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# Safety aspects of Chinese herbal medicine in pregnancy—Re-evaluation of experimental data of two animal studies and the clinical experience

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Experimental studies;
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**Summary**
*Introduction:* Chinese herbal medicine is an increasingly popular worldwide medical therapy which also has an impact in pregnancy. However, the question of its drug safety during pregnancy remains unresolved. Potential problems include teratogenicity, abortion, perinatal toxicity, pre- and postnatal developmental abnormalities, and eventually an increased risk for carcinomas in the offspring. Standard Materia Medica textbooks contain unreliable information when it comes to risks during pregnancy. Wang and co-workers conducted an experimental study (WS) on mice in which they investigated the effects of 17 Chinese medicinals regarding embryotoxicity and fetotoxicity. All these drugs seemed to exhibit multiple significant toxic effects. Another study by Li and co-workers (LS) investigated the reproductive toxicity of Atractylodis macrocephalae Rhizoma in mice, rats and rabbits. They described an increased pre- and postnatal mortality and, at high doses, congenital malformations. In an attempt to identify the risks of the tested medicinals during pregnancy, we analysed these two experimental studies and compared their results with possible safety data for humans from two reviews of clinical studies on threatened miscarriage (AR and CR).
*Methods:* We re-evaluated WS and LS in relation to accordance with internationally accepted rules, equivalence to human dose, biometric accuracy, plausibility, and coherence. Eligible studies of the two reviews on threatened miscarriage were evaluated for specific pregnancy risks concerning the 17 medicinals tested in WS and LS.
*Results:* We found that WS does not conform to international ICH guidelines and includes many inconsistencies, implausibilities and several severe biometrical flaws. It reported a total of 364 significant events out of which 145 false significant results are expected. The data-handling pointed to irregularities. Analysis of LS exhibited also many inconsistencies. The results

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regarding congenital malformations were statistically insignificant and are based on small case numbers. Insofar as the safety data of the 17 medicinals were documented by eligible studies of the two reviews, there was no indication of an increased abortion rate in humans. Fetal growth retardation was not observed in the human studies. For neonatal health and postnatal development, there were sufficient safety data only for a few medicinals in the human studies. As for teratogenicity, only small case numbers (0 to 109) were available from the human data.
*Conclusion:* WS and LS are not reliable data sources for deriving pregnancy risks in humans for the tested Chinese medicinals. In addition, the results appear to contradict the outcomes observed in the treatment of humans. Regarding teratogenicity, for most Chinese medicinals, neither the safety nor the risk during pregnancy can be definitively ascertained. Further studies on the risks of Chinese medicinals during pregnancy are urgently needed.


## Contents



## Introduction

Chinese herbal medicine (CHM) is an increasingly popular medical therapy which is practiced world-wide.[1,2] Despite its ancient roots, Chinese medicine may be able to offer modern patients treatment options especially in cases in which Western medicine has not been able to provide satisfactory clinical results.[3] In order to fulfil its role as a treatment option for contemporary patients, CHM must conform to modern safety requirements. These are particularly crucial in the treatment of pregnant women because any therapy will affect the health of the developing embryo or foetus, respectively. Chinese medicine offers many treatment options for pregnancy-related indications such as threatened abortion, hyperemesis gravidarum, or intercurrent diseases. In treatment of patients for infertility, this may also impact the course of an undiagnosed pregnancy or any incipient pregnancy occurring after successful treatment.

The question of safety during pregnancy is already a difficult one for Western drugs due to insufficient data. An important concern is potential teratogenic risks. Other possible hazards include abortion, perinatal toxicity, pre- and postnatal developmental abnormalities, and an increased risk for carcinomas for the child later in his or her lifetime.

Standard Materia Medica textbooks providing excellent information about the properties, functions and actions of Chinese medicinals contain unreliable and sometimes even inconsistent information when it comes to risks during pregnancy. Examples of different safety classifications of some well-known standard textbooks[4–6] are provided in Table 1. In Chen and Chen[6] which focuses on Chinese pharmacology, terms such as embryotoxicity or fetotoxicity appear only twice (in relation to the plant substances Arecae Semen and Arecae Pericarpium).

In order to improve the unsatisfactory situation concerning the available data on pregnancy risks of CHM, Wang and co-workers conducted an experimental study (the ''Wang study'', WS) in mice in which they selected 17 Chinese medicinals commonly used during pregnancy and administered them at different periods of pregnancy.[7] Their effects regarding embryotoxicity and fetotoxicity were then investigated. The results caught the TCM community unaware. All the drugs investigated seemed to exhibit multiple significant toxic effects for several periods of drug administration, especially regarding fetal resorptions, stillbirths, fetal and postnatal deaths, postnatal growth retardation, and teratogenicity. Significant results for skeletal malformations were found for Rehmanniae Radix praeparata, Chuanxiong Rhizoma, and Citri reticulati Pericarpium. Minor malformations were found for Cuscutae Semen, Dipsaci Radix, Taxilli Herba, Glycyrrhizae Radix, Codonopsis Radix, Dioscoreae Radix, Amomi Fructus, Chuanxiong Rhizoma, Artemisiae argyi Folium and Citri reticulatae Pericarpium (Table 2). However, the results appear to show implausibilities and the effort to re-analyse the data was considered justified.