Pregnancy and lactation advice: How does Australian Product Information compare with established information resources?

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Abstract

Background: Product information is a popular medicines information resource; however, there is some evidence that its pregnancy and lactation information is overconservative, which can lead to inadequate treatment of pregnant and lactating women.

Methods: A thorough analysis of pregnancy and lactation information within Australian Product Information and Consumer Medicines Information was performed. The statements within these resources were compared with established clinical resources: Australian Medicines Handbook, Therapeutic Guidelines, South Australian Perinatal Practice Guidelines, Organization of Teratology Information Specialists, LactMed, Motherisk and the Pregnancy and Breastfeeding Medicines Guide published by the Royal Women's Hospital Melbourne.

Results: Product Information was found to be the most cautious resource, with 44.5% of pregnancy recommendations and 69% of lactation recommendations reviewed being more conservative than other resources.

Conclusion: Product Information is an imperfect and often overconservative reference for pregnant and lactating women. Health professionals are urged to review established clinical resources to inform decision making.

Keywords

Drugs (medication), maternal–fetal medicine, clinical pharmacology

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Introduction

Long-standing public opinion is that pregnant and lactating women should avoid all medication, with the perception that exposure to any foreign substance during pregnancy causes harm to the fetus¹ and the misconception ‘*when in doubt, don't breastfeed*’.² This admonition results in underestimation by the public, and regrettably some health professionals, of the maternal benefits of pharmacological treatment and indirect benefits to the child.³

As women may require chronic or acute medication, it is crucial they have access to evidence-based information, with opinions of physicians and pharmacists highly sought.^{4–7} Increasing maternal age⁸ may contribute to greater use of medication during childbearing years.

Although a variety of information is available to health professionals, pharmaceutical company information (Product Information or Prescribing Information (PI)) appears to be most frequently used internationally, with authors from Australia,⁹ the United States,^{7,10} Canada^{11,12} and the Netherlands^{12,13} reporting this preference. Australian PI is assessed by the Therapeutic Goods Administration (TGA) and is available through information providers including Monthly Index of Medical Specialities and AusDI.¹⁴ In the US, PI is compiled within the Physician's Desk Reference; in Canada within the Compendium of Pharmaceuticals and Specialties; in the Netherlands, the Farmacotherapeutisch Kompas and the Felleskatalog in Norway. Pharmaceutical companies also produce patient information, Consumer Medicines Information (CMI). CMI is based on PI and has been described as ‘*the most important*’ information to ‘*help bridge the information gap*’ between physicians and the public, increasing consumers' knowledge.¹⁵

Despite considerable use of PI, evidence suggests that its currency and accuracy is unreliable for pregnant and lactating women. A small US study revealed that PI classified the lowest number of medications as ‘safe’ for lactation, even if use was widely accepted.² A Norwegian study found that almost 50% of advice on medications in pregnancy differed between PI and drug information centres, with PI significantly more restrictive.¹⁶ As PI is country-specific, it would be valuable to conduct an analysis of Australian PIs to confirm whether the

Australian situation is reflective of that internationally. The only currently reported Australian study reviewed four thyroid medications and concluded that PI did not reflect clinical practice, and that alternate, more up-to-date guidelines should be used.^{17,18}

Evaluating Australian PI recommendations against credible clinical resources for a range of medications used by pregnant and lactating women would provide valuable assessment.

Method

Pregnancy and lactation statements within Australian PI and CMI for selected medications were compared with other established clinical resources, both Australian and international, including: Australian Medicines Handbook (AMH), Therapeutic Guidelines (TG), South Australian Perinatal Practice Guidelines, Organization of Teratology Information Specialists, LactMed, Motherisk and the Pregnancy and Breastfeeding Medicines Guide published by the Royal Women's Hospital (RWH), Melbourne. Statements were classified into one of four categories: reassuring, cautionary, suggesting avoidance and giving no specific recommendation (see Table 1).

Medicines from 10 therapeutic groups were selected for review including those for the treatment of common acute illnesses experienced in pregnancy and lactation and for relatively common chronic diseases (see Table 2).

Recommendations were compared for each medication to determine agreement of resources. Outcomes were placed into one of four

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Table 1. Classification of statements from information resources.

Statement category	Examples included within the category
Reassuring	May be used Unlikely to be harmful Compatible
Cautionary	Only use if clearly needed Should not be used unless benefit justifies the risk Caution should be exercised
Suggesting avoidance	Do not take Not recommended Make an alternate feeding arrangement for your baby
No specific recommendation	Safety has not been established Limited experience No human data

Table 2. Examples of medicines included.

Therapeutic group	Examples
Anti-infectives	Cephalexin Aciclovir
Ear eye nose throat	Chloramphenicol eye drops Phenylephrine nasal spray
Respiratory	Salbutamol Fluticasone
Gastrointestinal	Ranitidine Omeprazole
Antidepressants	Sertraline Duloxetine
Analgesics	Codeine Diclofenac
Endocrine	Metformin Thyroxine
Dermatology	Topical hydrocortisone Topical miconazole
Antihypertensives	Nifedipine Methyldopa
Antihistamines	Loratidine Doxylamine

groups outlined in Table 3. Where there was disagreement, the resource/s with the most conservative recommendation was recorded (This was the recommendation most likely to discourage therapy).

Results

A total of 245 pharmaceutical products were included. A summary is depicted in Table 4.

Discordant advice for medication use in both pregnancy and lactation was apparent, with disagreement occurring for 75.9% (186/245) and 87.3% (214/245) of medications, respectively. The most conservative resources are illustrated in Figure 1. As not every resource had recommendations for every medication, a percentage figure was calculated to indicate conservatism ([conservative statements]/[total number of statements]). Both PI and CMI contained the highest percentage of

Table 3. Inclusion criteria for information resource comparisons.

1. PI agrees with all other resources.
2. PI and/or CMI have different recommendations from other information resources but those resources are in agreement
Subgroups:
 - *PI is most conservative* compared with CMI and the other resources.
 - *CMI is most conservative* compared with PI and the other resources.
 - *PI is least conservative* compared with CMI and the other resources.
 - *PI and CMI have the same recommendation* which is more conservative than the other resources.
3. One or more of the non-PI/CMI resources has a recommendation different from the others
 - The resource/s which contained the most conservative statement/s were recorded for each medication.
For example, with vancomycin, the AMH reassured use in pregnancy when all other available resources (RWH, PI and CMI) are cautionary; therefore, RWH, PI and CMI were noted most conservative.
 - For example, with cetirizine in lactation, PI and RWH statements suggest avoidance, TG is cautionary and the AMH and LactMed reassured use; therefore, PI and RWH were noted most conservative.
4. Unclassifiable
 - Information unable to be categorised within the above three categories.
For example, for pyrantel in lactation, PI is non-specific, there is no CMI, but all other resources were reassuring.

CMI: Consumer Medicines Information; PI: Product Information or Prescribing Information; AMH: Australian Medicines Handbook; RWH: Royal Women's Hospital; TG: Therapeutic Guidelines.

Table 4. Summary of recommendation comparisons for all products (n = 245).

	Pregnancy n (%)	Lactation n (%)
PI agrees with all other resources	59 (24.1)	31 (12.7)
PI and/or CMI have different recommendations from other information resources but those resources are in agreement	97 (39.6)	115 (46.9)
PI is most conservative	26	51
CMI is most conservative	22	16
PI is least conservative	5	1
PI and CMI have the same, more conservative recommendation	44	47
One or more of the non-PI/CMI resources has a recommendation different from the others	79 (32.2)	97 (39.6)
Unclassifiable	10 (4.1)	2 (0.8)

CMI: Consumer Medicines Information; PI: Product Information or Prescribing Information.

conservative statements, 44.5% and 50.9% for pregnancy and 69.0% and 57.9% for lactation, respectively.

The PI and CMI's conservative nature is exemplified by their recommendations for ibuprofen in lactation. Both contraindicated ibuprofen, with the CMI stating: 'Do not take Brufen® [ibuprofen] if you are breastfeeding or intend to breastfeed. Brufen® passes into the milk and may affect your baby'. Contrary to this advice, all other resources advocated use, with RWH, LactMed and TG stating ibuprofen as the

Figure 1. Percentage of information resource advice which was most conservative.

CMI: Consumer Medicines Information; PI: Product Information or Prescribing Information; AMH: Australian Medicines Handbook; RWH: Royal Women's Hospital; TG: Therapeutic Guidelines; OTIS: Organization of Teratology Information Specialists; SAPPG: South Australian Perinatal Practice Guidelines.

preferred choice for lactating women. Similarly, ranitidine's use in pregnancy was reassured by all non-PI/CMI sources, with both Motherisk and the RWH stating that it is the medication of choice. However, its use was cautioned by both PI and CMI, with PI stating

Zantac® [ranitidine] should only be used during pregnancy if considered essential. If the administration of Zantac® is considered to be necessary, its use requires that the potential benefits be weighed against possible hazards to the patient and to the fetus.

PI and CMI discrepancies

Recommendations within PI and its respective CMI were not consistent for all medications. Due to inclusion of Schedule 2 products (Note: *Also known as Pharmacy Medicines. The safe use of these products may require advice from a pharmacist and should be available from a pharmacy or from a licensed person if pharmacy services are unavailable.*), 31 agents did not have CMI as it is not required by the TGA, resulting in only 214 medications (of 245) with CMI. Of these, inconsistencies between PI and its CMI were apparent for 39.3% (84) and 45.3% (97) of medications in pregnancy and lactation, respectively. For example, PI for metronidazole cream warned 'A decision should be made to discontinue breastfeeding or to discontinue the drug', while the CMI contained no warning for use in lactation.

Category A discrepancies

Of the 57 Category A products reviewed, 36 (63.2%) had statements in the PI that contradicted the Category A definition (*Drugs which have been taken by a large number of pregnant women and women of child-bearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the fetus having been observed*). Some statements cautioned or discouraged use of category A products, while non-PI/CMI sources advocated use of doxylamine and

salbutamol in pregnancy, their PIs stated: 'Do not use during pregnancy' (doxylamine) and 'Salbutamol is known to cross the placental barrier in humans. Safety for use in pregnancy has not been demonstrated, therefore the drug should not be used... unless the expected benefit outweighs any potential risk'. Other PI statements advised that a Category A medicine lacked safety data; for example, PI for metoclopramide warned that 'adequate human data on use during pregnancy are not available' and PI for dextromethorphan, implied potential birth defects, stating 'Because animal studies are not always predictive of human response, Bisolvon Dry® (dextromethorphan) should not be used in the first three months of pregnancy'.

Discussion

Limited research has explored the dissonance between PI and established clinical pregnancy and lactation information resources, with the majority of studies conducted outside Australia.

Comparison of PI with established clinical resources, both Australian and international, determined the frequent occurrence of discrepancies for both pregnancy and lactation 76% and 87% of medications, respectively. This was largely attributed to PI and CMI containing significantly more conservative statements than other resources. Within PI, 44% of pregnancy statements and 69% of lactation statements were more conservative. For CMI, 51% of pregnancy and 58% of lactation statements were more conservative. In contrast, the next most conservative resource, the RWH, had a more conservative approach for 23% of medications in pregnancy and 16% in lactation.

These Australian findings support international research which showed the conservative nature of PI^{2,16} and confirm this as an issue of concern.

Overconservative PI was exemplified by the safety advice given for ADEC category A medications; statements for 63% of these medications contradict the definition of category A. These statements lead to public confusion and uncertainty, particularly if a health professional speaks of a medication's safety but PI or CMI indicates otherwise.³

Earlier published work revealed that a majority of pharmacists and obstetric practitioners are dissatisfied with the content of PI, with these

health professionals stating it lacked pharmacokinetic insight.³ This review has highlighted that omission of key clinical information is common. For example, according to PI, ibuprofen is contraindicated during lactation. However, it is listed as a medication of choice by established clinical resources. Ibuprofen is a preferred analgesic due to its high degree of maternal plasma protein binding and therefore insignificant levels in breast milk.^{19,20}

It has earlier been reported that PI does not align with current clinical practice.^{2,17,18} By contraindicating relatively safe, essential treatment or breastfeeding, PI has potential to negatively impact on maternal, fetal and infant health. This review highlighted several recommendations made by PI which are not supported by clinical practice. One was the statement that women should not use doxylamine during pregnancy. In clinical practice, doxylamine is used first line for hyperemesis in pregnancy due to its well-known safety profile.²¹

Current literature attributes the general overconservative nature of PI to pharmaceutical company concerns of litigation arising from use in pregnancy and lactation.^{16,22} Its 'protective legalese' neglects the needs of health professionals and the public²³ with an abrogation of ethical obligations to provide high quality, relevant information to ensure optimal therapy, rather than 'empty and unhelpful risk-benefit statements'.²⁴

Discordance between PI and CMI

Surprising and concerning was the finding that information differed between PI and CMI, particularly as CMI is purportedly based on the respective PI. This was predominantly evident when one of the two documents contained a statement suggesting caution, while the other did not recommend the product. However, there were other instances where cautionary or avoidance warnings were provided by one document, while the other contained reassurance or no warning at all, as for metronidazole mentioned earlier. The discordance between PI and CMI is likely to impact negatively on patient–professional relationship; pharmaceutical company information provided to patients may differ from that of their health professional.³

This research not only found discrepant recommendations between PI and other resources but also between the non-PI/CMI resources themselves, which accords with recent research outside Australia.² Approximately 32% of medications in pregnancy and 40% in lactation had at least one established clinical resource with a different recommendation from the others. This was predominately attributable to advice differing between 'cautionary' or 'safe', or between 'cautionary' or 'avoidance'. A similar study reported that discrepancies resulted from a failure to consider the most up-to-date findings in establishing recommendations.² Further, textbooks (as compared to peer-reviewed online resources) require considerable time to reach publication, so data may not reflect current opinion, even at the time of release. Since this review has occurred RWH has switched from a book to an online resource.

Conclusion

In Australia, the current state of pregnancy and lactation advice provided by PI and CMI is inconsistent, often lacking in clinical perspective and more conservative than other established specialist references. This needs to be addressed promptly in Australia as it does internationally.

Pharmaceutical companies, due to their concerns about litigation, provide information on pregnancy and lactation which appears to be often driven by legal and not clinical imperatives. To ensure currency, both the TGA and pharmaceutical companies should engage with clinical experts before PI and CMI approval. Mandating frequency of revision would ensure that new research and clinical opinion are incorporated, because human pregnancy and lactation data become available after product release. However, any revision incurs in-house costs

and regulatory fees for the pharmaceutical company involved. Regrettably, companies may be unwilling to bear these costs, especially for a product with low profitability. The US Food and Drug Administration have set new, improved standards ('final rule') for labelling medications in pregnancy and lactation which could become the benchmark internationally.²⁵

Until reliable PI is produced there needs to be heightened health-care professional education, firstly, of the principles of pharmacological treatment of pregnant and lactating women and secondly, of the importance of using established clinical resources.

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