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Investigation and Analysis of the Information Available for Pregnant Women in 1102 Antibiotic Package Inserts

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Abstract: Objective To understand the current status of information on use by pregnant women in antibiotic package inserts. Methods Information related to use by pregnant women, was obtained from the package inserts of 66 commercially available antibiotics and was investigated and analyzed. The drugs were classified as follows according to their pharmacological effects: penicillins; first-, second-, third-, and fourth-generation cephalosporins; cephamycins; aminoglycosides; macrolides; tetracyclines; lincosamides; glycopeptide antibiotics; carbapenems; third- and fourth-generation quinolones; sulfonamides; and nitroimidazoles. Results A total of 1102 package inserts of 66 common commercially available antibiotics were obtained. Among them, 72.14% (795) package inserts included labels with advice for pregnant women, backed by relevant research data, whereas 23.23% (256) included labeling on the use by pregnant women without such experimental or relevant research data. In addition, 2.00% (22) of these inserts included unclear information, whereas the information was missing in 2.63% (29). Finally, 10.60% (7) of the package inserts contained contradictory information across manufacturers. Package inserts of some antibiotics are either not standardized or lack relevant information for use of these drugs by pregnant women, making it difficult to meet the needs of users and ensure medication safety. Conclusion Standardized management of drug package inserts must thus be enhanced.

Keywords: Antibiotics, Package Inserts, Pregnant Women, Medication Labeling, Investigation and Analysis

1. Introduction

A package insert is a statutory document that directs the clinical use of drugs approved by the former China Food and Drug Administration (CFDA), guides the safe and rational use of drugs, and forms the basis of medical malpractice arbitration [1]. The unique physiological, pregnancy-induced characteristics determine medication specificity during pregnancy [2]. On one hand, changes in various body functions and metabolic conditions have an impact on the metabolism of some drugs. If a drug is not easily excreted or detoxified, drug accumulation and toxicity can occur [3]. On the other hand, many drugs have the tendency to pass through the placental barrier, and therefore act on the fetus. Improper medication can cause severe adverse effects such as fetal dysfunction, deformity, and death [4]. Pregnant women are prone to infectious diseases. Thus, failure to receive timely and effective treatment may result in severe complications in both the mother and child, such as premature birth, miscarriage, and fetal growth restriction [5]. Pathogens that infect pregnant women can directly infect the fetus through the reproductive system or invade the blood through the placenta, affecting fetal growth [6]. In addition, given the widespread antibiotic use and the high incidence of adverse reactions [7], drug package inserts should be standardized. In this study, 1102 package inserts of commonly used antibiotics were investigated, and any information on the use of these drugs in pregnant women was extracted from these inserts, investigated, and analyzed with the aim of contributing to the improvement and standardization of drug package inserts and providing references for the clinical rational and safe use of medication.

2. Materials and Methods

2.1. General Data

A total of 1102 package inserts of 66 commercially available antibiotics were collected. The contents related to use in pregnant and lactating women for each package insert were individually reviewed, classified, and recorded for statistical analyses.

2.2. Methods

Drug package inserts were individually read, with particular attention on “Regulations for the Specification of Chemical Drugs and Therapeutic Biological Products” [8] and their standards while referencing the “Drug Administration Instructions and Labeling Management Regulations.” The labeling of pregnant women's medication information To conduct statistics and analysis by category.

3. Results

In this investigation, a total of 1102 antibiotic package inserts were analyzed. The drugs were classified as follows according to their pharmacological effects: penicillins; first-, second-, third-, and fourth-generation cephalosporins; cephamycins; aminoglycosides; macrolides; tetracyclines; lincosamides; glycopeptide antibiotics; carbapenems; third- and fourth-generation quinolones; sulfonamides; and nitroimidazoles (Table 1).

Table 1. *Status of information on antibiotic use in pregnant women, from 1102 antibiotic package inserts.*

Class	Medication	Total number of product inserts	Loopholes in the medication labeling for their use in pregnant women				
			Missing descriptions	Labeling for use in pregnant women with mention of experimental and research data	Only labeling for use in pregnant women without mention of relevant experimental and research data	Only labeling with unclear or no information	Contradictions between indications and contraindications
Penicillins	Ampicillin sodium	13	0	13	0	0	N
	Penicillin sodium	11	0	11	0	0	N
	Penicillin V potassium tablets	4	0	4	0	0	N
	Mezlocillin sodium	11	0	11	0	0	N
	Azlocillin sodium	12	0	12	0	0	N
	Piperacillin sodium	5	0	5	0	0	N
	Piperacillin sodium /tazobactam	18	0	17	1	0	N
	Piperacillin sodium/sulbactam	9	0	9	0	0	N
	Amoxicillin	27	0	22	4	1	N
	Ampicillin-probenecid	5	0	4	1	0	Y
First-generation cephalosporins	Cephalothin sodium	6	0	6	0	0	N
	Cephalexin-trimethoprim	3	0	3	0	0	N
	Cephalexin	13	0	9	3	1	Y
	Cephathiamidine	8	0	8	0	0	N
	Cephradine	33	0	33	0	0	N
	Cefazolin sodium	20	19	1	0	0	N
Second-generation cephalosporins	Cefuroxime sodium	29	0	29	0	0	N
	Cefotiam HCl injection	7	0	7	0	0	N
	Cefuroxime axetil tablets	10	0	9	1	0	N
	Cefamandole sodium	7	0	7	0	0	N
	Cefaclor	30	0	25	5	0	N
Third-generation cephalosporins	Cefodizime sodium	7	0	6	1	0	N
	Cefoperazone sodium	10	6	4	0	0	N
	Cefoperazone sodium/sulbactam	9	0	7	2	0	N
	Cefmenoxime HCl	5	0	4	1	0	N
	Cefixime	23	0	8	14	1	N
	Ceftriaxone sodium	27	0	7	20	0	N
	Ceftazidime	25	0	22	2	1	N
	Cefotaxime	20	0	20	0	0	N
	Ceftizoxime sodium	19	0	19	0	0	N
	Cefdinir	8	0	3	5	0	N
	Latamoxef sodium	2	0	0	2	0	N
Fourth-generation cephalosporins	Cefpirome sulfate	10	0	10	0	0	N

Class	Medication	Total number of product inserts	Loopholes in the medication labeling for their use in pregnant women				
			Missing descriptions	Labeling for use in pregnant women with mention of experimental and research data	Only labeling for use in pregnant women without mention of relevant experimental and research data	Only labeling with unclear or no information	Contradictions between indications and contraindications
Cephamycins	Cefepime HCl	15	0	15	0	0	N
	Cefoxitin sodium	14	0	0	5	9	N
	Cefmetazole sodium	12	0	12	0	0	N
Aminoglycosides	Streptomycin sulfate	5	0	5	0	0	N
	Gentamicin sulfate	28	0	26	2	0	N
	Amikacin	12	0	12	0	0	N
	Isepamicin sulfate	3	0	3	0	0	N
Macrolides	Erythromycin lactobionate	4	0	3	1	0	N
	Clarithromycin	32	0	24	4	4	N
	Azithromycin	50	1	48	0	1	N
	Erythromycin tablets	16	2	14	0	0	Y
	Roxithromycin	29	0	21	8	0	N
Tetracyclines	Doxycycline HCl	11	0	10	0	1	N
Lincosamides	Lincomycin HCl injection	14	0	13	1	0	Y
	Clindamycin phosphate	57	0	37	20	0	N
Glycopeptide antibiotics	Vancomycin HCl	4	0	2	2	0	Y
	Norvancomycin HCl	2	0	1	1	0	N
	Teicoplanin	3	0	3	0	0	N
Carbapenems	Imipenem/cilastatin sodium salt	8	0	8	0	0	N
	Meropenem	6	0	1	5	0	N
	Aztreonam	21	0	21	0	0	N
Third-generation quinolones	Norfloxacin	34	0	32	2	0	Y
	Ofloxacin	22	1	14	6	1	Y
	Ciprofloxacin	23	0	18	4	1	N
	Enoxacin	15	0	14	1	0	N
	Lomefloxacin HCl	22	0	10	12	0	N
	Levofloxacin	55	0	18	36	1	N
Fourth-generation quinolones	Gatifloxacin	36	0	0	36	0	N
Sulfonamides	Sulfadiazine sodium salt	2	0	2	0	0	N
	Sulfamethoxazole compound	18	0	18	0	0	N
Nitroimidazoles	Metronidazole	43	0	6	37	0	N
	Tinidazole	28	0	27	1	0	N
	Ornidazole	12	0	2	10	0	N
Total	66	1102	29	795	256	22	7
Proportion			2.63%	72.14	23.23%	2.00%	10.60%

Table 1 shows that 29 (2.63%) of the 1102 antibiotic package inserts had no information directing the use of such antibiotics in pregnant women, indicating the suboptimal regulatory standard of drug package inserts in China. Some of these medications may be toxic and/or teratogenic to the fetus, emphasizing the need for a pregnant woman on such a drug, to exercise caution. It is important to ensure the strict implementation of existing regulations, as this will help curb the absence of relevant package insert information. Seven hundred and ninety-five (72.14%) package inserts contained complete information on the directions of use in pregnant women backed with relevant research, while 256 (23.23%) package inserts only included information without relevant research data, although these drugs had undergone relevant experiments or research. This indicates that the manufacturers failed to provide this relevant data, attributable to a blind follow-up of CFDA template instructions, with little attention to updating drug safety information. In 22 package inserts (2.00%), the labeling was present, but with no or unclear data. Finally, seven drugs (10.60%) had contradictory drug contraindications and warnings; literature reports indicate that such contradictions are not limited to antibiotics [9]. Such contradictions may have serious consequences because prescription drug package inserts are intended for reference, and use by medical professionals, and major medical accidents can occur if the data is ambiguous or lacks validity.

4. Discussion

4.1. Poor Labeling for Use of Drugs in Pregnant Women

Pregnant women experience a unique physiological period,

making them vulnerable to certain disease, and most disease states need to be treated with drugs. In a previous study, 90% of pregnant women took at least one drug, and 4% took at least 10 drugs [10]. Therefore, considering the drug effects on both mother and fetus or newborn is equally important. In our study, 23.23% of 1102 package inserts only included labeling on use in pregnant women without mention of experimental or relevant research data, 2.00% (22) included no information or only unclear information, and this information was missing in 2.63% (29). Moreover, 10.60% (7) of the package inserts contained contradictory information between different manufacturers. This implies pharmaceutical manufacturers do not pay adequate attention to drug labeling.

4.2. Inconsistency in Package Insert Contents of the Same Drug by Different Manufacturers

In this study (Table 1), inconsistency in antibiotic package insert contents was observed as common practice in China. Using amoxicillin as an example, the section for drug use in pregnant and lactating women of some package inserts indicated that "reproductive experiments in rats and mice showed that, 10 times the human dose of amoxicillin has no adverse effects on fertility and the fetus. However, there are still insufficient controlled studies in humans. Given that reproductive experiments in animals are not fully predictive of reactions in humans, pregnant women should only take this product when necessary. Because a small amount of amoxicillin can be secreted in milk, use by nursing mothers can lead to allergy in the infant." Contrarily, some package inserts only stated that "experiments have not been conducted, and no reliable references exist, and the relationship is not clear." This indicates the absence of a unified standard in the CFDA package insert review, as well as ineffective implementation of relevant policies or regulations.

4.3. Contradictions in Contraindications and Warnings in Package Inserts

The package inserts for the same antibiotic drug produced by different manufacturers may contain obvious contradictions in the information on use by pregnant women. Ciprofloxacin, a third-generation quinolone antibiotic, is a broad-spectrum drug with good antibacterial activity that is used primarily for treatment of urinary tract infections, intestinal infections, and gonorrhea, among others. and is widely used commercially. Animal experiments have shown that quinolones can cause articular cartilage injury in juveniles [11]. Conversely, quinolones rarely cause articular cartilage injury in pregnant women in the clinic. However, most package inserts for commercially available ciprofloxacin indicate that "animal experiments have not confirmed that quinolones have teratogenic effects, but studies on use in pregnant women are inconclusive. Given that this drug can cause joint disease in immature animals, it is contraindicated in pregnant women, and lactating women should stop breastfeeding when using this product." A small number of products are labeled as "unsuitable for pregnant women," and none of the package inserts provide experimental data on the toxicity of these drugs to fetal cartilage. These package inserts contain vague content, indicating an existing controversial use of ciprofloxacin in pregnant women.

4.4. Comparison Between Chinese and American Package Inserts

Comparing ofloxacin package inserts from China and the USA indicated a significant difference. First, with regard to "warning words," China's "Regulations for the Specification of Chemical Drugs and Therapeutic Biological Products" [8] defines "Warning words" as warnings regarding serious adverse reactions to medications and their potential safety problems, which generally include drug contraindications, precautions, overdose, and other issues that must be indicated to the users of the medication. After investigating the ofloxacin package inserts from various Chinese manufacturers, we observed the lack of "warning words" in most of them, with only a few containing warnings about the need to drink more water in case of crystalluria. In the American package inserts, a black box and bold text were used to list the precautions for the drug, and ofloxacin was clearly indicated to increase the risks of tendonitis and tendon rupture, especially in elderly patients. The package inserts also mentioned that ofloxacin exacerbates the symptoms of myasthenia gravis, and advised patients with these symptoms to avoid taking ofloxacin. The "warning words" in the American package inserts were highly detailed, the text clearly visible, and the warnings had noticeable effects. This indicates non-standardized content in Chinese package inserts, as well as the on-going challenge of updating the content of package inserts, despite existing regulations.

5. Conclusion

Package inserts play an important role in clinical medication, as the accuracy of the information they contain directly affects the efficacy of clinical medication [12]. Their completeness and standardization also play an essential role in guiding clinical medication [13]. According to a study conducted in Australia, only 40% of the target patients of a drug could understand the information in the package insert [14], completely nullifying the original intent of a package insert. A package insert is classified as a statutory document and serves as a basis for guiding patients toward safe medication use. Patients must fully understand adverse reactions, contraindications, and precautions that come with that medication. Currently, regulations in this area are below ideal in China, and patients' comprehension of package inserts is not considered. Because clinical trials on medications used by pregnant women are limited, evidence can only be accumulated from animal experiments and clinical practice, resulting in poor labeling instructions for this population in drug package inserts [15]. Obviously, information on use by pregnant women in drug package

inserts in China has been suboptimal. From this investigation, we observed that American drug package inserts have many advantages over those in China. The United States FDA is rigorous in the management of package inserts, and many laws and regulations ensure the accuracy and validity of the contents of the manual; these aspects should be adopted in China as well. Therefore, we believe that China should establish a specialized agency that regularly monitors the dynamics of drug labeling for special populations and should notify the CFDA in a timely manner to modify the contents of relevant package inserts. With respect to the content of package inserts, a more rigorous set of guidelines should be formulated to regulate the use of text to avoid ambiguous wording. More so, patient education enhancement remains challenging in our society. Different levels of education and comprehension can easily lead to misunderstanding by pregnant women when selecting medications [16-18]. Medication during pregnancy is related to the health of both the mother and fetus, and it is unrealistic for all drugs to be contraindicated during this period. In addition, drug teratogenicity is non-hereditary, preventable, and controllable; so, creating awareness in pregnant patients is relatively important. When selecting medications, their durations should be short and their dosages should be low. In addition, prenatal health education should be enhanced to increase parent's knowledge on prenatal health and its importance and to improve their awareness on self-care. Carrying out a planned pregnancy and choosing to be pregnant in the best health state possible can help prevent pregnancy and other conditions from only being discovered after receiving teratogenic medications.

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References

[1] National Medical Products Administration, "Drug product insert and labeling management regulations," March 15, 2006.

[2] Q. M. Wang, "Investigation and analysis of medication labeling for pregnant and lactating women in 616 drug product inserts," Journal of Practical Medical Techniques, vol. 23, pp. 667, 2016.

[3] J. L. Cao, H. Li, X. R. Fan, and P. Fu, "Main factors and prevention of drug accumulation toxicity," Chinese Community Doctors, pp. 21-22, 2008.

[4] M. Wang, Y. Q. He, and Y. S. Xin, "The effect of medication during pregnancy on the fetus," Chinese Journal of Family Planning. vol. 09, pp. 572-574, 2003.

[5] H. X. Yang, "Paying attention to the diagnosis and treatment of inflammatory diseases during pregnancy," Chinese General Practice, vol. 10, pp. 472-473, 2007.

[6] N. Li, "Pregnancy with concomitant infectious disease and the impact of antibiotic use on pregnancy outcomes," Master's degree thesis. Wuhan: Huazhong University of Science and Technology, 2013.

[7] D. S. Xia, "Recommendations on risk control and analysis of the problems existing on labeling contents of medicines used for pregnant and lactating women in package inserts in China," Chinese Journal of Pharmacovigilance, vol. 12, pp. 211-218, 2015.

[8] J. H. Yang, J. Tang, Y. T. Zhang, *et al*, "Analysis of the labeling contents of drug instructions for pregnant women and lactating women in China," Chinese Journal of Drug Evaluation, vol. 33, pp. 235-238, 2016.

[9] J. W. Huang, J. F. Li, Z. D. Zhang, X. Q. Liu, and M. Yang, "Analysis of drug information on pregnant women in 247 package inserts of antiviral drugs," Pharmacy Today, vol. 26, pp. 522-524, 2016.

[10] X. Q. Chen, Y. Y. Jin, and G. Tang, Pharmacology New Edition, 17th ed. Beijing: People 's Medical Publishing House, 2011, pp. 21.

[11] H. Lan, F. Qu, S. C. Jiang, *et al*, "Immunohistochemistry study of ciprofloxacin on fetal cartilage,' Chinese Journal of Antibiotics, vol. 26, pp. 298-301, 2001.

[12] R. Bi and X. J. Hong, "Analysis of the drug package inserts of 4 different specifications of piperacillin sodium and tazobactam sodium," China Pharmaceuticals, vol. 23, pp. 10-11, 2014.

[13] J. Qiu, W. J. Zhu, and J. Xu, "Analysis and suggestion on the label information of dispensing method and storage time in 266 pieces of intravenous drug instructions of our hospital," China Pharmacy, vol. 27, pp. 1433-1435, 2016.

[14] S. J. Dong and S. D. Zhai, "A review of design and practice of patient medication information in foreign countries," Chinese Journal of Drug Application and Monitoring, vol. 10, pp. 227-231, 2013.

[15] J. R. Niu, J. Li, S. Wu, *et al*, "Analysis of drug use labeling for pregnant and lactating women in 762 drug package inserts," China Pharmacy, pp. 992-994, 2016.

[16] Pizzol TDSD, Moraes CG, Arrais PSD, *et al*, "Medicine package inserts from the users' perspective: are they read and understood?" Brazilian Journal of Epidemiology, vol. 22, e190009, 2019.

[17] Pires C, Vigário M, Cavaco A. "Factors influencing subjects' comprehension of a set of medicine package inserts," International Journal of Clinical Pharmacy, vol 4, pp. 888-898, 2016.

[18] Pons EDS, Moraes CG, Falavigna M, *et al*, "Users' preferences and perceptions of the comprehensibility and readability of medication labels," PLoS One, Vol 2, e0212173, 2019.