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 child bearing 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 counselling, contraceptive counselling, 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 counselling (9.5-99.3%), contraceptive counselling (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/gynaecologists), for etretinate (by pregnant women), and for misoprostol (by pregnant and non-pregnant women). An under-estimation was reported for warfarin and retinoids (by general practitioners and obstetric/gynaecologists). 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 child bearing age is reported in the literature. A common tendency to over-estimate the risk of teratogenic medications was evident.

Introduction

A teratogen is a substance that can adversely affect the development of an embryo or a foetus on exposure during pregnancy. A wide range of substances have been recognised as teratogens, including some medications [1, 2]. There is a need to ensure that potential teratogens are used as safely as possible by women of child bearing 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 [3, 4].

To support healthcare professionals' and patients' understanding regarding the relative of safety of using different medications during pregnancy, evidence-based classification systems have been developed [5]. Within such systems, medications are assigned into different risk categories based on available data on their harm to the foetus, including type, subjects, and results of the available teratogenicity studies [5, 6]. One example of a classification system is the Food and Drug Administration (FDA) pregnancy categories, which classifies any medication within one of five categories (A, B, C, D, or X) based on its degree of safety, with class A being the safest and class X being the most harmful to the foetus [7].

To minimise 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 [4, 8]. Subsequently, the use of teratogenic

medications has been increasingly controlled through the development of risk minimisation activities and programmes [8]. Elements to ensure safe use of teratogenic medications include certification of prescribers and dispensers, patient counselling regarding contraception use and monitoring patient contraception behaviours through regular pregnancy testing and use of contraception [8, 9].

The development and implementation of teratogenic risk management programmes should also take into consideration patient's experience of using a medication [10]. The value of recognising patient's 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 [11]. Medicines optimisation is a patient-centred approach for achieving optimal use of medications by providing personalised care for each patient [12]. Conceptualised 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 [13, 14]. 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 [10]. In fact, evidence from the literature suggests that the patient-physician relationship and teratogenic risk communication have a significant impact on patients' medication utilisation [13]. 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 [15-17].

A growing body of literature has investigated the implementation of pregnancy prevention measures while prescribing teratogenic medications to women of child bearing age [18-22]. Additionally, research has focused on the perceived risk of teratogenic medications of various populations [15, 23, 24]. 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 child bearing age in combination with a review of patients' experience of using teratogenic medications in terms of reported perceptions of teratogenic risk.

Methods

The protocol for this systematic review was registered with PROSPERO (International Prospective Register of Systematic Reviews) registration number CRD42019142944 [25]. The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement has guided the write-up of this review paper [26].

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 perceive*. 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 1.

Inclusion/exclusion criteria:

Risk management : the review aimed to establish the implementation of risk management for teratogenic medications used by women of child bearing age. Therefore, papers were included in the review if they reported the use of at least one teratogenic medication by females of child bearing 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. Safety of teratogenic medications use is further monitored against Elements to Assure Safe Use (ETASU), see Table 1 [27, 28].

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.

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.

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.

Data extraction

Data were extracted by the three authors and synthesised 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 was compared to the true value of the teratogenic risk that was extracted either from the methods or the results section. 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.

Quality assessment:

The critical appraisal tool developed by Hawker et al. [29] 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.

Data analysis:

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

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:

Prevalence of risk minimisation measure implementation/ 100 patients = total number of patients implementing the measure / total number of patients using the teratogenic medication x 100

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). Categorised results were presented in tabular form.

Results

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. More than half of the included studies (n=29; 52.7%) were conducted in the USA [3, 17-20, 30-53], nine (16.4%) originated from the UK [21, 54-61], and the rest were from Canada (n=3; 5.5%) [62-64], Netherlands (n=3; 5.5%)[65-67], Poland (n=2;3.6%) [68, 69], Ireland (n=1;1.8%) [70], Belgium (n=1;1.8%) [71], Estonia (n=1;1.8%) [22], France (n=1;1.8%) [72], Iran (n=1;1.8%) [73], Turkey (n=1;1.8%) [74], Israel (n=1;1.8%) [75], Uganda (n=1;1.8%) [76], and Saudi Arabia (n=1;1.8%) [77]. Publication dates ranged from 1988 to 2019, with nearly two thirds (n=35, 63.6%) published after 2010 [3, 18-22, 34-39, 41-43, 46, 48-53, 58, 61, 65, 67-74, 76, 77].

Data sources included medical records (n=26; 47.3%) [17, 19, 21, 22, 31, 32, 34, 36, 37, 40, 41, 43, 44, 46, 49, 54, 57, 58, 60, 61, 65-67, 70, 72, 78], patient surveys (n=21; 38.2%) [18, 20, 30, 33, 35, 39, 45, 47, 48, 52, 53, 55, 56, 62, 64, 69, 71, 74-77] or a combination of patient surveys and medical records (n=5; 9.1%) [38, 50, 63, 68, 73]; patient logs [42], reproductive life plans [51], and physician surveys [59] were used less frequently (n= 3; 5.4%). Most studies (n=16; 29.1%) investigated the use of multiple teratogenic medications [17, 32, 36-40, 43, 44, 48-51, 60, 65, 78]. Sixteen studies (29.1%) reported on the use of isotretinoin [22, 30, 31, 33, 34, 47, 53, 63, 64, 66, 67, 71, 73-75, 77], five (9.1%) reported on the use of antiepileptic or anticonvulsant medications [46, 54, 56, 58, 68], four (7.3%) reported on the use of arthritis or lupus medications [20, 35, 52, 69], four (7.3%) reported on the use of valproate/valproic acid [21, 41, 61, 70], and three (5.5%) reported on the use of thalidomide or lenalidomide [18, 45, 59]. Each of the following medications was reported by one study (1.8%) in the review: acitretin [72], chemotherapy for breast cancer [55], deferoxamine and deferiprone [62], cyclophosphamide [19], isotretinoin and oral contraceptives [42], mood stabilisers [57] and warfarin [76]. A risk management programme or a pregnancy risk classification system was reported in 28 studies (50.9%) [17, 18, 21, 30-32, 34, 36, 37, 39-45, 47-51, 53, 54, 56, 65, 66, 71]. More than half of the studies (n=31; 56.4%) were of medium quality [17, 18, 21, 30-34, 36, 41, 43, 45, 46, 51, 54-57, 59, 61-63, 65, 67-72, 74, 77], while 23 (41.8%) were of high quality [19, 20, 22, 35, 37-40, 42, 44, 47-50, 52, 53, 58, 64, 66, 73, 75, 76, 78] and one study (1.8%) was of low quality [60].

Teratogenic counselling was reported in 19 studies (34.5%) [18, 21, 30, 38, 39, 41, 46, 50, 54, 56-58, 61, 64, 68, 70, 75-77], contraceptive counselling in 22 studies (40%) [17, 18, 21, 30, 35, 38, 40, 43, 46, 50, 52-55, 57, 58, 64, 68, 70, 71, 77], pregnancy testing before starting treatment in 10 studies (18.2%) [30, 31, 47, 48, 59, 64, 70-72, 75], pregnancy testing during treatment in eight studies (14.5%) [19, 44, 57, 64, 71, 72, 75, 77], contraception use before starting treatment in four studies (7.3%) [18, 22, 30, 55], and contraception use during treatment in 35 studies (63.6%) [18, 20-22, 32-37, 40-42, 44-46, 49-51, 55, 57, 60, 62-69, 73-76, 78]. No studies reported on all aspects of risk management included in the current review, see Table 3.

Prevalence of teratogenic counselling ranged from 9.5% [70] to 99.3% [18], contraceptive counselling from 6.1% [17] to 98% [18], pregnancy testing before starting treatment from 0% [59, 70] to 95.1% [31], pregnancy testing during treatment from 12.7% [72] to 100% [19], contraception use before starting treatment from 15.7% [22] to 94% [18], and contraception use during treatment from 1.7% [75] to 100% [74].

Perceptions of teratogenic risk

A total of 6000 articles were initially screened. Of those, 141 were removed because of duplication, 5725 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 [24, 79], and the rest were from Denmark (n=1; 14.3%) [15], Norway (n=1; 14.3%) [80], France (n=1; 14.3%) [81], Spain (n=1; 14.3%) [16], and Brazil (n=1; 14.3%) [82]. All studies had a cross sectional design and were published after the year 2000. Four studies out of seven (57.1%) utilised online questionnaires for data collection [15, 24, 79, 80], two studies used questionnaires filled during a continuous educational course [16, 81], and one study collected data within prenatal services in primary care [82]. 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%) [15, 24, 79, 80, 82] and a visual analogue scale was used in two studies (28.6%) [16, 81]. Five studies (71.4%) [15, 24, 79, 80, 82] were of high quality and two (28.6%) were of medium quality [16, 81].

A proper estimation of the teratogenic risk was reported for thalidomide (by general practitioners and obstetric/gynaecologists) [15], for etretinate (by pregnant women) [16], and for misoprostol (by pregnant and non-pregnant women) [82]. An under-estimation of the teratogenic risk was reported for warfarin and retinoids (by general practitioners and obstetric/gynaecologists) [15]. And over-estimation of the teratogenic risk was reported for thalidomide (by pregnant and non-pregnant women, healthcare professionals, and medical students) [16, 24, 79-81], for valproate, lithium, isotretinoin, and warfarin (by healthcare professionals) [81], for phenytoin and warfarin (by pregnant and non-pregnant women, healthcare professionals, and medical students) [16], and for etretinate (by non-pregnant women, healthcare professionals, and medical students) [16]. Details are presented in Table 5.

Discussion

Guided by principles of medicines optimisation [11], 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 summarising published studies that report perceptions of potential teratogens.

Risk management

Measures to minimise 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 counselling, contraceptive counselling, 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 [83].

Isotretinoin was the most commonly prescribed teratogenic medication covered by the studies included in this review (n= 16; 29.1%) [22, 30, 31, 33, 34, 47, 53, 63, 64, 66, 67, 71, 73-75, 77]. 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 [84]. Secondly, it is one of the most cost-effective acne treatments used by patients from different age groups including women of child bearing age [4, 77, 85].

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 [18, 21, 41, 45, 59, 61, 70], 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 [11].

Results of teratogenic risk management implementation showed a wide variation among studies. Some studies

reported surprisingly low rates of implementation. For example, only 9.5% of women of child bearing age using valproate received teratogenic counselling in the study by Mulryan et al. [70], and 6.1% of women using medications of class D or X received contraceptive counselling in the study by Schwarz et al. [17]. Additionally, rates of pregnancy testing before starting treatment with valproate or thalidomide were as low as 0% in two studies [59, 70], and pregnancy testing during treatment with acitretin was 12.7% in the study by Raguideau et al. [72]. Low rates of contraceptive use were also reported. Uuskula et al. reported that 15.7% of women of child bearing age on isotretinoin treatment in their study used a contraceptive before starting treatment [22], and Tsur et al. reported that only 1.7% of women in their study group used contraception during treatment with isotretinoin [75].

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 [17, 19, 21, 22, 31, 32, 34, 36, 37, 40, 41, 43, 44, 46, 49, 54, 57, 58, 60, 61, 65-67, 70, 72, 78], while others used patients surveys [18, 20, 30, 33, 35, 39, 45, 47, 48, 52, 53, 55, 56, 62, 64, 69, 71, 74-77], a combination of medical records and patient surveys [38, 50, 63, 68, 73], or other sources (patient logs [42], reproductive life plans [51], and physician surveys [59]). Having patients as the only source of information can lead to several forms of self-reporting bias [86]. Recall bias can lead to an erroneous estimation of risk management variables if the patient's recall of information is inaccurate [87]. Another form of self-reporting bias associated with the disclosure of sensitive data is the social desirability bias [86]. Social desirability bias might have led to an overestimated adherence to risk management and pregnancy prevention measures [88]. On the other hand, if data were extracted from the medical records, several issues like incomplete records, non-captured data, and low quality data might have an effect on the research outcomes [89, 90]. Therefore, it is important to bear in mind the possible types of bias associated with each source of data.

Another well recognised 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, linaledomide, and isotretinoin, detailed risk management programmes that aim to prevent foetal exposure to the drug are in place [4, 8]. However, for other teratogenic medications, managing their risk is limited to the use of product labelling and patient information leaflets rather than rigorous monitoring [91]. The effectiveness of drug labelling as a risk management tool has been a matter of debate as research suggests a lack of effect on physicians' prescribing behaviours or patients' understanding of instructions [91].

Results of the current review can be considered as a compliance assessment of teratogenic risk management (whether through existing risk management programmes or through labelling recommendations) [91]. Based on the findings of this review, safety of the utilisation 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 minimise foetal exposure to cytotoxic effects, and thus future research utilising multiple data sources is needed. Drawing on the strengths of data extracted from medical records and patient reported data, mixed methods research that utilises quantitative and qualitative methods could yield more rigorous results than research utilising quantitative or qualitative methods alone [92, 93].

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.

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 [16]. 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 [15, 24, 79, 80, 82] or a visual analogue scale [16, 81]. One major issue regarding the use of a numeric scale to estimate the risk is its dependence on numeracy skills of participants [82, 94]. 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 [94, 95]. 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 [16, 96], while others suggest that a visual analogue scale can provide a wide range of responses that can be chosen by research participants [97]. 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. [96]. Furthermore, it is recommended that future research exploring perceptions of teratogenic risk needs to utilise 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 [92].

It is clear from the results of the review that teratogenic risk of medications tends to be over-estimated [16, 24, 79-81], while proper estimation [15, 82] or under-estimation [15] 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 [98, 99], a realistic perception of teratogenic risk is needed by women in child bearing age to adhere to their therapy [100].

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 [13, 98, 101]. 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 [81], or the lack of relevant resources being utilized when needed [102]. 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 [102]. Subsequently, future research needs to focus on understanding how teratogenic risk is conceptualised 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 child bearing age. It utilises 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.

Conclusion

Considerable variation in the implementation of risk management measures when prescribing teratogenic medications to women of child bearing age is reported in the literature. Factors contributing to this vari-

ation 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 conceptualised can usefully inform medicines optimisation so that patients derive the intended outcomes of a prescribed medication.

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Table 1. Specific risk minimisation measures reported in the included papers.

Components of Risk Evaluation and Mitigation Strategies (REMS) with Elements to Assure Safe Use (ETA
Patient information
Safe use conditions

Table 2. Characteristics of studies reporting risk minimisation measures implemented when prescribing teratogenic medicines for women of child bearing age.

Study	Country: setting	Age	Time	Data source	Teratogenic medication	Risk management programme or pregnancy risk classification system	Quality assessment score (out of 36)
Algoblan et al. (2019)	Saudi Arabia: outpatient clinics including private clinics and governmental hospitals	33 to 40	6/2017 – 11/2017	Patient survey	Isotretinoin	NS	28
Mitchell et al. (1995)	USA: Telephone or mailed survey	12 to 59	1/1989 - 12/1993	Patient survey	Isotretinoin	Pregnancy Prevention Program for isotretinoin	25
Cheetham et al. (2006)	USA: Kaiser Permanente (a national, non-profit, managed care organization)	NS	2000 - 2004	Medical records	Isotretinoin	Kaiser Permanente Southern California isotretinoin risk management program	28
Rao et al. (2000)	USA: Telephone or mailed survey	NS	1990 - 1993	Patient survey	Isotretinoin	NS	28
Uusküla et al. (2018)	Estonia: The Estonian Health Insurance Fund (EHIF)	15 to 45	1/2012 - 10/2016	Medical records	Isotretinoin	NS	31

Study	Country: setting	Age	Time	Data source	Teratogenic medication	Risk management programme or pregnancy risk classification system	Quality assessment score (out of 36)
Pinheiro et al. (2013)	USA: IMS Health, Vector One®: Data Extract Tool (DET)	13 to 45	3/2004 - 2/2008	Medical records	Isotretinoin	iPledge	28
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
Lelubre et al. (2018)	Belgium: Questionnaires delivered online by email	NS	12/2014 - 10/2015	Patient survey	Isotretinoin	Pregnancy Prevention Program for isotrentinoin	29
Teichert et al. (2010)	Netherlands: The Dutch Foundation for Pharmaceutical Statistics (SFK)	15 to 45	1/2005 - 12/2008	Medical records	Isotretinoin	The Dutch pregnancy prevention program	31
Boucher and Beaulac-Baillargeon (2006)	Canada: Telephone interview	[?]14	11/2003 - 7/2004	Patient survey	Isotretinoin	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)
Crijns et al. (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
Ozyurt and Kaptanoglu (2015)	Turkey: Dermatology clinic in a Hospital	14 to 35	1/2012 for 18 months	Patient survey	Isotretinoin	NS	24
Tsur et al. (2008)	Israel: Drug Consultation Centre	16 to 45	7/2005 - 10/2005	Patient survey	Isotretinoin	NS	31
Brinker et al. (2005)	USA: 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

Study	Country: setting	Age	Time	Data source	Teratogenic medication	Risk management programme or pregnancy risk classification system	Quality assessment score (out of 36)
Werner et al. (2014)	USA: Urban community via flyers displayed on college campuses, at dermatology clinics, and at student health facilities	14 to 45	1/2012 - 9/2012	Patient survey	Isotretinoin	iPledge	32
Hogan et al. (1988)	Canada: Dermatology clinic and general practitioner clinic	NS	4/1983 - 3/1985	Patient survey and medical records	Isotretinoin	NS	24
Bhakta et al. (2015)	USA: Outpatient Neurology Clinics in a hospital	15 to 44	7/2011 - 6/2012	Medical records	Anti-epileptic drugs (phenobarbital, primidone, phenytoin, fosphenytoin, ethosuximide, carbamazepine, sodium valproate, and topiramate)	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)
Wieck et al. (2007)	UK: Psychiatric departments of three teaching hospitals	16 to 47	11/2004 - 10/2005	Medical records	Sodium valproate, semisodium valproate or carbamazapine	National Institute for Health and Clinical Excellence for epilepsy (2004)	24
Bell et al. (2002)	UK: General practices and outpatient department of hospital consultants (neurologists, paediatricians and paediatric neurologists), in addition to mailed questionnaire	14 to 55	2000	Patient survey	Anti-epileptic drugs	Services for patients with epilepsy: report of a CSAG Committee chaired by Professor Alison Kitson	28
Langan et al. (2013)	UK: Secondary care psychiatric contacts	16 to 50	2002 - 2005	Medical records	Sodium valproate, carbamazepine, lamotrigine and topiramate	NS	31
Bosak et al. (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)
Leverenz et al. (2019)	USA: 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)
Yazdany et al. (2011)	USA: Academic rheumatology offices , community rheumatology offices, and nonclinical sources, including patient support groups and conferences and other forms of media	[?]45	2008 - 2009	Patient survey	Methotrexate, mycophenolate mofetil, azathioprine, cyclosporine, tacrolimus, leflunomide, cyclophosphamide, or biologic agent	NS	33
Ferguson et al. (2016)	USA: Academic and community practices , lupus support groups and conferences , and newsletters, websites and other forms of publicity	[?]45	2003 - 2010	Patient survey	Azathioprine, mycophenolate, methotrexate, cyclosporine, leflunomide, cyclophosphamide, rituximab, abatacept, or belimumab	NS	31
Banas et al. (2014)	Poland: NS	NS	NS	Patient survey	Leflunomide	NS	26

Study	Country: setting	Age	Time	Data source	Teratogenic medication	Risk management programme or pregnancy risk classification system	Quality assessment score (out of 36)
Paton et al. (2018)	UK: Mental health provider organisations	[?] 50		Medical records	Sodium valproate	NICE guideline for bipolar disorder (NICE 2014)	25
Gotlib et al. (2016)	USA: A tertiary medical centre	15 to 49	1/2013 - 7/2014	Medical records	Sodium valproate	American Psychiatry Association, American Congress of Obstetrics and Gynaecologists, National Institute for Health and Care Excellence and American Academy of Neurology and American Epilepsy Society	29
Mulryan et al. (2018)	Ireland: Irish mental health service	18 to 49	42370	Medical records	Sodium valproate	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)
Atturu and Odelola (2015)	UK: Adult Psychiatric service	18 to 45	2005 - 2012	Medical records	Sodium valproate	Bipolar disorder: The management of bipolar disorder in adults, children and adolescents, in primary and secondary care (NICE) 2006	29
Brandenburg et al. (2017)	USA: Mandatory and voluntary surveys of the REMS program	NS	6/2012 - 6/2013	Patient survey	Thalidomide and lenalidomide	REMS for thalidomide and lenalidomide	29
Castaneda et al. (2008)	USA: REMS	females of child bearing potential	12/2005 - 12/2007	Patient survey	Lenalidomide	RevAssist®	29
Chave et al. (2001)	UK: Dermatologists	NS	36434	Physician questionnaire	Thalidomide	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)
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
Valle et al. (1998)	UK: Cancer care hospital	NS		Patient survey	Chemotherapy for breast cancer	NS	25
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
Hayward et al. (2016)	USA: Children's Hospital	12 to 21	7/2011 - 6/2015	Medical records	Cyclophosphamide	NS	31

Study	Country: setting	Age	Time	Data source	Teratogenic medication	Risk management programme or pregnancy risk classification system	Quality assessment score (out of 36)
Landis et al. (2012)	USA: The National Ambulatory Medical Care Survey (NAMCS)	12 to 55	1993 - 2008	Patient log	Isotretinoin and oral contraceptives	iPledge	31
James et al. (2007)	UK: A mental health trust	18 to 45	2006	Medical records	Lithium, carbamazepine or sodium valproate	NS	26
Chang et al. (2018)	Uganda: Uganda Heart Institute (UHI)	15 to 59	NS	Patient survey	Warfarin	NS	35
Steinkellner et al. (2010)	USA: Database from Medco Health Solutions, Inc.(Franklin Lakes, NJ), a pharmacy benefits manager	18 to 44	1/2008 - 6/2009	Medical records	Category X	FDA, validated by Micromedex and Clinical Pharmacology ref	28
Schwarz et al. (2007)	USA: Kaiser Permanente (a health maintenance organization)	15 to 44	2001	Medical records	Category D or X	FDA	30

Study	Country: setting	Age	Time	Data source	Teratogenic medication	Risk management programme or pregnancy risk classification system	Quality assessment score (out of 36)
Schwarz et al. (2005)	USA: The National Ambulatory Medical Care Survey (NAMCS), an annual survey of non-federal employed, office-based physicians	14 to 44	1998 - 2000	Medical records	Category D or X	FDA	27
Goyal et al. (2015)	USA: National Hospital Ambulatory Medical Care Survey (NHAMCS)	14 to 40	2005 - 2009	Patient survey	Category D or X	FDA	35
Stancil et al. (2016)	USA: Academic paediatric medical centre	14 to 25	1/2008 - 12/2012	Medical records	Category D or X	FDA	30

Study	Country: setting	Age	Time	Data source	Teratogenic medication	Risk management programme or pregnancy risk classification system	Quality assessment score (out of 36)
Mody et al. (2015)	USA: Family medicine at an academic institution	18 to 45	4/2011 - 4/2012	Medical records	Category D or X	Review of the category D and X medications in 2012 by a counsellor for California Teratogen Information Specialists	32
Mody et al. (2015)	USA: An academic outpatient family medicine clinic	18 to 45	4/2012 - 4/2013	Patient survey and medical records	Category D or X	FDA	33
Schwarz et al. (2010)	USA: Pharmacy Benefits Management Database (PBM)	18 to 45	10/2006 - 9/2008	Medical records	Category D or X	FDA	35
Mager et al. (2018)	USA: 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	FDA	25

Study	Country: setting	Age	Time	Data source	Teratogenic medication	Risk management programme or pregnancy risk classification system	Quality assessment score (out of 36)
Fritsche et al. (2011)	USA: 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

Study	Country: setting	Age	Time	Data source	Teratogenic medication	Risk management programme or pregnancy risk classification system	Quality assessment score (out of 36)
Ruiter et al. (2012)	Netherlands: The Dutch Foundation for Pharmaceutical Statistics (SFK)	15 to 45	1/2005 - 12/2009	Medical records	Category D or X 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. (2012)	USA: Academic general internal medicine practice	18 to 50	10/2008 - 4/2010	Medical records	Potential teratogens	NS	33
Force et al. (2012)	USA: Family medicine clinics	18 to 44	NS	Medical records	Angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers or statin	FDA	28

Study	Country: setting	Age	Time	Data source	Teratogenic medication	Risk management programme or pregnancy risk classification system	Quality assessment score (out of 36)
Schwarz et al. (2013)	USA: 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

Study	Country: setting	Age	Time	Data source	Teratogenic medication	Risk management programme or pregnancy risk classification system	Quality assessment score (out of 36)
Schwarz et al. (2013)	USA: 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
Martin et al. (2008)	UK: 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

CSAG: Clinical Standards Advisory Group, FDA: Food and Drug Administration Pregnancy Categories, NICE: The National Institute for Health and Care Excellence, NS: Not specified, OEF/OIF: Operation Enduring Freedom/Operation Iraqi Freedom, REMS: Risk Evaluation and Mitigation Strategies, TNF: Tumour Necrosis Factor, USA: United States of America, UK: United Kingdom, VA: Veterans Affairs

Table 3. Risk minimisation measures reported by studies of prescribing teratogenic medicines for women of child bearing age.

Study	Teratogenic counselling	Contraceptive counselling	Pregnancy testin
Algoblan et al. (2019)	[?]	[?]	-
Mitchell et al. (1995)	[?]	[?]	[?]
Cheetham et al. (2006)	-	-	[?]
Rao et al. (2000)	-	-	-
Uusküla et al. (2018)	-	-	-
Pinheiro et al. (2013)	-	-	-

Study	Teratogenic counselling	Contraceptive counselling	Pregnancy testin
Entezari-Maleki et al. (2012)	-	-	-
Lelubre et al. (2018)	-	[?]	[?]
Teichert et al. (2010)	-	-	-
Boucher and Beaulac-Baillargeon (2006)	[?]	[?]	[?]
Crijns et al. (2012)	-	-	-
Ozyurt and Kaptanoglu (2015)	-	-	-
Tsur et al. (2008)	[?]	-	[?]
Brinker et al. (2005)	-	-	[?]
Werner et al. (2014)	-	[?]	-
Hogan et al. (1988)	-	-	-
Bhakta et al. (2015)	[?]	[?]	-
Wieck et al. (2007)	[?]	[?]	-
Bell et al. (2002)	[?]	-	-
angan et al. (2013)	[?]	[?]	-
Bosak et al. (2019)	[?]	[?]	-
Leverenz et al. (2019)	-	-	-
Yazdany et al. (2011)	-	[?]	-
Ferguson et al. (2016)	-	[?]	-
Banas et al. (2014)	-	-	-
Paton et al. (2018)	[?]	[?]	-
Gotlib et al. (2016)	[?]	-	-
Mulryan et al. (2018)	[?]	[?]	[?]
Atturu and Odelola (2015)	[?]	[?]	-
Brandenburg et al. (2017)	[?]	[?]	-
Castaneda et al. (2008)	-	-	-
Chave et al. (2001)	-	-	[?]
Raguideau et al. (2015)	-	-	[?]
Valle et al. (1998)	-	[?]	-
Shilalukey et al. (1997)	-	-	-
Hayward et al. (2016)	-	-	-
Landis et al. (2012)	-	-	-
James et al. (2007)	[?]	[?]	-
Chang et al. (2018)	[?]	-	-
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)	-	-	-

Table 4. Characteristics of studies reporting perceptions of teratogenic medicines.

Study	Year	Country	Setting	Sample	Study design	Data source	Measurement of teratogenicity perception	Quality assessment score (of 36)
Lupattelli et al.	2014	18 countries*	On-line questionnaire	4999 pregnant women	Cross-sectional	On-line questionnaire	Numeric scale	33
Gils et al.	2016	Denmark	On-line questionnaire	143 general practitioners and 138 obstetricians/gynaecologists	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

Study	Year	Country	Setting	Sample	Study design	Data source	Measurement of teratogenicity perception	Quality assessment score (of 36)
Sanz et al.	2001	Spain	A continuous educational course, outpatient obstetrics and gynaecology clinic, School of Medicine and participants' homes	15 general practitioners, 10 gynaecologists, 106 preclinical students, 150 students in their clinical training, 81 pregnant women and 63 non-pregnant 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 non-pregnant women)	Cross-sectional	Structured interviews to fill a questionnaire	Numeric scale	33
Petersen et al.	2015	18 countries*	On-line questionnaire	9113 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
Lupattelli et al.	thalidomide	10 to 40	Low health literacy: 84.5 Medium health literacy: 8 High health literacy: 94.8

Study	Medications included	The true value of teratogenic risk (%)	The perceived value of
Gils et al.	thalidomide	20 to 50	GP: 20 OB/GYN: 20
	warfarin	10 to 20	GP: 3 OB/GYN: 5
	retinoids	30 to 38	GP: 10 OB/GYN: 5
Nordeng et al.	thalidomide	10 to 40	All included women: 75
Damase-Michel et al.	sodium valproate	10	All healthcare professional
	lithium	12	All healthcare professional
	isotretinoin	25	All healthcare professional
	warfarin	30	All healthcare professional
	thalidomide	50	All healthcare professional
Sanz et al.	phenytoin	[?] 10	Physicians: 37.9 Clinical students: 41.3 Pre-clinical students: 58.9 Non-pregnant women: 67.9 Pregnant women: 59.5
	warfarin	6 to 25	Physicians:53.2 Clinical students: 44.6 Pre-clinical students: 63.1 Non-pregnant women: 68.4 Pregnant women: 42.8
	etretinate	16 to 30	Physicians: 95.9 Clinical students: 55.1 Pre-clinical students: 59.7 Non-pregnant women: 45.8 Pregnant women: 16.4
	thalidomide	11 to 35	Physicians: 81.6 Clinical students: 73.4 Pre-clinical students: 79.3 Non-pregnant women: 91.1 Pregnant women: 82.6
Pons et al.	misoprostol	>3	Non-pregnant women: 50 Pregnant women: 50
Petersen et al.	thalidomide	10 to 40	All included women: 94

Figure legends:

Figure 1. Method for determining category for perceived teratogenic risk.

Figure 2. Flow diagram of studies selection (risk management).

Figure 3. Flow diagram of studies selection (perceptions of teratogenic risk).

Appendix 1: Search strategy for the systematic review.

Review topic	MEDLINE	CINAHL	Scopus	Embase	IPA
Perception of teratogenic risk	1. exp Perception/ or risk perception.mp. 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] 3. exp Teratogens/ or teratogen*.mp. 4. 1 or 2 5. 3 and 4	risk perception or perceived risk AND teratogen*	(TITLE-ABS-KEY (risk AND perception)) OR (TITLE-ABS-KEY (perceiv* AND risk)) AND (TITLE-ABS-KEY (teratogen*))	1. exp perception/ or risk perception.mp. or exp risk/ 2. exp risk/ or exp perception/ or perceiv* risk.mp. 3. exp teratogenicity/ or teratogen*.mp. 4. 1 or 2 5. 3 and 4	1. risk perception.mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name] 2. perceiv* risk.mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name] 3. teratogen*.mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name] 4. 1 or 2 5. 3 and 4
Date exported to Endnote	07/02/2019	08/02/2019	14/02/2019	07/02/2019	07/02/2019

Review topic	MEDLINE	CINAHL	Scopus	Embase	IPA
Risk management for teratogenic medicines	1. pregnancy prevent*.mp. 2. exp Risk Management/ or risk manag*.mp. 3. exp Contraception Behavior/ or contracep*.mp. or exp Contraception/ 4. exp Teratogens/ or teratogen*.mp. 5. 1 or 2 or 3 6. 4 and 5	risk manag* OR pregnancy prevent* OR contracep* AND teratogen* Limiters Full Text Age Groups: All Adul	(TITLE-ABS-KEY (risk AND management) OR TITLE-ABS-KEY (risk 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. 2. pregnancy prevent*.mp. 3. exp contraception/ or exp family planning/ or contracep*.mp. 4. teratogen*.mp. or exp teratogenicity/ 5. 1 or 2 or 3 6. 4 and 5 Filters Applied Publication Type : Article	1. risk management.mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name] 2. pregnancy prevent*.mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name] 3. contracep*.mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name] 4. teratogen*.mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name] 5. 1 or 2 or 3 6. 4 and 5
Date exported to Endnote	24/03/2019	24/03/2019	24/03/2019	24/03/2019	24/03/2019

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`Figure 1. Method for determining category for perceived teratogenic risk..docx` available at https://authorea.com/users/316033/articles/446263-risk-management-of-teratogenic-medicines-a-systematic-review

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`Figure 2. Flow diagram of studies selection (risk management)..docx` available at https://authorea.com/users/316033/articles/446263-risk-management-of-teratogenic-medicines-a-systematic-review

Hosted file

Figure 3. Flow diagram of studies selection (perceptions of teratogenic risk)..docx available at https://authorea.com/users/316033/articles/446263-risk-management-of-teratogenic-medicines-a-systematic-review