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Assessing the information in the Summaries of Product Characteristics for the use of medicines in pregnancy and lactation

Blanca Arguello,[1] Teresa M. Salgado[1] & Fernando Fernandez-Llimos[2]

[1]Research Institute for Medicines (iMed.ULisboa), Faculty of Pharmacy, University of Lisbon, Lisbon and [2]Research Institute for Medicines (iMed.ULisboa), Department of Social Pharmacy, Faculty of Pharmacy, University of Lisbon, Lisbon, Portugal

Correspondence
Dr Fernando Fernandez-Llimos PhD MBA, Departamento de Sócio-Farmácia, Faculdade de Farmacia, Universidade de Lisboa, Av. Prof. Gama Pinto, 1649-003 Lisboa – Portugal.
Tel.: +351 217 946 400
Fax: +351 217 946 470
E-mail: f-llimos@ff.ul.pt

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Reliable information regarding the use of many medicines during pregnancy is critical for researchers and healthcare professionals who work in antenatal care, but this information has been found to differ across different sources.
- The Summary of Product Characteristics (SmPCs) is the European official medicines information source for professionals and contains a specific section to include information on medicines use during pregnancy and lactation to guide decision making.
- Future electronic versions of SmPCs to be included in clinical decision support systems will require intelligible and logical electronic information.

WHAT THIS STUDY ADDS

- Important information deficits on the use of medicines during pregnancy and lactation were found in European SmPCs, and the time elapsed since a SmPC's marketing authorization was not associated with an increase in information quality.
- Post-authorization data on the exposure to medicinal products during pregnancy and lactation should be actively collected and included in official information sources to keep them updated and to assist decision making.

AIMS

To assess the completeness and applicability of information for the use of medicines in pregnancy and lactation contained in European Summaries of Product Characteristics (SmPCs).

METHODS

SmPCs available on the EMA website in April 2011 were retrieved, and information on the use of medicines during pregnancy and lactation was analyzed. A form was designed to extract information regarding drug concentrations crossing the placenta, excretion of the drug in milk, the existence of pre-clinical and clinical studies and clinical experience describing the use of the medicine in pregnancy and lactation, medicine effects on human fertility, medicines use in women of child-bearing potential and specific recommendations for use during pregnancy and breastfeeding. SmPCs were classified as containing 'conclusive' or 'ambiguous' information depending on whether (or not) they provided clear instructions regarding medicine use in pregnancy and lactation.

RESULTS

Of the 534 SmPCs, 89.3% did not mention whether the drug crossed the placenta, 67.6% indicated that there was no clinical experience during pregnancy and in 61.4% it was unknown whether the medicine was excreted in human milk. Recommendations for medicine use during pregnancy and breastfeeding were ambiguous in 57.0% and 16.5% of the SmPCs, respectively, and medicine use was restricted in over 90% SmPCs for both pregnancy and breastfeeding, despite no information supporting these restrictions being reported. The time elapsed since a SmPCs first approval was not associated with an increase in information quality.

CONCLUSIONS

Important information deficits on the use of medicines during pregnancy and breastfeeding were found in European SmPCs.

Introduction

Major congenital abnormalities occur in approximately 2–4% of all pregnancies, of which 20–25% have a genetic origin and around 10% have an exogenous and potentially preventable cause (e.g. use of medicines, maternal diabetes, alcohol abuse) [1]. Medicines usage during pregnancy is common with more than 80% of women reporting having used at least one medicine during their pregnancy [2, 3]. Even with excluding common medicines such as folic acid, iron preparations and vitamins, 69% of pregnant women still use at least one medicine during their prenatal period [2]. Although the teratogenic effects of medicines have been estimated to cause approximately 1% of birth defects, many health professionals and patients tend to overestimate their prevalence [1]. Whenever drug therapy is considered during pregnancy, both the potential teratogenic risks of treatment on the foetus and the potential risks of not treating the mother need to be carefully balanced [2]. Failure to treat some maternal conditions may also lead to increased foetal risks, including foetal abnormalities, intrauterine growth restrictions and stillbirth [4].

For a physician to make an informed decision about prescribing a medicine during pregnancy or lactation, relevant evidence-based information is required to help decide whether a treatment is appropriate during pregnancy or lactation, as well as to identify the risks of inadvertent exposure of a pregnant woman or a breastfeeding neonate to the particular treatment [5, 6]. One of the main concerns of researchers and healthcare professionals who work in antenatal care is the lack of information regarding the use of many medicines during pregnancy [7]. Additionally, information that is available about the use of certain medicines during pregnancy has been found to differ across different sources of information, which can make clinical decisions difficult for this patient group [4]. Information on excretion of the medicine in human milk is also critical in clinical practice. For many conditions such as epilepsy, rheumatoid arthritis or dermatologic pathologies, some drug therapy is compatible with breastfeeding and therefore there would be no need to withdraw the neonate from the benefits of breastfeeding [8–11].

The Summaries of Product Characteristics (SmPCs) are the official medicines information sources for healthcare professionals in the European Union [12]. SmPCs are an integral part of the marketing authorization process and constitute 'the basis of information for health care professionals on how to use the medicinal product safely and effectively' [12]. Specific safety information regarding the use of medicines in pregnancy, lactation and women of child-bearing potential, as well as the influence of the medicine on human fertility, are included in a specific section of SmPCs. Although different classification systems have been created to stratify medicines into risk groups according to their known or suspected adverse effects to the foetus [13], SmPCs do not make use of any of these systems. Rather, information is provided as narrative statements, the content and structure being set by the European Commission [12, 14].

Despite being considered a leading source of information for safety data and evidence-based prescribing decisions [15], SmPCs have been criticized for containing important clinical pharmacology information deficits [16], for being suboptimal sources of information for drug–drug interactions [17], food–drug interactions [18], therapeutic drug monitoring [19], or dose adjustment in renal impairment [20]. In addition, SmPCs have also been criticized for being too verbose, lacking standardization and being heterogeneous [21]. As highlighted above, given that many healthcare professionals who work in antenatal care are concerned about the availability of information regarding the use of medicines in pregnancy and lactation, this study aimed to assess the completeness and applicability of information contained in European SmPCs for these patient groups.

Methods

SmPCs of all the 582 medicines granted a marketing authorization through a centralized procedure in the European Union were retrieved from the European Medicines Agency (EMA) website (http://www.ema.europa.eu) on April 29 2011. Available versions corresponded to the latest update of the respective SmPC. For the purpose of the analysis, SmPCs referring to medicines with a main indication for (1) post-menopausal women, (2) paediatric use, (3) the male population, (4) contraception purposes or (5) assisted reproduction techniques were excluded since they were not meant to be used in pregnant or lactating women. Section 4.6 'Fertility, pregnancy and lactation' of included SmPCs was retrieved. An *ad hoc* form was designed to extract information from SmPCs after accessing scientific literature and European Union Regulations on the provision of safety information during pregnancy and lactation. The form was then piloted until the best structure to collect all the relevant information was obtained. The final structure of the form extracted information on whether the drug crosses the placenta and is excreted in human milk, the existence of pre-clinical and clinical studies as well clinical experience of the use of the medicine in pregnant and lactating women, the influence of the medicine on human fertility, the use of the medicine in women with child-bearing potential and specific recommendations for the use of the medicine during pregnancy and breastfeeding.

To overcome a potential lack of homogeneity in terminology across SmPCs and to facilitate consensus between the researchers during data gathering, a brochure containing instructions for data extraction was created, standardizing some terms and definitions. The

term 'human studies' and the word 'trial' were considered synonymous with clinical studies. Terms such as 'epidemiological use', 'epidemiological evidence' or 'experience' were regarded as being indicative of clinical experience. If expressions such as 'clinical data' or 'clinical data on exposure' were used in reference to the use of the medicine in humans but without specifying whether it resulted from clinical studies or clinical experience, the origin of this information was considered unclear. Additionally, SmPCs were classified as containing 'conclusive' information if they clearly stated that the medicine could be used without any restrictions or if they used expressions such as 'contraindicated', 'must not', 'should not' or 'not recommended' to restrict the use of the medicinal product. In contrast, statements such as 'use with caution', 'it is preferable to', 'should be used . . . only if [plus ambiguous situation]', or 'should not be used, unless clearly necessary/ the benefits outweigh the risks' were considered to be 'ambiguous' information.

Data extraction was performed independently by two authors (T.M.S and B.A.). When discrepancies existed, a discussion was held until consensus was reached and disagreements were adjudicated by a third reviewer (F.F-L.). The inter-rater agreement was estimated by calculating the prevalence-adjusted bias-adjusted kappa (PABAK) coefficient using the software WinPepi version 11.25 (http://www.brixtonhealth.com). The PABAK was used over kappa to avoid potential effects of component low prevalence [22]. As standards for the strength of agreement for the PABAK coefficient it was assumed that ≤ 0 = poor, 0.01–0.20 = slight, 0.21–0.40 = fair, 0.41–0.60 = moderate, 0.61–0.80 = substantial and 0.81–1 = almost perfect [23]. Other statistical analyses were performed using the software package SPSS version 16. Normality was assessed using the Kolmogorov–Smirnov test. Non-parametric tests were used to explore the association between the time since marketing authorization of the SmPCs and categorical variables of two levels (Mann–Whitney test). The tests were two tailed and statistical significance was defined as $P < 0.05$.

Results

The mean elapsed time since marketing authorization of the 582 SmPCs analyzed was 2084 days [standard deviation (SD) = 1595], approximately 5.7 years, and the mean time since last update of the SmPC was 220 days (SD = 225). The Kolmogorov–Smirnov test revealed that both the time since the first authorization and the time since the last update were not normally distributed ($P < 0.001$).

Application of the exclusion criteria resulted in removal of 12 (2.1%) SmPCs based on the first criterion (medicines for post-menopausal women), 14 (2.4%) based on the second criterion (medicines for paediatric use), 11 (1.9%) based on the third criterion (medicines for the male population), two (0.3%) based on the fourth criterion (medicines for contraceptive purposes) and nine (1.5%) based on the fifth criterion (medicines for assisted reproduction techniques). Ultimately, 534 (91.8%) SmPCs were included in the analyses. The inter-rater agreement for data extraction yielded a PABAK mean of 0.86 (SD = 0.11) (range 0.60–0.99), denoting an 'almost perfect' agreement between the two researchers.

Pregnancy information

Of the 534 SmPCs analyzed, 89.3% (477/534) did not state whether the drug crossed (or not) the placental barrier, 8.6% (46/534) indicated that the drug was able to cross the placenta, 1.3% (7/534) reported that the drug did not cross the placental barrier and 0.7% SmPCs (4/534) declared that it was unknown whether the drug crossed the placenta. No significant differences existed in the time since marketing authorization between 53 (46 + 7) SmPCs that provided information on whether (or not) a drug crosses the placental barrier and the four SmPCs that stated that this information was unknown (Mann–Whitney $P = 0.574$).

A total of 76.4% SmPCs (408/534) reported the existence of pre-clinical studies that assessed the teratogenic effect of the medicine in animals and 9% SmPCs (48/534) reported that no animal studies had been conducted. Of the 408 SmPCs reporting the existence of pre-clinical studies, 99.5% (406/408) described the results of the studies. Information regarding the conduct of pre-clinical studies was absent in 14.6% (78/534) of the SmPCs analyzed. Regarding the information on the conduct of clinical studies, 67.2% (359/534) of SmPCs mentioned that no clinical studies had been carried out in pregnant women, 1.5% (8/534) declared the existence of clinical studies in this population and 2.6% (14/534) provided unclear information. Information regarding the conduct of clinical studies was not provided in 28.7% (153/534) of the SmPCs analyzed.

Information about the existence of clinical experience with the use of the medicine in pregnant women was given in 16.7% (89/534) of SmPCs, 67.6% (361/534) stated that there was no clinical experience and 2.6% (14/534) provided unclear information. In 13.1% (70/534) of SmPCs no information referring the clinical experience with the medicine in pregnant women was available. Of the 89 SmPCs mentioning the existence of clinical experience in pregnant women, 62.9% (56/89) SmPCs did not declare the number of pregnant women that this clinical experience applied to. Of the 106 SmPCs referring to the existence of both clinical studies and clinical experience in pregnant women, 14.2% (15/106) did not provide information regarding potential adverse effects for the embryo, foetus or neonate that might result from the use of the medicine. No statistical differences were found in the time since marketing authorization of SmPCs providing information on the existence of clinical experience in

pregnancy and SmPCs not mentioning the existence of clinical experience in this patient group (Mann–Whitney $P = 0.185$).

Recommendations for the use of medicines in pregnancy restricted the usage of medicines in these patients in 94.6% of SmPCs (505/534), 3.7% SmPCs (20/534) allowed the use in pregnant women and 1.7% (9/534) did not provide a recommendation for use during pregnancy. Of the 505 SmPCs that restricted the use of the medicine during pregnancy, 89.7% (453/505) did not provide information on whether the drug crossed the placental barrier, 13.1% (66/505) did not provide any information about the existence of pre-clinical studies, 26.9% (136/505) did not provide any information about the conduct of clinical studies in pregnant women and 12.3% (62/505) did not provide any information regarding the existence of clinical experience in using the medicine in antenatal care. Recommendations provided in the 525 SmPCs were ambiguous with respect to the use of the medicine during pregnancy in 57.0% (299/525) of the SmPCs. Of the 299 SmPCs providing ambiguous recommendations, 91.6% (274/299) lacked information about the drug crossing the placental barrier, 9.4% (28/299) and 21.4% (64/299) did not provide any information about the conduct of studies in animals or pregnant women, respectively, and 10.7% (32/299) lacked information regarding the existence of clinical experience in this population. Assuming the inadvertent use of a medicine in pregnant women, 87.3% (448/534) SmPCs did not provide any information on how to manage the exposure of the pregnant woman to the medicine. Some anecdotal statements contained in SmPCs are presented in Table 1.

Information about the use of the medicine in women of child-bearing potential was not provided for 70.6% (377/534) of the SmPCs analyzed. In 29.4% (157/534) of SmPCs a recommendation for women of child-bearing potential to use contraceptive measures while taking the medicinal product was stated. Of these, 79% (124/157) SmPCs specifically indicated how long contraceptive measures should be continued for.

Information about the effect of the medicine on human fertility was absent in 79% (422/534) of SmPCs, 2.2% (12/534) declared that the medicine affected fertility, 1.1% (6/534) stated that the medicine did not affect fertility and 17.6% (94/534) of SmPCs indicated that the effect of the medicine on human fertility was unknown. No significant difference was found in the time since the first marketing authorization between the 18 (12 + 6) SmPCs that provided information on the influence of the medicine on human fertility and the 94 SmPCs which stated that this information was unknown (Mann–Whitney $P = 0.412$).

Breastfeeding information

In total, 16.5% (88/534) of the 534 SmPCs analyzed reported that the drug was excreted in human milk, 0.6% (3/534) indicated that the drug was not excreted in human milk, 61.4% (328/534) stated that this information was not known and 21.5% SmPCs (115/534) did not provide any information relating to the excretion of the drug in human milk. No difference was found in the time since the first marketing authorization between the 91 (88 + 3) SmPCs providing information on milk excretion of a particular drug and the 328 SmPCs for which that information was unknown (Mann–Whitney $P = 0.613$).

Of the 88 SmPCs that indicated that the particular drug was excreted in human milk, 88.6% (78/88) did not inform of possible adverse drug reactions that could occur from neonates ingesting the milk, 9.1% (8/88) provided information about potential reactions in lactating neonates and 2.3% (2/88) indicated that no information was available.

Recommendations for the use of medicines while breastfeeding restricted their use in 92.1% SmPCs (492/534), even though 16.9% (83/492) of these did not provide any information on whether the drug was excreted in human milk. In contrast 6.7% (36/534) of SmPCs stated

Table 1

Illustration of some anecdotal statements contained in SmPCs regarding the use of a medicine during pregnancy or breastfeeding

Issue	Quoting
Illogical recommendations	• *Can be used during pregnancy if the dosage recommendation in section 4.2 is respected.* (SmPC number 141) • *Can be used during pregnancy if clinically needed.* (SmPC number 149) • *The use of* [brand] *may be considered during pregnancy if this is thought to be necessary, taking into account official recommendations.* (SmPC numbers 204, 391) • *The use of* [brand] *during pregnancy has to take into account official recommendations.* (SmPC number 180)
Recommend monitoring without specifying the parameters to be monitored	• *If* [brand] *is prescribed, careful monitoring is recommended.* (SmPC number 574) • *If a pregnant woman is treated with* [brand]*, close monitoring by a multidisciplinary team is desirable.* (SmPC number 201)
Unclear origin of clinical data	• *For* [brand] *no clinical data on exposed pregnancies are available.* (SmPC number 226) • *Data on a limited number of exposed pregnancies indicate abnormalities on the adrenals of the foetus after exposure to* [brand]. (SmPC number 282)
Overcautious breastfeeding information	• *No effects on the breastfed newborn/infant are anticipated since the systemic exposure of the breastfeeding woman to* [brand] *is negligible. As a precautionary measure, the use of* [brand] *during lactation should be avoided.* (SmPC number 242)

that the medicine could be safely used by breastfeeding women whereas 1.1% (6/534) did not provide a recommendation for use during lactation. A total of 16.5% (87/525) of SmPCs provided an ambiguous recommendation for the use of the medicine during breastfeeding of which 26.4% (23/87) lacked information about the drug being excreted in human milk.

Discussion

Our analysis revealed that important information on the use of medicines during pregnancy and breastfeeding is missing in European SmPCs. Of the 534 SmPCs analyzed, around 90% did not mention whether the drug crossed the placental barrier, almost 70% stated that there was no clinical experience of the use of the medicine during pregnancy and more than 60% indicated that excretion of the drug in human milk was unknown. Recommendations for the use of the medicine during pregnancy and breastfeeding were ambiguous in almost 60% and 20% of SmPCs, respectively.

SmPCs collected from the EMA website were on average 5.7 years old since their marketing authorization was issued, but the time since last update was on average less than 1 year (220 days). This implies that the SmPCs included in our study have been updated, on average, more than nine times, which reflects a willingness of the Agency to keep SmPCs updated as recommended in the literature [24]. All of this effort in updating SmPCs is expected to result in a continuous increase of the quality of information over time. However, this was not demonstrated in our study, particularly for information regarding the drug crossing the placenta, the existence of clinical experience in pregnancy, the influence of the medicine on human fertility, and excretion of the drug in human milk.

The information content of SmPCs has been subject to considerable research over the past years [16, 19, 25, 26]. Completeness of information is an essential prerequisite of any medicines information source and this has been pointed out as an issue in SmPCs [16]. In our study, completeness was also a major concern, with around 90% of SmPCs not mentioning whether the drug crossed the placental barrier, 70% lacking information about the use of the medicine in women of child-bearing potential and almost 80% SmPCs not providing information concerning the effect of the medicine on human fertility.

Despite the EMA highlighting the importance of performing non-clinical studies, especially during drug development and the early post-marketing period [14], in our analysis 9% of SmPCs still declared that no animal studies had been conducted and almost 15% did not contain any information on the conduct of these studies. Although non-clinical studies can be useful to predict human risk, application of the information to humans needs to be done with caution [27]. Regarding information on the conduct of clinical studies, only 1.5% SmPCs mentioned the existence of clinical studies to test the medicine during pregnancy. Pregnant women have traditionally been excluded from biomedical research, which results in a lack of knowledge about the risks and potential benefits of medicinal products in this population [28]. However, a call to include pregnant women in clinical studies was made by the Institute of Medicine in 1994 [29] and recent publications advocate a change in the presumption of exclusion of pregnant women from clinical studies to one of inclusion [30]. This has resulted in more than 250 clinical trials in pregnancy being registered between 2009 and 2011 [31].

Considering that the effects of medicines during pregnancy are largely unknown prior to post-marketing experience [32], clinical experience is paramount to provide this information to clinicians. In 2005, the EMA proposed an active post-marketing surveillance for collecting data on the use of medicines during pregnancy for newly marketed medicines and also for established products [27]. However, our study showed that fewer than 17% SmPCs provided any information regarding the existence of clinical experience in pregnant women. The inclusion of this information is critical to guide health care professionals when deciding to initiate or stop a given therapy. Five years, which is the average age of SmPCs in our study, should be considered a reasonable amount of time to gain experience through post-marketing surveillance. Several methods have been employed to collect data on medicines safety during pregnancy, including spontaneous reporting, congenital malformation registries, follow-up data from teratology information services, pregnancy registries and computerized population data [33]. These should be taken into account when designing strategies to improve data collection from clinical experience. In addition, medicines manufacturers should be responsible for collecting medicines safety data in pregnant women and designing effective methods for data collection as part of their pharmacovigilance planning [33].

Applicability of information is another critical feature of any medicines information source to enable decision making. Our study revealed that SmPCs use ambiguous recommendations for the use of medicines during pregnancy and breastfeeding in almost 60% and 20% of cases, respectively. Ambiguous recommendations leave the decision to use a medicine up to the clinician. Given that for most medicines the information available is inadequate to determine whether the benefits exceed the teratogenic risks [2], a decision on whether to use a medicine is often difficult, particularly for clinicians who may not be experts in teratology. The Food and Drug Administration (FDA) category system of risk of medicines for pregnancy is, in theory, helpful in assisting clinician's decision making as it places medicines under a specific category (A, B, C, D and X) that is objectively described [34].

However, clinicians expressed their concern to the FDA over the confusing and overly simplistic way the information was presented, stating that it provided an evidence base which was deemed insufficient to make informed decisions [35], consequently leading physicians to resort to other means to assess pregnancy risk [36]. Therefore, the FDA recently proposed a new system using narrative statements instead of categories, including a risk summary, clinical considerations to support patient care decisions, counselling and a data section with more detailed information [37]. Advantages and drawbacks of this new system have been explored elsewhere [38], but more time will be needed to assess fully the benefits of this new system.

Our study also demonstrated that the use of medicines was restricted in over 90% of SmPCs for both pregnant and breastfeeding mothers. For many SmPCs, the use of the medicine is restricted not because the potential adverse effects to the foetus are known, but because data are not available. In fact, some authors have argued that, although only a few medicines are known to cause birth defects in humans, it is the uncertainty about the safety of the majority that may lead to under-prescribing for pregnant women [1]. Others agree that information to determine the risks of treatment with a particular medication during pregnancy is unavailable for more than 90% of the medicines [39, 40]. Previous studies have also argued that recommendations for a restrictive use might be derived from legal safety concerns of the pharmaceutical industry [4]. Before approving SmPCs during the authorization procedure, regulatory agencies should bear in mind that, apart from their legal implications, SmPCs are primarily a medicines information source. Such a defensive position from companies limits guidance to prescribing physicians. However, the decision of a prescriber to withhold a medicine indicated for a chronic condition may pose a greater risk to the foetus than prescribing it [41, 42]. As an example, in women with epilepsy physicians may consider withdrawing an antiepileptic medicine 6 months before conception, or maintaining drug therapy to avoid risks of potential maternal and foetal injury with convulsive seizures by monitoring antiepileptic drug concentrations [42].

In addition to completeness and applicability issues, this study also found a considerable lack of homogeneity and standardization of terminology throughout SmPCs, which has also been previously recognized [21]. Although a brochure with clear instructions for data extraction was created for the study, some expressions and the use of the same words to mean different things across SmPCs led to difficulties in interpretation during the analysis. An example is the use of the word 'limited', which in some SmPCs was meant to refer to the total absence of data, but in others was used to quantify a small amount of clinical experience. It was also surprising to find recommendations in SmPCs that advise professionals to consult official recommendations when using a medicine during pregnancy, when SmPCs themselves are considered official medicines information sources.

Regulatory agencies play a pivotal role in solving the problem of poor information regarding the use of medicines in pregnancy and lactation in two distinct ways. First of all, whilst it should be recognized that SmPCs are produced by the pharmaceutical companies, they are ultimately approved by regulatory agencies, becoming an 'official' medicines information source. In case the regulatory agency considers that the information provided is sub-optimal or insufficient, more information should be requested from the pharmaceutical companies during the authorization procedure. Secondly, regulatory agencies establish the pre-clinical and clinical studies that are required to submit a medicine for approval. Agencies should consider making the conduct of studies in pregnant and lactating women a requirement for the submission of applications for authorization.

Our study has some limitations. The analysis was performed with SmPCs of medicinal products authorized through a centralized procedure. As these represent only part of all the products authorized in the European Union, our results cannot be generalized to SmPCs of medicinal products authorized through National regulatory agencies. However, National agencies are compelled to use the guidelines approved and published by the EMA and the European Commission and therefore other SmPCs, not included in this study, are expected to present similar issues.

In conclusion, important information on the use of medicines during pregnancy and breastfeeding is missing in European SmPCs, and the time elapsed since a SmPC's marketing authorization was issued was not associated with an increased information quality. Post-authorization data on the exposure to medicinal products during pregnancy should be actively collected and included in official information sources to keep them updated and to provide a useful evidence base to inform decision making when caring for these patients.

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare no support from any organization for the submitted work, no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years and no other relationships or activities that could appear to have influenced the submitted work.

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Authors' contributions

BA, TMS and FFL: Conception and design of the study, data gathering and interpretation of information contained in SmPCs, manuscript preparation, critical review of the manuscript, and approval of the final version.

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