

BRIEF REPORT

Safe lists for medications in pregnancy: inadequate evidence base and inconsistent guidance from Web-based information, 2011

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ABSTRACT

Purpose Medication use during pregnancy is common and increasing. Women are also increasingly getting healthcare information from sources other than their physicians.

Methods This report summarizes an environmental scan that identified 25 active Internet sites that list medications reported to be safe for use in pregnancy and highlights the inadequate evidence base and inconsistent guidance provided by these sites.

Results These lists included 245 different products, of which 103 unique components had been previously evaluated in terms of fetal risk by the Teratogen Information System (TERIS), a resource that assesses risk of birth defects after exposure under usual conditions by consensus of clinical teratology experts. For 43 (42%) of the 103 components that were listed as 'safe' on one or more of the Internet sites surveyed, the TERIS experts were unable to determine the fetal risk based on published scientific literature. For 40 (93%) of these 43, either no data were available to assess human fetal risk or the available data were limited.

Conclusions Women who see a medication on one of these 'safe' lists would be led to believe that there is no increased risk of birth defects resulting from exposure. Thus, women are being reassured that fetal exposure to these medications is safe even though a sufficient evidence base to determine the relative safety or risk does not exist. Copyright © 2013 John Wiley & Sons, Ltd.

KEY WORDS—medication; pregnancy; women; drug safety; Internet; TERIS; pharmacoepidemiology

Received 7 March 2012; Revised 28 September 2012; Accepted 21 December 2012

INTRODUCTION

Recent data from the Health Information National Trends Survey revealed a fundamental shift in the ways in which the public obtains health information, with individuals tending to search online prior to consulting a healthcare provider.¹ In the 2002–2006 HealthStyles survey, 50% of reproductive-aged women reported seeking health information on the Internet.² Between 2006 and 2008 in the USA, over 90% of women reported using at least one medication during pregnancy, and 70% reported using at least one prescription medication.³

Among medications approved for use in the USA from 2000 to 2010, over 70% had no published human data on which to assess teratogenic risk (potential to cause birth defects), and 98% had insufficient published data to characterize such risk.⁴ The objectives of the current study were to (i) document Internet-accessible guidance via published/posted lists of 'safe' medications during pregnancy; (ii) compare the consistency of information contained across multiple lists; and (iii) assess the quality and quantity of scientific evidence on which these safe medication lists are based.

METHODS

To locate available Internet lists, Google searches were conducted using the following terms: 'safe

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medications and pregnancy/pregnant', 'prescription drugs and pregnancy', 'medications and pregnancy and safe', 'medications safe to take during pregnancy', 'prescription drugs safe during pregnancy', and 'prescription drugs ok to take while pregnant'. Medication names were abstracted and compared across sites. Vitamins, herbals, intravenous medications, and topical cutaneous medications were excluded from the analysis, and equivalent medications (e.g., acyclovir and valacyclovir) were combined. Components of over-the-counter (OTC) and prescription medications listed as 'safe' by any source were searched in the Teratogen Information System (TERIS),⁵ and frequencies were tabulated by risk rating. TERIS is a database housing expert assessments of the teratogenic risk of medications in human pregnancy after exposure under usual conditions. The magnitude of risk is categorized as none, unlikely, minimal, small, moderate, high, or undetermined (<http://depts.washington.edu/terisweb/teris/>). Published clinical, experimental, and epidemiologic literature is used to determine the risk rating, and a data quality and quantity score ranging from none to excellent is also assigned. Given that this study was conducted solely using Internet sources and an electronic database, the study was deemed not to constitute human subjects research.

RESULTS

The environmental scan identified 'safe medication' lists from 28 sources. Of these, 26 were still available in September 2011; upon further verification of website data in August 2012 at the journal's request, one additional site was excluded as the current information was inconsistent with that gathered in the initial search. Analyses were restricted to this subset of 25, which included three medical, one professional organization, four pregnancy information, and 17 clinical practice sources (Table 1). Only three lists displayed references, and only one of these (Netdoctor) provided references from peer-reviewed scientific literature. From the 25 lists (none of which were identical), a total of 245 medication products were identified as 'safe' for use by pregnant women. Eight of the 25 lists offered some type of safety definition, two of which defined it in the context of the medication not having been shown to cause birth defects, and two others defined safety based on the Food and Drug Administration use in pregnancy labels (categories A–X).⁶ There was a mean of 34 medication products per list. Twenty-two (9%) of the products listed as safe

by one or more sites were stated not to be safe by one or more of the other sites (Table 2). The active components from each product were identified, and duplicate components (e.g., acetaminophen from multiple acetaminophen-containing products) were removed, resulting in 164 unique components that were included in the analysis.

After applying the exclusion criteria noted in the methods, TERIS was searched for the remaining 114 components, of which 103 (90%) had existing evaluations. None had a small, moderate, or high risk rating (Figure 1). Seven components (7%) of 103 were rated as having no risk; three (3%) had a 'none to minimal' risk rating; one (1%) was rated as posing a minimal risk (pseudoephedrine); 49 (48%) were rated as unlikely to pose a risk; and 43 (42%) were of undetermined risk.

Regardless of risk rating, 42 components were given a data quality and quantity score of none to limited, 40 (95%) of which corresponded with 'undetermined' risk ratings (data not shown). At the other end of the scale, only 7% of the components had data quality and quantity scores ranging from good to excellent. Of interest, among the four medication components with TERIS risk ratings of either 'none to minimal' or 'minimal' (erythromycin, metronidazole, phenylephrine, and pseudoephedrine), all had data quality and quantity scores ranging only from fair to good.

Only 13 (52%) of the websites encouraged consultation with a healthcare provider before stopping or starting a medication during pregnancy, and less than half (40%) recommended taking medications during pregnancy only when necessary.

DISCUSSION

This report identifies inconsistencies in publicly available information on the safety of medications during pregnancy and shows that a large proportion of currently available information for products frequently used in pregnancy lacks data to support safety claims. Although it is reassuring that no medications from any identified 'safe' lists had evidence suggesting a moderate or high teratogenic risk, it was often the case that these medications had an as yet undetermined teratogenic risk; therefore, caution is advised in interpreting the majority of these medications as 'safe' for use during pregnancy. The existence of lists purporting safety might encourage use of medications during pregnancy even when they are not necessary.

WEB SAFE LISTS FOR MEDICATIONS IN PREGNANCY

Table 1. Evaluated lists grouped by website type and including number of medications listed as 'safe' for use during pregnancy—Active, August 2012

Website type	Source name	URL	Medication products* (N)
Medical site	Livestrong	http://www.livestrong.com/article/26729-list-safe-otc-medications-pregnancy/	8
	Netdoctor	http://www.netdoctor.co.uk/health_advice/facts/medicinesinpregnancy.html	15
	OBFocus	http://www.obfocus.com/high-risk/medsprint.htm	51
Professional organization	American College of Nurse–Midwives	http://www.midwife.org/documents/TakingMedicineDuringPregnancy52-5.pdf	16
Pregnancy information	BabyCenter	http://www.babycenter.com/0_chart-over-the-counter-medications-during-pregnancy_1486462.bc	54
	Dr. Lera	http://drlera.com/health_beauty/healthy_baby/Medications_for_Pregnant_Women.htm	39
	She Knows, Pregnancy & Baby	http://www.pregnancyandbaby.com/pregnancy/articles/945667/medications-during-pregnancy-list-of-safe-and-unsafe-drugs	7
	Pregnancy etc.	http://www.pregnancyetc.com/what-are-some-safe-medications-to-take-during-pregnancy.htm	37
Clinical practice	Bend OBGYN	http://www.bendobgyn.net/Safe_Medications_When_Pregnant.htm?m=45&s=39	30
	Boojum OBGYN	http://www.drkells.com/Medication.pdf	35
	Budge Clinic OBGYN	http://intermountainhealthcare.org/services/medicalgroup/clinics/physicianclinics/budgeobgyn/Documents/Medications_While_Pregnant.pdf	21
	Diamond Women's Center	http://www.diamondobgyn.com/Groups/1000050633/Diamond_Womens_Center/Early_Life_Services/Pregnancy_Info/General_Medication_Use/General_Medication_Use.aspx	34
	Fayetteville Woman's Care	http://www.fwc.net/expecting-mothers/safe-meds-during-pregnancy	40
	Kristin Miller OBGYN	http://www.kristinmillermd.com/forms/obMedications.pdf	43
	Mercy OBGYN	http://mercyobgyn.com/docs/medicationapprovedduringpregnancy.pdf	20
	Midtown OBGYN	http://www.mymidtownobgyn.com/PDFDocuments/SAFEmedicationList.pdf	68
	Oakwood Women's Center	http://www.oakwoodwomens.com/files/safe_meds_list.pdf	25
	OBGYN Centers for Family Health	http://drmsg.com/new_page_2.htm	18
	Pacific Regional Medical Army Medical Center OBGYN	http://www.tamc.amedd.army.mil/offices/obgyn/PregnancyMedications.htm	18
	Providence Health and Services	http://www.providence.org/Oregon/health_resource_centers/Pregnancy_Center/Medication.htm	23
	Seasons Healthcare for Women	http://www.seasonshealthcare4women.com/docs/SafeMedicationsInPregnancy.pdf	34
	Women's Health Specialists of Fremont	http://www.womenshealthfremont.com/webdocuments/medications-in-pregnancy.pdf	77
	OBGYN Women's Physicians Assoc.	http://www.womendoctor.com/pdf/preg_meds.pdf	65
	Obstetrical Associates, Inc.	http://oba-ma.com/Medications.html	27
	Women's Health Consultants	http://www.whcobgyn.com/Medication_List.pdf	44

*The total number of medication products is at least that listed in the table—some sites listed a group of similar products as 'safe', such as, Tylenol[®] products.

Only three of the 25 sites surveyed provided references or source material to support their claims of safety, and only half of the included websites encouraged consultation with a healthcare provider about medication use during pregnancy. This means many websites lack a critical message that should be paramount in any website that provides information to pregnant women. However, given the limited availability of human data on the teratogenic risks associated with most medications,⁴ healthcare providers frequently also do not have the information needed to provide informed guidance to their patients.

The proportion of women who take medication during pregnancy has increased by 60% since the 1970s, as has the average number of medications pregnant women take.³ These trends can be accounted for, at least

in part, by increasing maternal age⁷ and concomitant comorbidities that often require treatment. Both OTC and prescription use is high (70–80% of women report taking at least one medication) during the first trimester of pregnancy,³ a critical period for embryonic development during which the potential for teratogenic risk may be of greatest concern. The prevalence of unintended pregnancy (nearly 50%) in the USA⁸ also contributes to inadvertent medication exposures in the critical time period before pregnancy recognition.

This analysis excluded herbal/dietary supplements because these products often have an uncertain safety profile given the absence of data. Use of herbal products is relatively common, with nearly 10% of women reporting exposures at some point

Table 2. Medications listed as 'safe' for use in pregnancy by one or more websites and 'unsafe' by one or more other sites

Cold/flu/allergy	
Actifed [®]	(chlorpheniramine and phenylephrine)
Afrin [®]	(oxymetazoline)
Claritin-D [®]	(loratadine and pseudoephedrine)
Chlor-Trimeton [®]	(chlorpheniramine)
Dimetapp [®]	(brompheniramine and pseudoephedrine)
Diphenhydramine	
Loratadine	
Phenylephrine	
Pseudoephedrine	
Theraflu [®]	(acetaminophen, pheniramine, and phenylephrine)
Zyrtec-D [®]	(cetirizine and pseudoephedrine)
Pain relief	
Acetaminophen	(extra strength)
Codeine	
Constipation	
Dulcolax [®]	(bisacodyl)
Surfak [®]	(docusate calcium)
Vaginal yeast infection	
Gyne-Lotrimin [®]	(clotrimazole)
Heartburn	
Rolaids [®]	(calcium carbonate and magnesium hydroxide)
Upset stomach/nausea	
Bismuth subsalicylate	
Insomnia	
Unisom [®]	(SleepTabs: doxylamine; SleepGels/SleepMelts: diphenhydramine)
Anticholinergic	
Scopolamine	
Antidiarrheal	
Loperamide	
Antifungal	
Lamisil [®]	(terbinafine)

Trade/generic names are listed as provided by the websites, with generic components provided in parentheses for completeness.

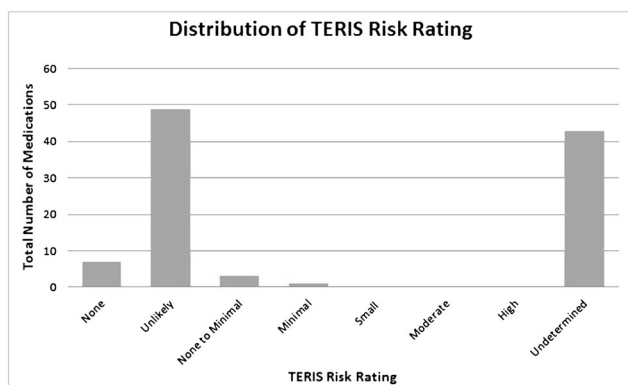


Figure 1. Frequency distribution of Teratogen Information System (TERIS) risk ratings for 103 medications listed as safe for use in pregnancy by one or more of the websites

during pregnancy.⁹ Substances marketed as natural products can be incorrectly perceived as harmless to both a pregnant woman and her developing fetus,

even though no evidence of safety (or risk) exists.¹⁰ In fact, herbal and dietary products are less studied than prescription medications prior to marketing. Under the Dietary Supplement Health and Education Act, the Food and Drug Administration can take regulatory action against a supplement only if the agency can prove that a marketed supplement is unsafe, and post-marketing safety concerns have emerged for several products.^{9,11}

Similarly, a product's availability as OTC does not necessarily mean that it is 'safe' for use during pregnancy. However, one of the factors considered prior to designation of (or switch to) OTC status is the potential for risk if taken during pregnancy (or taken by women of reproductive potential). Furthermore, these products tend to have multiple active ingredients, which complicate the characterization of risks associated with their use.

This environmental scan evaluated all Internet sources that could be identified during the period November 2010–September 2011 and that could be verified as of August 2012. The analysis used an existing independent resource to evaluate the evidence base for the medications deemed to be 'safe' for use during pregnancy. Assumptions had to be made about the exact nature of some of the medications because of the unclear terminology used in the 'safe' lists. In addition, for most medications, these websites did not specify dosage, routes, or timing of exposure in pregnancy, which can be critical factors in assessing safety.¹²

The findings in this report are subject to several limitations. First, while no two lists were identical, some lists might have borrowed from other existing lists. Thus, the sources are not likely to be completely independent. Second, because only English language sources were evaluated, this environmental scan probably underestimates the diversity of available Internet sources on this topic and may underestimate the inconsistency that exists. Third, this environmental scan did not include paper lists that may be distributed by prenatal care providers or other non-Internet sources. Finally, the investigators were unable to determine the frequency of use of the included websites. The implications of inaccurate guidance probably depend on which sites are most frequently visited.

Women or healthcare providers relying on Internet sources of information on 'safe' medications for use in pregnancy may be inappropriately reassured because many medications listed as 'safe' lack evidence that actually demonstrates safety. The wide availability of 'safe' medication lists suggests

a consumer demand for information on what medications are appropriate for use in pregnancy. This review of the products found on the Internet lists revealed a continued absence of a reliable evidence base upon which assessments for teratogenic risk should be made. Because there is currently no comprehensive monitoring program for the effects of medication use in pregnancy, one initiative that has been developed to fill this unmet need is the Centers for Disease Control and Prevention's TR_xeating for Two: Safe Medication Use in Pregnancy Initiative (<http://www.cdc.gov/pregnancymedication>). Through this initiative, the Centers for Disease Control and Prevention is committed to working with its partners, other federal agencies, and the public to build a comprehensive approach to improve the quality of data on medication use in pregnancy, translate this information into safe and effective healthcare for pregnant women, and make this information easily accessible to healthcare providers. Until such data are collected and made available, there is no reassurance that Internet 'safe lists' are indeed safe.

ACKNOWLEDGEMENT

This study was supported by the Centers for Disease Control and Prevention.

Employees of the Centers for Disease Control and Prevention supervised the design and conduct of the study, the analysis and interpretation of the data, and the preparation, review, and approval of the manuscript.

DISCLAIMER

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

CONFLICT OF INTEREST

Dr. Friedman developed the TERIS system and is senior author of all its content. Dr. Moore was a member of the TERIS Advisory Board from 1998 to 2004.

KEY POINTS

- This report highlights the inadequate evidence base and inconsistent guidance provided by Internet sites that list medications reported to be safe for use in pregnancy.
- Women or healthcare providers visiting these Internet sites are being reassured that fetal exposure to these medications is safe even though a sufficient evidence base to determine the relative safety or risk does not exist.
- Half of the included websites were missing a critical message that should be paramount—pregnant women should consult a healthcare provider about any medication that is being considered for use during pregnancy.
- The wide availability of 'safe' medication lists suggests a consumer demand for information on what medications might or might not be appropriate for use in pregnancy.

REFERENCES

1. Hesse BW, Nelson DE, Kreps GL, Croyle RT, Arora NK, Rimer BK, Viswanath K. Trust and sources of health information: the impact of the Internet and its implications for health care providers: findings from the first Health Information National Trends Survey. *Arch Intern Med* 2005; **165**(22): 2618–2624. DOI: 10.1001/archinte.165.22.2618.
2. Petersen EE, Rasmussen SA, Daniel KL, Yazdy MM, Honein MA. Prescription medication borrowing and sharing among women of reproductive age. *J Womens Health (Larchmt)* 2008; **17**(7): 1073–1080. DOI: 10.1089/jwh.2007.0769.
3. Mitchell AA, Gilboa SM, Werler MM, Kelley KE, Louik C, Hernandez-Diaz S. Medication use during pregnancy, with particular focus on prescription drugs: 1976–2008. *Am J Obstet Gynecol* 2011; **205**: 51.e1–51.e8. DOI: 10.1016/j.ajog.2011.02.029.
4. Adam MP, Polifka JE, Friedman JM. Evolving knowledge of the teratogenicity of medications in human pregnancy. *Am J Med Genet Part C Semin Med Genet* 2011; **157**: 175–182. DOI: 10.1002/ajmg.c.30313.
5. Friedman JM, Polifka JE. 2011. TERIS. Micromedex reproductive risk information system (REPRORISK). Englewood, Colorado: Thomson MICROMEDEX (accessed 2 November 2011).
6. U.S. Food and Drug Administration. Summary of Proposed Rule on Pregnancy and Lactation Labeling. <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093310.htm> (accessed 15 December 2011).
7. National Center for Health Statistics. National Vital Statistics Report. Births: Preliminary data for 2008. Hyattsville, MD: 2009.
8. Finer LB, Zolna MR. Unintended pregnancy in the United States: incidence and disparities, 2006. *Contraception* 2011; **84**(5): 478–485. DOI: 10.1016/j.contraception.2011.07.013.
9. Broussard CS, Louik C, Honein MA, Mitchell AA. Herbal use before and during pregnancy. *Am J Obstet Gynecol* 2010; **202**(5): e441–e446. DOI: 10.1016/j.ajog.2009.10.865.
10. Friedman JM. Teratology society: presentation to the FDA public meeting on safety issues associated with the use of dietary supplements during pregnancy. *Teratology* 2000; **62**(2): 134–137. DOI: 10.1002/1096-9926(200008)62:2<134::aid-tera10>3.0.co;2-d.
11. U.S. Food and Drug Administration. Dietary Supplement Labeling Guide. Updated April 2005. <http://www.fda.gov/Food/GuidanceComplianceRegulatoryInformation/GuidanceDocuments/DietarySupplements/DietarySupplementLabelingguide/default.htm> (accessed 6 March, 2012).
12. Obican S, Scialli AR. Teratogenic exposures. *Am J Med Genet C Semin Med Genet* 2011; **157**(3): 150–169. DOI: 10.1002/ajmg.c.30310.