) | United States: Suburban, community-based family practice and an academic general internal medicine | 18 to 50 | 10/2008–6/2009 | Patient survey and medical records                     | Benzodiazepines, antimicrobials (i.e., doxycycline and fluconazole), angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers, cardiovascular medications (e.g., beta-blockers, spironolactone), psychiatric medications (e.g., lithium and some antidepressants), and statins | NS                                                                | 32                       |
| Schwarz et al. (2013) | United States: The OEF/OIF roster, provided to the VA by the Department of Defense Manpower Data Center’s (DMDC) Contingency Tracking System | ≤50  | 7/2008–10/2011 | Patient survey                  | Angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, benzodiazepine or statin | FDA                                                               | 33                       |
| Shilalukey et al. (1997) | Canada: Haemoglobinopathy Clinics of a children's hospital and a general hospital | Teenagers | 7/1993–7/1994 | Patient survey                        | Deferoxamine and deferiprone                                                        | NS                                                                | 25                       |
| Study                          | Country: setting                                      | Age | Time          | Data source   | Teratogenic medication | Risk management programme or pregnancy risk classification system | Quality assessment score (out of 36) |
|-------------------------------|------------------------------------------------------|-----|---------------|---------------|------------------------|------------------------------------------------------------------|----------------------------------|
| Stancil et al. (2016)         | United States: Academic pediatric medical centre      | 14  | 1/2008–12/2012| Medical records| Category D or X<sup>a</sup> | FDA                                                              | 30                               |
| Steinkellner, Chen, and Denison (2010) | United States: Database from Medco Health Solutions, Inc. (Franklin Lakes, NJ), a pharmacy benefits manager | 18  | 1/2008–6/2009 | Medical records| Category X<sup>a</sup> | FDA, validated by Micromedex and Clinical Pharmacology ref         | 28                               |
| Teichert et al. (2010)        | Netherlands: The Dutch Foundation for Pharmaceutical Statistics (SFK) | 15  | 1/2005–12/2008| Medical records| Isotretinoin           | The Dutch pregnancy prevention program                             | 31                               |
| Tsur, Kozer, and Berkovitch (2008) | Israel: Drug Consultation Centre                      | 16  | 7/2005–10/2005| Patient survey | Isotretinoin           | NS                                                               | 31                               |
| Uusküla et al. (2018)         | Estonia: The Estonian Health Insurance Fund (EHIF)    | 15  | 1/2012–10/2016| Medical records| Isotretinoin           | NS                                                               | 31                               |
| Valle, Clemons, Hayes, Fallowfield, and Howell (1998) | United Kingdom: Cancer care hospital                  | NS  | Patient survey | Chemotherapy for breast cancer | NS                                                               | 25                               |
| Werner et al. (2014)          | United States: Urban community via flyers displayed on college campuses, at dermatology clinics, and at student health facilities | 14  | 1/2012–9/2012 | Patient survey | Isotretinoin           | iPledge                                                          | 32                               |
| Wieck, Rao, Sein, and Haddad (2007) | United Kingdom: Psychiatric departments of three teaching hospitals | 16  | 11/2004–10/2005| Medical records| Sodium valproate, semisodium valproate or carbamazepine | National Institute for Health and Clinical Excellence for epilepsy (2004) | 24                               |
| Yazdany et al. (2011)         | United States: Academic rheumatology offices, community | ≤45 | 2008–2009     | Patient survey | Methotrexate, mycophenolate mofetil, azathioprine, | NS                                                               | 33                               |

(Continues)
misoprostol (by pregnant and nonpregnant women) (Pons Eda et al., 2014). An under-estimation of the teratogenic risk was reported for warfarin and retinoids (by general practitioners and obstetric/gynecologists) (Gils et al., 2016). And over-estimation of the teratogenic risk was reported for thalidomide (by pregnant and nonpregnant women, healthcare professionals, and medical students) (Damase-Michel et al., 2008; Lupattelli et al., 2014; Nordeng et al., 2010; Petersen et al., 2015; Sanz et al., 2001), for valproate, lithium, isotretinoin, and warfarin (by healthcare professionals) (Damase-Michel et al., 2008), for phenytoin and warfarin (by pregnant and nonpregnant women, healthcare professionals, and medical students) (Sanz et al., 2001), and for etretinate (by nonpregnant women, healthcare professionals, and medical students) (Sanz et al., 2001). Details are presented in Table 5.

4 | DISCUSSION

Guided by principles of medicines optimisation (Royal Pharmaceutical Society, 2013), to our knowledge this is the first systematic review that synthesizes the available literature on the safe use of teratogenic medications. Additionally, this review extends our understanding of patients’ experience of using teratogenic medications by systematically summarizing published studies that report perceptions of potential teratogens.

4.1 | Risk management

Measures to minimize foetal exposure to potential teratogens investigated in this review were based on components of Risk Evaluation and Mitigation Strategies (REMS) with Elements to Assure Safe Use (ETASU). These measures were: teratogenic counseling, contraceptive counseling, pregnancy testing before or at start of treatment, pregnancy testing while on treatment, use of contraception before or on starting treatment, and use of contraception during treatment. Since 2007, implementation of REMS with ETASU have been required by the FDA for medications with serious safety issues like teratogenic medications to ensure that the benefits of a medication outweigh the risks to patients (Leiderman, 2009).

Isotretinoin was the most commonly prescribed teratogenic medication covered by the studies included in this review (n = 16; 29.1%) (Algoblan, Bakhsh, Alharithy, 2019; Boucher & Beaulac-Baillargeon, 2006; Brinker et al., 2005; Cheetham et al., 2006; Crijns et al., 2012; Entezari-Maleki et al., 2012; Hogan et al., 1988; Lelubre et al., 2018; Mitchell et al., 1995;
| Study                        | Teratogenic counseling | Contraceptive counseling | Pregnancy testing before starting treatment | Pregnancy testing during treatment | Contraceptive use before starting treatment | Contraceptive use during treatment |
|------------------------------|------------------------|--------------------------|-----------------------------------------------|-----------------------------------|---------------------------------------------|----------------------------------|
| Algoblan et al. (2019)       | ×                      | ×                        | -                                             | ×                                 | -                                           | -                                |
| Mitchell et al. (1995)       | ×                      | ×                        | ×                                             | ×                                 | -                                           | ×                                |
| Cheetham et al. (2006)       | -                      | -                        | ×                                             | -                                 | -                                           | -                                |
| Rao et al. (2000)            | -                      | -                        | -                                             | -                                 | -                                           | ×                                |
| Uusküla et al. (2018)        | -                      | -                        | -                                             | -                                 | ×                                           | ×                                |
| Pinheiro et al. (2013)       | -                      | -                        | -                                             | -                                 | -                                           | ×                                |
| Entezari-Maleki et al. (2012)| -                      | -                        | -                                             | -                                 | -                                           | ×                                |
| Lelubre et al. (2018)        | -                      | x                        | ×                                             | ×                                 | -                                           | -                                |
| Teichert et al. (2010)       | -                      | -                        | -                                             | -                                 | -                                           | ×                                |
| Boucher and Beaulac-Baillargeon (2006) | × | x | x | x | - | × |
| Crijns et al. (2012)         | -                      | -                        | -                                             | -                                 | -                                           | ×                                |
| Ozyurt and Kaptanoglu (2015) | -                      | -                        | -                                             | -                                 | -                                           | ×                                |
| Tsur et al. (2008)           | -                      | -                        | ×                                             | ×                                 | x                                           | -                                |
| Brinker et al. (2005)        | -                      | -                        | ×                                             | -                                 | -                                           | -                                |
| Werner et al. (2014)         | -                      | x                        | -                                             | -                                 | -                                           | -                                |
| Hogan et al. (1988)          | -                      | -                        | -                                             | -                                 | -                                           | ×                                |
| Bhakta et al. (2015)         | x                      | x                        | -                                             | -                                 | -                                           | ×                                |
| Wieck et al. (2007)          | x                      | x                        | -                                             | -                                 | -                                           | -                                |
| Bell et al. (2002)           | x                      | -                        | -                                             | -                                 | -                                           | -                                |
| Langan et al. (2013)         | x                      | x                        | -                                             | -                                 | -                                           | -                                |
| Bosak et al. (2019)          | x                      | x                        | -                                             | -                                 | -                                           | x                                |
| Leverenz et al. (2019)       | -                      | -                        | -                                             | -                                 | -                                           | ×                                |
| Yazdany et al. (2011)        | -                      | x                        | -                                             | -                                 | -                                           | ×                                |
| Ferguson et al. (2016)       | -                      | x                        | -                                             | -                                 | -                                           | -                                |
| Banas et al. (2014)          | -                      | -                        | -                                             | -                                 | -                                           | ×                                |
| Paton et al. (2018)          | x                      | x                        | -                                             | -                                 | -                                           | ×                                |
| Gotlib et al. (2016)         | x                      | -                        | -                                             | -                                 | -                                           | -                                |
| Mulryan et al. (2018)        | x                      | x                        | x                                             | -                                 | -                                           | -                                |
| Atturu and Odelola (2015)     | x                      | x                        | -                                             | -                                 | -                                           | -                                |
| Brandenburg et al. (2017)    | x                      | x                        | -                                             | -                                 | ×                                           | ×                                |
| Castaneda et al. (2008)      | -                      | -                        | -                                             | -                                 | -                                           | ×                                |
| Chave et al. (2001)          | -                      | -                        | x                                             | -                                 | -                                           | -                                |
| Raguideau et al. (2015)      | -                      | -                        | x                                             | x                                 | -                                           | -                                |
| Valle et al. (1998)          | -                      | x                        | -                                             | -                                 | ×                                           | x                                |
| Shilalukey et al. (1997)     | -                      | -                        | -                                             | -                                 | -                                           | ×                                |
| Hayward et al. (2016)        | -                      | -                        | x                                             | -                                 | -                                           | -                                |
| Landis et al. (2012)         | -                      | -                        | -                                             | -                                 | -                                           | ×                                |
| James et al. (2007)          | x                      | x                        | -                                             | x                                 | -                                           | x                                |
| Chang et al. (2018)          | x                      | -                        | -                                             | -                                 | -                                           | x                                |

(Continues)
Ozyurt & Kaptanoglu, 2015; Pinheiro et al., 2013; Rao et al., 2000; Teichert et al., 2010; Tsur et al., 2008; Uuskula et al., 2018; Werner et al., 2014). This may be because of two reasons. Firstly, isotretinoin is a relatively old medication that has been in the market since 1982–1983, and has been prescribed under a pregnancy prevention programme since 1988 (Crijns, Straus, Gispen-de Wied, & de Jong-van den Berg, 2011). Secondly, it is one of the most cost-effective acne treatments used by patients from different age groups including women of childbearing age (Algoblan et al., 2019; Bérard et al., 2007; Honein et al., 2004).

By contrast, it was observed that there were fewer publications on medications prescribed under more recent risk management programmes such as thalidomide, lenalidomide, and valproic acid (Atturu & Odelola, 2015; Brandenburg et al., 2017; Castaneda et al., 2008; Chave et al., 2001; Gotlib et al., 2016; Mulryan et al., 2018; Paton et al., 2018), indicating a need for further investigation of the safety of these medications in terms of adherence to risk management measures for such medications. Good practice guidance suggests that ensuring safe use of medications can have a number of positive effects on treatment outcomes. For teratogenic medications in particular, this includes reducing the incidents of medication-induced foetal harm and empowering patients to make the most of their treatment (Royal Pharmaceutical Society, 2013).

Of the studies included in the review, 11 publications used the FDA pregnancy labeling categories (A, B, C, D, X) (DiPietro Mager et al., 2018; Fritsche et al., 2011; Goyal et al., 2015; Mody, Farala, Wu, Felix, & Chambers, 2015; Mody, Wu, et al., 2015; Ruiter et al., 2012; E. B. Schwarz et al., 2010; E. B. Schwarz et al., 2005; E. B. Schwarz et al., 2007; Stancil et al., 2016; Steinkellner et al., 2010). However, it is worth mentioning that the FDA requested removal of these categories from the labels of all prescription drugs and biological products in 2015. The pregnancy labeling categories (A, B, C, D, X) were replaced by the Pregnancy and Lactation labeling Rule (PLLR) since 2015 ("Content and format of labeling for human prescription drug and biological products; requirements for pregnancy and lactation labeling. Final rule," FDA, 2014; Pernia & DeMaagd, 2016). Reasons behind this change in labeling included concerns regarding the clarity of the content of the old pregnancy categories labeling, a possibility of misinterpreting the categories, inability to provide significant information about drug exposure during pregnancy, and inability to identify the consequences of stopping the use of needed drugs during pregnancy (Pernia & DeMaagd, 2016).

| Study                  | Teratogenic counseling | Contraceptive counseling | Pregnancy testing before starting treatment | Pregnancy testing during treatment | Contraceptive use before starting treatment | Contraceptive use during treatment |
|------------------------|------------------------|--------------------------|---------------------------------------------|----------------------------------|-------------------------------------------|-----------------------------------|
| Steinkellner et al. (2010) | -                      | -                        | -                                           | -                                | -                                         | ×                                  |
| Schwarz et al. (2007)    | -                      | ×                        | -                                           | -                                | -                                         | ×                                  |
| Schwarz et al. (2005)    | -                      | ×                        | -                                           | -                                | -                                         | -                                  |
| Goyal et al. (2015)      | -                      | -                        | ×                                           | -                                | -                                         | -                                  |
| Stancil et al. (2016)    | -                      | -                        | -                                           | -                                | -                                         | ×                                  |
| Mody et al. (2015)       | -                      | -                        | -                                           | -                                | ×                                         | -                                  |
| Mody et al. (2015)       | ×                      | ×                        | -                                           | -                                | ×                                         | -                                  |
| Schwarz et al. (2010)    | -                      | -                        | ×                                           | -                                | -                                         | -                                  |
| Mager et al. (2018)      | -                      | -                        | -                                           | -                                | ×                                         | -                                  |
| Fritsche et al. (2011)   | -                      | ×                        | -                                           | -                                | -                                         | -                                  |
| Ruiter et al. (2012)     | -                      | -                        | -                                           | -                                | ×                                         | -                                  |
| Schwarz et al. (2012)    | -                      | -                        | -                                           | -                                | -                                         | ×                                  |
| Force et al. (2012)      | -                      | -                        | -                                           | -                                | -                                         | ×                                  |
| Schwarz et al. (2013)    | ×                      | ×                        | -                                           | -                                | -                                         | -                                  |
| Schwarz et al. (2013)    | ×                      | -                        | -                                           | -                                | -                                         | ×                                  |
| Martin et al. (2008)     | -                      | -                        | -                                           | -                                | -                                         | ×                                  |
Results of teratogenic risk management implementation showed a wide variation across studies. Some studies reported surprisingly low rates of implementation. For example, only 9.5% of women of childbearing age using valproate received teratogenic counseling in the study by Mulryan et al. (Mulryan et al., 2018). Additionally, rates of pregnancy testing before starting treatment with valproate or thalidomide were as low as 0% in two studies (Chave et al., 2001; Mulryan et al., 2018), and pregnancy testing during treatment with acitretin was 12.7% in the study by Raguideau et al. (Raguideau et al., 2015). Low rates of contraceptive use were also reported. Uuskula et al. reported that 15.7% of women of childbearing age on isotretinoin treatment in their study used a contraceptive before starting treatment (Uuskula et al., 2018), and Tsur et al. reported that only 1.7% of women in their study group used contraception during treatment with isotretinoin (Tsur et al., 2008).

The wide variation in the results of implementing risk management measures can be discussed in the light of several factors. One factor could be the data sources used by the different studies. Some studies relied on medical records as their source of data (Atturu & Odelola, 2015; Bhakta et al., 2015; Cheetham et al., 2006; Crijns et al., 2012; Force et al., 2012; Fritsche et al., 2011; Gottlib et al., 2016; Hayward et al., 2016; James et al., 2007; Langan et al., 2013; Martin et al., 2008; Mody, Farala, et al., 2015; Mulryan et al., 2018; Paton et al., 2018; Pinheiro et al., 2013; Raguideau et al., 2015; Ruiter et al., 2012; E. B. Schwarz et al., 2010; E. B. Schwarz et al., 2005; E. B. Schwarz, Parisi, Williams, Shevchik, & Hess, 2012; E. B. Schwarz et al., 2007; Stancil et al., 2016; Steinkellner et al., 2010; Teichert et al., 2010; Uuskula et al., 2018; Wieck et al., 2007), while others used patients surveys (Algoblan et al., 2019; Banas et al., 2014; Bell et al., 2002; Boucher & Beaulac-Baillargeon, 2006; Brandenburg et al., 2017; Brinker et al., 2005; Castaneda et al., 2008; Chang et al., 2018; Ferguson et al., 2016; Goyal et al., 2015; Lelubre et al., 2018; Leverenz et al., 1995; Ozyurt & Kaptanoglu, 2015; Rao et al., 2000; E. B. Schwarz, Mattocks, et al., 2013; Shilalukey et al., 1997; Tsur et al., 2008; Valle et al., 1998; Werner et al., 2014; Yazdany et al., 2011), a combination of medical records and patient surveys (Bosak et al., 2019; Entezari-Maleki et al., 2012; Hogan et al., 1988; Mody, Wu, et al., 2015; E. B. Schwarz, Parisi, et al., 2013), or other sources [patient logs (Landis et al., 2012), reproductive life plans (DiPietro Mager et al., 2018), and physician surveys (Chave et al., 2001)]. Having patients as the only source of information can lead to several forms of self-reporting bias (Althubaiti, 2016). Recall bias can lead to an
**Table 4** Characteristics of studies reporting perceptions of teratogenic medicines

| Study                      | Country         | Setting                                                                 | Sample                                                                 | Study design  | Data source                        | Measurement of teratogenicity perception | Quality assessment score (out of 36) |
|----------------------------|-----------------|-------------------------------------------------------------------------|------------------------------------------------------------------------|---------------|------------------------------------|------------------------------------------|----------------------------------------|
| Lupattelli et al. (2014)   | 18 countries    | On-line questionnaire                                                   | 4,999 pregnant women                                                   | Cross-sectional | On-line questionnaire               | Numeric scale                           | 33                                     |
| Gils et al. (2016)         | Denmark         | On-line questionnaire                                                   | 143 general practitioners and 138 obstetricians/gynecologists         | Cross-sectional | On-line questionnaire               | Numeric scale                           | 30                                     |
| Nordeng et al. (2010)      | Norway          | On-line questionnaire                                                   | 1793 eligible women                                                    | Cross-sectional | On-line questionnaire               | Numeric scale                           | 32                                     |
| Damase-Michel et al. (2008)| France          | A continuous educational course                                         | 103 general practitioners and 104 community pharmacists               | Cross-sectional | Self-administered questionnaire      | Visual analogue scale                    | 26                                     |
| Sanz et al. (2001)         | Spain           | A continuous educational course, out-patient obstetrics and gynecology clinic, School of Medicine and participants’ homes | 15 general practitioners, 10 gynecologists, 106 preclinical students, 150 students in their clinical training, 81 pregnant women and 63 nonpregnant women | Cross-sectional | Questionnaire                        | Visual analogue scale                    | 28                                     |
| Pons et al. (2014)         | Brazil          | Three prenatal services in the municipal primary care system             | 287 (144 pregnant and 143 nonpregnant women)                          | Cross-sectional | Structured interviews to fill a questionnaire | Numeric scale                           | 33                                     |
| Petersen et al. (2015)     | 18 countries    | On-line questionnaire                                                   | 9,113 women                                                            | Cross-sectional | On-line questionnaire               | Numeric scale                           | 30                                     |

*Australia, Austria, Canada, Croatia, Finland, France, Iceland, Italy, The Netherlands, Norway, Poland, Russia, Serbia, Slovenia, Sweden, Switzerland, United Kingdom and United States.
TABLE 5  Results of comparing the reported teratogenic risk perception to the true value of teratogenic risk as found in the literature

| Study              | Medications included | The true value of teratogenic risk (%) | The perceived value of teratogenic risk (%) | The perceived value compared to the true value of teratogenic risk |
|--------------------|----------------------|---------------------------------------|--------------------------------------------|---------------------------------------------------------------|
| Lupattelli et al.  | thalidomide          | 10 to 40                               | Low health literacy: 84.5                  | Over-estimated                                                |
|                    |                      |                                       | Medium health literacy: 89.5               | Over-estimated                                                |
|                    |                      |                                       | High health literacy: 94.8                 | Over-estimated                                                |
| Gils et al.        | thalidomide          | 20 to 50                               | GP: 20                                     | Properly-estimated                                            |
|                    | warfarin             | 10 to 20                               | GP: 3                                      | Properly-estimated                                            |
|                    | retinoids            | 30 to 38                               | GP: 10                                     | Under-estimated                                               |
| Nordeng et al.     | thalidomide          | 10 to 40                               | All included women: 75                     | Over-estimated                                                |
| Damase-Michel et al.| valproate            | 10                                     | All healthcare professionals: 41.8         | Over-estimated                                                |
|                    | lithium              | 12                                     | All healthcare professionals: 55.8         | Over-estimated                                                |
|                    | isotretinoin         | 25                                     | All healthcare professionals: 89           | Over-estimated                                                |
|                    | warfarin             | 30                                     | All healthcare professionals: 58.7         | Over-estimated                                                |
|                    | thalidomide          | 50                                     | All healthcare professionals: 91.7         | Over-estimated                                                |
| Sanz et al.        | phenytoin            | ≤ 10                                   | Physicians: 37.9                           | Over-estimated                                                |
|                    |                      |                                       | Clinical students: 41.3                    | Over-estimated                                                |
|                    |                      |                                       | Preclinical students: 58.9                 | Over-estimated                                                |
|                    |                      |                                       | Nonpregnant women: 67.9                   | Over-estimated                                                |
|                    |                      |                                       | Pregnant women: 59.5                      | Over-estimated                                                |
|                    | warfarin             | 6 to 25                                | Physicians: 53.2                           | Over-estimated                                                |
|                    |                      |                                       | Clinical students: 44.6                    | Over-estimated                                                |
|                    |                      |                                       | Preclinical students: 63.1                 | Over-estimated                                                |
|                    |                      |                                       | Nonpregnant women: 68.4                   | Over-estimated                                                |
|                    |                      |                                       | Pregnant women: 42.8                      | Over-estimated                                                |
|                    | etretinate           | 16 to 30                               | Physicians: 95.9                           | Over-estimated                                                |
|                    |                      |                                       | Clinical students: 55.1                    | Over-estimated                                                |
|                    |                      |                                       | Preclinical students: 59.7                 | Over-estimated                                                |
|                    |                      |                                       | Nonpregnant women: 45.8                   | Over-estimated                                                |
|                    |                      |                                       | Pregnant women: 16.4                      | Properly-estimated                                            |
|                    | thalidomide          | 11 to 35                               | Physicians: 81.6                           | Over-estimated                                                |
|                    |                      |                                       | Clinical students: 73.4                    | Over-estimated                                                |
|                    |                      |                                       | Preclinical students: 79.3                 | Over-estimated                                                |
|                    |                      |                                       | Nonpregnant women: 91.1                   | Over-estimated                                                |
|                    |                      |                                       | Pregnant women: 82.6                      | Over-estimated                                                |

(Continues)
erroneous estimation of risk management variables if the patient’s recall of information is inaccurate (Schmier & Halpern, 2004). Another form of self-reporting bias associated with the disclosure of sensitive data is the social desirability bias (Althubaiti, 2016). Social desirability bias might have led to an overestimated adherence to risk management and pregnancy prevention measures ("Social Desirability Bias,"). On the other hand, if data were extracted from the medical records, several issues like incomplete records, noncaptured data, and low quality data might have an effect on the research outcomes (Herrett et al., 2015; Zozus et al., 2015). Therefore, it is important to bear in mind the possible types of bias associated with each source of data.

Another well recognized variable leading to variations in the implementation of risk management for the different teratogenic medications is the availability of risk management programmes. For certain medications like thalidomide, linoleamide, and isotretinoin, detailed risk management programmes that aim to prevent foetal exposure to the drug are in place (Honein et al., 2004; Mayall & Banerjee, 2014). However, for other teratogenic medications, managing their risk is limited to the use of product labeling and patient information leaflets rather than rigorous monitoring (Freeman, Bwire, Houn, Sheehan, & Backstrom, 2014). The effectiveness of drug labeling as a risk management tool has been a matter of debate as research suggests a lack of effect on physicians’ prescribing behaviors or patients’ understanding of instructions (Freeman et al., 2014).

Results of the current review can be considered as a compliance assessment of teratogenic risk management (whether through existing risk management programmes or through labeling recommendations) (Freeman et al., 2014). Based on the findings of this review, safety of the utilization of teratogenic medications is sub-optimal, and entails a risk of foetal exposure to the harmful effect of potential teratogens. Consequently, it is recommended that the implementation of the existing teratogenic risk management programmes be monitored more carefully, and the criteria for the optimal management of teratogenic risk for potential teratogens be reviewed and revised based on the available evidence.

Exploring the implementation of risk management for teratogenic medications can help to develop interventions designed to minimize foetal exposure to cytotoxic effects, and thus future research utilizing multiple data sources is needed. Drawing on the strengths of data extracted from medical records and patient reported data, mixed methods research that utilizes quantitative and qualitative methods could yield more rigorous results than research utilizing quantitative or qualitative methods alone (Shorten & Smith, 2017; Tisnado et al., 2006).

Consequently, results of this review raise two important issues. First, the review uncovers deficiencies in the implementation of risk management of teratogenic medications which constitutes a serious public health concern that needs further investigation. Second, it highlights a potential need to reinforce policies and regulations that aim to reduce foetal exposure to the cytotoxic effects of teratogenic medications.

### 4.2 Perceptions of teratogenic risk

To help patients get the most from their treatment, it is important that their experience of medication use be explored and understood. In recent years, there has been an increasing interest in research on the perception of teratogenic risk (Sanz et al., 2001). This is corroborated by results of the current review, which shows that all papers included were published only in the last two decades. Additionally, the relatively small number of studies included in the review (seven studies) indicates that the study of perceptions of teratogenic risk is an important area for further research.

Two methods were used to measure the perception of teratogenic risk of participants, and those were either a numeric scale (Gils et al., 2016; Lupattelli et al., 2014; Nordeng et al., 2010; Petersen et al., 2015; Pons Eda et al., 2014) or a visual analogue scale (Damase-Michel et al., 2008; Sanz et al., 2001). One major issue regarding the use of a numeric scale to estimate the risk is its dependence on numeracy skills of participants (Peters, Hibbard, Slovic, & Dieckmann, 2007; Pons Eda...
et al., 2014). Evidence from the literature shows that correct estimation and understanding of health related risk information is significantly correlated with an ability to understand numbers and mathematical concepts (Peters et al., 2007; Rothman, Montori, Cherrington, & Pignone, 2008). The second method to measure the perception of teratogenic risk was the use of a visual analogue scale. There is an ongoing debate on the utility of visual analogue scales in measuring risk perception. Some argue that responses of participants to questions including a visual analogue scale tend to cluster around the middle point of the scale and might over-estimate the risk when it is low (Pons, Guimarães, Knauth, & Pizzol, 2014; Sanz et al., 2001), while others suggest that a visual analogue scale can provide a wide range of responses that can be chosen by research participants (Harland, Dawkin, & Martin, 2015). Pons et al. investigated the level of agreement between a visual analogue scale and a numeric scale in estimating the teratogenic risk. In their research, they concluded that there was no agreement between the two methods in estimating teratogenic risk. (Pons et al., 2014). Furthermore, it is recommended that future research exploring perceptions of teratogenic risk needs to utilize qualitative methods in addition to quantitative research. This is one way to overcome the ongoing controversy regarding how to reliably measure perception of teratogenic risk and will provide a deeper understanding of how risk is perceived (Shorten & Smith, 2017).

It is clear from the results of the review that teratogenic risk of medications tends to be over-estimated (Damase-Michel et al., 2008; Lupattelli et al., 2014; Nordeng et al., 2010; Petersen et al., 2015; Sanz et al., 2001), while proper estimation (Gils et al., 2016; Pons Eda et al., 2014) or under-estimation (Gils et al., 2016) occurs less frequently. Yet while there is agreement in the literature about the difficulty of understanding the teratogenic risk of medications due to scientific uncertainty (Polifka, Faustman, & Neil, 1997; Twigg, Lupattelli, & Nordeng, 2016), a realistic perception of teratogenic risk is needed by women in childbearing age to adhere to their therapy (Lennon, 2016).

Over-estimating the teratogenic risk of medications might be due to several factors. For women, pregnancy is viewed as a sensitive phase of their lives which can be easily adversely affected by exposure to a number of teratogens (such as alcohol) and including medications. In addition, pregnancy entails a significant responsibility to the mother to keep her foetus as safe as possible. These attitudes are further emphasized by social norms and cultural beliefs and can affect women’s ideas about medications (Twigg et al., 2016; Widnes & Schjott, 2017; Widnes, Schjott, Eide, & Granas, 2013). On the other hand, for health care professionals and particularly for physicians, exaggerating the teratogenic risk of medications can be a result of inadequate knowledge, which in turn might be the result of insufficient training and education provided for physicians (Damase-Michel et al., 2008), or the lack of relevant resources being utilized when needed (E. B. Schwarz et al., 2009). Furthermore, physicians’ fear of legal liability or possible accusation of malpractice if anything goes wrong while prescribing a potential teratogen might underpin this over estimation of the teratogenic risk of medications (E. B. Schwarz et al., 2009). Subsequently, future research needs to focus on understanding how teratogenic risk is conceptualized and the reasons behind the tendency to exaggerate it.

The strength of this review relies in being the first attempt to shed light on the current status of implementing risk management measures when teratogenic medications are prescribed to women of childbearing age. It utilizes the principles of medicines optimisation, a paradigm that aims to help patients get the best outcomes from using medicines. However, this systematic review has some limitations. First, title and abstract screening were only carried out by one researcher which means that there is a possibility of missing publications. Second, for the section on perceptions of teratogenic risk, the number of included articles was relatively small, which is justified by the limited publications in this area.

5 CONCLUSION

Considerable variation in the implementation of risk management measures when prescribing teratogenic medications to women of childbearing age is reported in the literature. Factors contributing to this variation require further investigation to understand barriers and facilitators of teratogenic medication risk management within a health system. Further studies of risk management of teratogenic medications, which take these factors into account, will need to be undertaken.

Additionally, a common tendency to over-estimate the risk of teratogenic medications was observed. To achieve the best possible therapeutic outcomes of using teratogenic medications, there is a need to explore the reasons behind this over-estimation. Understanding how teratogenic risk is conceptualized can usefully inform medicines optimisation so that patients derive the intended outcomes of a prescribed medication.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.
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### APPENDIX A: Search strategy for the systematic review

| Review topic | MEDLINE | CINAHL | Scopus | Embase | IPA |
|--------------|---------|--------|--------|--------|-----|
| Perception of teratogenic risk | 1. exp Perception/ or risk perception.mp. | risk | (TITLE-ABS-KEY (risk AND risk perception mp. ) OR ( TITLE-ABS-KEY (perception AND risk)) AND ( TITLE-ABS-KEY (teratogen* ))) | 1. exp perception/ or risk perception.mp. or exp risk/ | 1. risk perception. mp. [mp = title, subject heading word, registry word, abstract, trade name/generic name] |
| | 2. perceiv* risk.mp. [mp = title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] | perceived risk AND teratogen* | 2. exp risk/ or exp perception/ or perceiv* risk.mp. | 2. exp. 1 or 2 and 3 | 2. perceiv* risk.mp. [mp = title, subject heading word, registry word, abstract, trade name/generic name] |
| | 3. exp Teratogens/ or teratogen*.mp. | 4. 1 or 2 | 3 and 4 | 3. exp teratogenicity/ or teratogen*.mp. | 3. teratogen*.mp. [mp = title, subject heading word, registry word, abstract, trade name/generic name] |
| | 5. 3 and 4 | | | 4. 1 or 2 | 4. 1 or 2 |
| Date exported to Endnote | February 7, 2019 | February 8, 2019 | February 14, 2019 | February 7, 2019 | February 7, 2019 |
| Risk management for teratogenic medicines | 1. pregnancy prevent*.mp. | risk manag* OR pregnancy prevent* OR contracep* AND teratogen* | (TITLE-ABS-KEY (risk AND manag* ) OR ( TITLE-ABS-KEY (pregnancy AND prevent* ) ) OR ( TITLE-ABS-KEY (contracep* ) ) AND ( TITLE-ABS-KEY (teratogen* ) ) AND ( LIMIT-TO (DOCTYPE, "ar") )) | 1. exp risk management/ or risk manag*.mp. | 1. risk management. mp. [mp = title, subject heading word, registry word, abstract, trade name/generic name] |
| | 2. exp Risk Management/ or risk manag*.mp. | Limiters | 2. pregnancy prevent*.mp. | 2. pregnancy prevent*.mp. | 2. pregnancy prevent*.mp. [mp = title, subject heading word, registry word, abstract, trade name/generic name] |
| | 3. exp Contraception Behavior/ or contracep*.mp. or exp Contraception | Full Text | 3. exp contraception/ or exp family planning/ or contracep*.mp. | 3. exp contraception/ or exp family planning/ or contracep*.mp. | 3. exp contraception/ or exp family planning/ or contracep*.mp. |
| | 4. exp Teratogens/ or teratogen*.mp. | Age Groups: All Adul | 4. teratogen*.mp. or exp teratogenicity/ | 4. teratogen*.mp. or exp teratogenicity/ | 4. teratogen*.mp. or exp teratogenicity/ |
| | 5. 1 or 2 or 3 | | 5. 1 or 2 or 3 | 5. 1 or 2 or 3 | 5. 1 or 2 or 3 |
| | 6. 4 and 5 | | 6. 4 and 5 | 6. 4 and 5 | 6. 4 and 5 |
| | | | Filters Applied | Filters Applied | Filters Applied |
| | | | Publication Type: Article | Publication Type: Article | Publication Type: Article |
| | | | | | |
APPENDIX B: Summary of the characteristics of studies of prescribing teratogenic medicines for women of child bearing age

| Study characteristic | n (%) | Citations of the studies |
|----------------------|-------|--------------------------|
| **Country of origin** |       |                          |
| United States        | 29 (52.7%) | (Bhakta et al., 2015; Brandenburg et al., 2017; Brinker et al., 2005; Castaneda et al., 2008; Cheetham et al., 2006; DiPietro Mager, Mills, & Snelling, 2018; Ferguson et al., 2016; Force et al., 2012; Fritsche et al., 2011; Gotlib et al., 2016; Goyal et al., 2015; Hayward et al., 2016; Landis et al., 2012; Leverenz et al., 2019; Mitchell et al., 1995; Mody, Farala, et al., 2015; Mody, Wu, et al., 2015; Pinheiro et al., 2013; Rao et al., 2000; E. B. Schwarz et al., 2010; E. B. Schwarz et al., 2005; E. B. Schwarz, Mattocks, et al., 2013; E. B. Schwarz, Parisi, Handler, et al., 2012; E. B. Schwarz, Parisi, et al., 2013; E. B. Schwarz et al., 2007; Stancil et al., 2016; Steinkellner et al., 2010; Werner et al., 2014; Yazdany et al., 2011) |
| United Kingdom       | 9 (16.4%) | (Atturu & Odelola, 2015; Bell et al., 2002; Chave et al., 2001; James et al., 2007; Langan et al., 2013; Martin et al., 2008; Paton et al., 2018; Valle et al., 1998; Wieck et al., 2007) |
| Canada               | 3 (5.5%)  | (Boucher & Beaulac-Baillargeon, 2006; Hogan et al., 1988; Shilalukey et al., 1997) |
| Netherlands          | 3 (5.5%)  | (Crijns et al., 2012; Ruiter et al., 2012; Teichert et al., 2010), |
| Poland               | 2 (3.6%)  | (Banas et al., 2014; Bosak et al., 2019) |
| Ireland              | 1 (1.8%)  | (Mulryan et al., 2018) |
| Belgium              | 1 (1.8%)  | (Lelubre et al., 2018), |
| Estonia              | 1 (1.8%)  | (Uuskula et al., 2018) |
| France               | 1 (1.8%)  | (Raguideau et al., 2015) |
| Iran                 | 1 (1.8%)  | (Entezari-Maleki et al., 2012) |
| Turkey               | 1 (1.8%)  | (Ozyurt & Kaptanoglu, 2015), |
| Israel               | 1 (1.8%)  | (Tsur et al., 2008), |
| Uganda               | 1 (1.8%)  | (Chang et al., 2018), |
| Saudi Arabia         | 1 (1.8%)  | (Algoblan et al., 2019) |

(Continues)
| Study characteristic                                      | n (%)     | Citations of the studies                                                                                                                                                                                                 |
|----------------------------------------------------------|-----------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Medical records                                          | 26 (47.3%)| (Atturu & Odelola, 2015; Bhakta et al., 2015; Cheetham et al., 2006; Crijns et al., 2012; Force et al., 2012; Fritsche et al., 2011; Gotlib et al., 2016; Hayward et al., 2016; James et al., 2007; Langan et al., 2013; Martin et al., 2008; Mody, Farala, et al., 2015; Mulryan et al., 2018; Paton et al., 2018; Pinheiro et al., 2013; Raguideau et al., 2015; Ruiter et al., 2012; E. B. Schwarz et al., 2010; E. B. Schwarz et al., 2005; E. B. Schwarz, Parisi, Williams, et al., 2012; E. B. Schwarz et al., 2007; Stancil et al., 2016; Steinkellner et al., 2010; Teichert et al., 2010; Uuskula et al., 2018; Wieck et al., 2007) |
| Patient surveys                                          | 21 (38.2%)| (Algoblan et al., 2019; Banas et al., 2014; Bell et al., 2002; Boucher & Beaulac-Baillargeon, 2006; Brandenburg et al., 2017; Brinker et al., 2005; Castaneda et al., 2008; Chang et al., 2018; Ferguson et al., 2016; Goyal et al., 2015; Lelubre et al., 2018; Leverenz et al., 2019; Mitchell et al., 1995; Ozyurt & Kapitanoglu, 2015; Rao et al., 2000; E. B. Schwarz, Mattocks, et al., 2013; Shilalukey et al., 1997; Tsur et al., 2008; Valle et al., 1998; Werner et al., 2014; Yazdany et al., 2011) |
| Combination of patient surveys and medical records        | 5 (9.1%)  | (Bosak et al., 2019; Entezari-Maleki et al., 2012; Hogan et al., 1988; Mody, Wu, et al., 2015; E. B. Schwarz, Parisi, et al., 2013)                                                                                     |
| Patient logs, reproductive life plans, and physician surveys | 3 (5.4%)  | (Chave et al., 2001; DiPietro Mager et al., 2018; Landis et al., 2012)                                                                                                                                                    |
| Teratogenic medication                                   |           |                                                                                                                                                                                                                         |
| Multiple teratogenic medications                         | 16 (29.1%)| (DiPietro Mager et al., 2018; Force et al., 2012; Fritsche et al., 2011; Goyal et al., 2015; Martin et al., 2008; Mody, Farala, et al., 2015; Mody, Wu, et al., 2015; Ruiter et al., 2012; E. B. Schwarz et al., 2010; E. B. Schwarz et al., 2005; E. B. Schwarz, Mattocks, et al., 2013; E. B. Schwarz, Parisi, et al., 2013; E. B. Schwarz, Parisi, Williams, et al., 2012; E. B. Schwarz et al., 2007; Stancil et al., 2016; Steinkellner et al., 2010) |
| Isotretinoin                                             | 16 (29.1%)| (Algoblan et al., 2019; Boucher & Beaulac-Baillargeon, 2006; Brinker et al., 2005; Cheetham et al., 2006; Crijns et al., 2012; Entezari-Maleki et al., 2012; Hogan et al., 1988; Lelubre et al., 2018; Mitchell et al., 1995; Ozyurt & Kapitanoglu, 2015; Pinheiro et al., 2013; Rao et al., 2000; Teichert et al., 2010; Tsur et al., 2008; Uuskula et al., 2018; Werner et al., 2014) |
| Antiepileptic or anticonvulsant medications               | 5 (9.1%)  | (Bell et al., 2002; Bhakta et al., 2015; Bosak et al., 2019; Langan et al., 2013; Wieck et al., 2007)                                                                                                                      |
| Arthritis or lupus medications                           | 4 (7.3%)  | (Banas et al., 2014; Ferguson et al., 2016; Leverenz et al., 2019; Yazdany et al., 2011)                                                                                                                                  |
| Valproate/valproic acid                                   | 4 (7.3%)  | (Atturu & Odelola, 2015; Gotlib et al., 2016; Mulryan et al., 2018; Paton et al., 2018)                                                                                                                                      |
| Thalidomide or lenalidomide                              | 3 (5.5%)  | (Brandenburg et al., 2017; Castaneda et al., 2008; Chave et al., 2001)                                                                                                                                                     |
| Acitretin                                                | 1 (1.8%)  | (Raguideau et al., 2015)                                                                                                                                                                                                  |
| Chemotherapy for breast cancer                           | 1 (1.8%)  | (Valle et al., 1998)                                                                                                                                                                                                     |
| Deferoxamine and deferiprone                             | 1 (1.8%)  | (Shilalukey et al., 1997)                                                                                                                                                                                                  |
| Cyclophosphamide                                         | 1 (1.8%)  | (Hayward et al., 2016)                                                                                                                                                                                                     |
| Isotretinoin and oral contraceptives                      | 1 (1.8%)  | (Landis et al., 2012)                                                                                                                                                                                                     |
| Mood stabilizers                                         | 1 (1.8%)  | (James et al., 2007)                                                                                                                                                                                                       |
| Warfarin                                                 | 1 (1.8%)  | (Chang et al., 2018)                                                                                                                                                                                                       |
| Available risk management programme or a pregnancy risk classification system | 28 (50.9%)| (Bell et al., 2002; Brandenburg et al., 2017; Brinker et al., 2005; Castaneda et al., 2008; Cheetham et al., 2006; DiPietro Mager et al., 2018; Force et al., 2012; Fritsche et al., 2011; Gotlib et al., 2016;
| Study characteristic | n (%) | Citations of the studies |
|----------------------|-------|--------------------------|
| Goyal et al., 2015; Landis, et al., 2012; Lelubre et al., 2018; Mitchell et al., 1995; Mody, Farala, et al., 2015; Mody, Wu, et al., 2015; Paton et al., 2018; Pinheiro et al., 2013; Ruiter et al., 2012; E. B. Schwarz et al., 2010; E. B. Schwarz et al., 2005; E. B. Schwarz, Mattocks, et al., 2013; E. B. Schwarz et al., 2007; Stancil et al., 2016; Steinkellner et al., 2010; Teichert et al., 2010; Werner et al., 2014; Wieck et al., 2007) |

**Quality assessment**

| Low quality | 1 (1.8%) | (Martin et al., 2008) |
|-------------|---------|----------------------|
| Medium quality | 31 (56.4%) | (Algoblan et al., 2019; Atturu & Odelola, 2015; Banas et al., 2014; Bell et al., 2002; Bhakta et al., 2015; Bosak et al., 2019; Brandenburg et al., 2017; Castaneda et al., 2008; Chave et al., 2001; Cheetham et al., 2006; Crijns et al., 2012; DiPietro Mager et al., 2018; Force et al., 2012; Fritsche et al., 2011; Gotlib et al., 2016; Hogan et al., 1988; James et al., 2007; Lelubre et al., 2018; Mitchell et al., 1995; Mulryan et al., 2018; Ozyurt & Kaptanoglu, 2015; Paton et al., 2018; Pinheiro et al., 2013; Raguideau et al., 2015; Rao et al., 2000; Ruiter et al., 2012; E. B. Schwarz et al., 2005; Shilalukey et al., 1997; Steinkellner et al., 2010; Valle et al., 1998; Wieck et al., 2007) |
| High quality | 23 (41.8%) | (Boucher & Beaulac-Baillargeon, 2006; Brinker et al., 2005; Chang et al., 2018; Entezari-Maleki et al., 2012; Ferguson et al., 2016; Goyal et al., 2015; Hayward et al., 2016; Landis et al., 2012; Langan et al., 2013; Leverenz et al., 2019; Mody, Farala, et al., 2015; Mody, Wu, et al., 2015; E. B. Schwarz et al., 2010; E. B. Schwarz, Mattocks, et al., 2013; E. B. Schwarz, Parisi, et al., 2013; E. B. Schwarz, Parisi, Williams, et al., 2012; E. B. Schwarz et al., 2007; Stancil et al., 2016; Teichert et al., 2010; Tsur et al., 2008; Uuskula et al., 2018; Werner et al., 2014; Yazdany et al., 2011) |
# APPENDIX C: Additional methodological information on studies reporting perceptions of teratogenic risk

| Study                  | Recruitment of participants                                                                                                                                                                                                 | Consent of participants                                                                                                                                  | Survey method                                                                                                                                                                                                 | Measurement of risk perception                                                                                                                                                                                                 |
|-----------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Lupattelli et al.     | An online questionnaire was open to the public via utilization of banners on one-four websites per country and/or social networks commonly visited by pregnant women. Websites with sufficiently high number of daily users were selected. | Informed consent was given by participants by ticking the answer “yes” to the question “Are you willing to participate in the study?” | An anonymous on-line questionnaire (http://www.questback.com) was utilized for data collection, accessible for a period of 2 months in each participating country between October 1, 2011 and February 29, 2012. | Subjects were provided with a numeric rating scales ranging from 0 (not harmful to the fetus) to 10 (very harmful to the fetus) to indicate the perceived risk of the included medicines. |
| Gils et al.           | An invitation to the study, including a link and a code to the questionnaire, were sent to the study participants by mail. The questionnaire was developed through SurveyXact and was made available at a website for internet surveys (https://www.survey-xact.dk). | This study was a completely anonymous questionnaire not involving person-specific healthcare related information. The Danish law does not require ethical approval or consent to participate in such cases. The study was approved by the Danish Data Protection Agency. | Information was gathered by anonymous self-completed questionnaires.                                                                                                                                          | To evaluate the perception of the teratogenic risk of medicines during pregnancy, the participants were asked to give their best estimate based on their active knowledge. Estimates were to be entered as an integer between 0 and 100%.                                      |
| Nordeng et al.        | An invitation to the study was posted on the following four Web pages for pregnant women and mothers: barnimagen.com (can be translated as “pregnant.com”), dinbaby.com (“yourbaby.com”), babyverden.no (“babyworld.no”) and mammanett.no (“mommynet.no”). These Web sites are edited by a midwife and a staff of health care professionals. The questionnaire was accessible during a period of 5 weeks. | NA                                                                                                                                             | Anonymous self-completed online questionnaire.                                                                                                                                                              | Numeric rating scales ranging from 0 (no risk to the foetus) to 10 (foetal malformation following each exposure) were used to evaluate the perception of teratogenic risk of the included medicines.                                                                                     |
| Damase-Michel et al.  | General practitioners (GPs) and community pharmacists (CPs) of Midi-Pyrenees area were interviewed at the beginning of continuous courses, the subjects of which were different from drug and pregnancy. | NA                                                                                                                                             | General practitioners (GPs) and community pharmacists (CPs) were asked to answer individually and spontaneously to the questionnaire. All questionnaires were collected at the end of the session. | For each drug, health professionals were asked to put a mark along the line of a visual analogue scale (VAS) to indicate their estimation of the potential teratogenic risk of the drug. The question was: “a drug may affect formation and...
| Study          | Recruitment of participants                                                                 | Consent of participants | Survey method                                                                 | Measurement of risk perception |
|---------------|------------------------------------------------------------------------------------------------|-------------------------|-------------------------------------------------------------------------------|--------------------------------|
| Sanz et al.   | The General Practitioners (GPs) were attending a continuing educational refresher course in therapeutics. The gynecologists were haphazardly selected in the out-patient clinic of the Obstetrics and Gynecology department of the University Hospital. The questionnaire was also given to preclinical medical students (first to third year) and clinical medical students (fourth to sixth year) who had already taken the course in Obstetrics and Gynecology with the standard subject requirements on malformations and teratogenicity. The students were recruited at the School of Medicine. Pregnant women attending the regular obstetric follow-up in the out-patient clinic of the University Hospital, and nonpregnant women, half of them interviewed in the obstetric and gynecological out-patient clinic of the Hospital, and | NA                       | GPs: the questionnaire was given before the beginning of the course. Gynecologists: NA Preclinical medical students (first to third year) and clinical medical students (fourth to sixth year): questionnaire given to this group Pregnant and nonpregnant women: interviewed | To evaluate the perception of the teratogenic risk of medication, a Visual Analogue Scale (VAS) was used: a 10 cm horizontal line with a short vertical line at each end, one marked 0% and the other 100%. The participants were asked to mark on the scale what they thought the potential risk for major malformations was for a given drug (between 0% and 100%). |

(Continues)
| Study     | Recruitment of participants                                                                 | Consent of participants                                                                 | Survey method                                                                 | Measurement of risk perception                                                                 |
|-----------|---------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|
| Pons et al. | Participants from three prenatal care services in the municipal primary care system were recruited in person or by telephone. | All participants received an explanation of the research project and signed a free and informed consent form. | Interviews with participants were conducted by two trained pharmacists.         | The quantitative data collection instrument used numerical questions to measure outcomes (perception of teratogenic risk). The instrument measured the perception of teratogenic risk for medicines frequently used during pregnancy. |
| Petersen et al. | The questionnaire was open to the public via utilization of banners on 1–4 websites, social networks and/or pregnancy forums per country commonly visited by pregnant women. Websites were selected on the basis of the number of daily users. | Informed consent was given by participants by ticking the answer "yes" to the question “Are you willing to participate in the study?” | An anonymous on-line questionnaire (http://www.questback.com) was utilized for data collection, accessible for a period of 2 months in each participating country between October 1, 2011 and February 29, 2012. | Women were asked the following question: “Here below is a list with various medicines. Please indicate how harmful you think they are for the foetus in a scale from 0 to 10, where 0 corresponds to ‘not harmful’ and 10 to ‘very harmful’.” |