



Centrum für Therapiesicherheit in der Chinesischen Arzneitherapie

Center for Safety of Chinese Herbal Medicine

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CTCALetter – February 2024

Dear Colleagues and Friends of the CTCA,

A recently published study on the use of Traditional Chinese Medicine (TCM) during pregnancy raised concerns due to several alarming claims; however, the paper was withdrawn in November. The CTCA has undertaken a thorough review of the study, and our formal statement is presented in this newsletter.

This year, we also intend to place the issue of pharmacovigilance on a more solid and systematic footing. In collaboration with the German Medical Society for Acupuncture (DÄGfA), we are planning a workshop this autumn entitled:

How are causal relationships in adverse events assessed, and according to which criteria and methods are medicinal risks evaluated?

The workshop will be open to all members of the participating societies and suitable for even advanced and experienced members with an interest in this field. The exact date and venue will be announced shortly.

As a general principle, your reporting of adverse effects remains essential. Such reports enable shared learning and contribute to making Chinese herbal medicine even safer. The CTCA will handle your report discreetly, evaluate the possible association between the observed reaction and the prescribed Chinese medicinal product, and provide an expert assessment.

With kind regards

Yours sincerely,

CTCA

CTCA statement on the retracted publication by Peng et al. concerning the potential teratogenicity of the use of Chinese herbal medicines prior to and during Pregnancy

The June 2023 publication, “*Maternal traditional Chinese medicine exposure and risk of congenital malformations: a multicenter prospective cohort study*” by Peng et al. (1), reported a significantly increased risk of teratogenic effects on the fetus associated with exposure to Chinese herbal medicines prior to and during pregnancy.

Traditional Chinese Medicine (TCM) offers a holistic and natural approach to supporting women during pregnancy. Acupuncture, herbal medicine, and other TCM modalities can help alleviate discomfort and manage pregnancy-related complications. In China, Chinese herbal therapies represent an important treatment option for managing maternal health during pregnancy. This holistic approach is also gaining recognition in Western countries, increasingly complementing conventional medical therapies.

The aforementioned study has since been retracted due to methodological flaws in study design and data collection, which undermine the validity of the conclusions (2). Nonetheless, questions remain as to whether the study may still suggest potential teratogenic risks.

Our member Axel Wiebrecht has conducted a systematic analysis of the study, which is scheduled to be published in March 2024 in the journal *Chinesische Medizin* (the official journal of the Societas Medicinae Sinensis, SMS) (3). The analysis arrives at the following conclusions:

The study exhibits significant methodological flaws, particularly in the following aspects:

- **Study design:** The investigation was not primarily designed to address the question of potential teratogenicity of Chinese herbal medicines. Rather, it appears to be a secondary analysis of another study that focused on the predictive value of ultrasound examinations for congenital malformations. As a secondary analysis, it may generate hypotheses but cannot provide confirmatory evidence.
- **Underreporting of TCM use:** The study clearly suffers from substantial underreporting of Chinese medicine intake during pregnancy. Only 1.4% of pregnant women were reported to have taken TCM medications in early pregnancy, whereas comparative figures from China range from 10% to 55% – although exact comparability is limited. This severely restricts the study’s ability to draw meaningful conclusions regarding potential teratogenicity.
- **Inclusion of preconception exposure:** The study also includes TCM use up to six months before conception, for which an influence on teratogenicity can be ruled out. Nonetheless, the study finds that, numerically, exposure during this preconception period shows a higher association with teratogenic outcomes than exposure during early pregnancy itself, artificially inflating the calculated teratogenic risk.
- **Comparison groups:** The study does not compare a group exposed solely to Chinese herbal medicines with a true unexposed control group. Instead, it compares a group

that received TCM either alone or in combination with Western medication. The number of women receiving only TCM is not reported. Particularly due to the last two limitations, the study addresses a flawed research question, which substantially undermines the validity of its results.

- **Small case number:** The number of congenital malformations occurring in the “TCM exposure” group (defined as 6 months preconception through the end of early pregnancy, with either exclusive TCM or mixed TCM/Western therapy) is very low. Of the 10 reported cases, two concerning intake prior to pregnancy and one further case involving mixed TCM/Western medication are to be excluded. In one additional case, the composition of the TCM medication is unknown, making its classification uncertain. This reflects the massive underreporting and demonstrates that any assessment of potential teratogenic risk is based on only six or seven cases. However, the study’s calculations include all 10 cases.
- **Group comparability:** The study neglects a fundamental prerequisite for group comparisons: that groups should be comparable with respect to demographic and other confounders that may influence the outcome. At minimum, these variables should be reported. The study does not provide such information; it only notes that certain variables (e.g., maternal age) influence the overall malformation rate. Potential imbalances in these variables between groups therefore cannot be assessed.

Further details will not be discussed here. The conclusion of the analysis is that, due to serious transparency deficiencies and a flawed study design, the study does not allow for a valid assessment of potential teratogenic risk associated with Chinese herbal medicines. However, this risk cannot be eliminated by rejecting the study.

Notably, among the six teratogenic cases occurring under exclusive TCM treatment with known composition, four involved the combination product **Pudilan**. This preparation contains, among other ingredients, a relatively uncommon component, **Corydalis bungeanae Herba** (*ku di ding*), which should not be confused with **Corydalis Rhizoma** (*yan hu suo*).

Response from the TCM Community to the Peng Study

The forthcoming publication (3) also includes an analysis of a response to the Peng study from TCM-oriented institutions in the USA and Australia (4). In brief, this response remains largely superficial in its critique and does not address the study’s fundamental weaknesses. At the same time, it advances a questionable position on the safety of Chinese medicine, citing a passage from the *Huangdi Neijing*. This source provides little relevance for assessing teratogenic risk, as such risks were traditionally not known at all.

The CTCA therefore recommends raising awareness among TCM practitioners regarding potential pregnancy-related risks associated with prescribing TCM formulations. Practitioners should be educated and sensitized to these risks to prevent adverse outcomes. Traditional knowledge concerning pregnancy-related risks – which mainly addresses general toxicity and miscarriage – is insufficient. Contemporary modern scientific evidence, including potential teratogenic and genotoxic effects, must also be incorporated into risk assessment (5).

The risk-benefit ratio of any medicinal therapy during pregnancy must be carefully evaluated on a case-by-case basis. In this context, the CTCA particularly emphasizes the importance of sound, high-quality training for TCM practitioners and the exclusive use of quality-assured medicines.

References

1. Peng T, Yin LL, Xiong Y, et al. Maternal traditional Chinese medicine exposure and risk of congenital malformations: a multicenter prospective cohort study. *Acta Obstet Gynecol Scand.* 2023;102(6):735–743.
2. *Acta Obstetricia et Gynecologica Scandinavica*. Retracted: Maternal traditional Chinese medicine exposure and risk of congenital malformations: a multicenter prospective cohort study. *Acta Obstet Gynecol Scand.* 2023;102(11):1602.
3. Wiebrecht A. [Analysis of a study on the potential teratogenicity of Chinese medicines and the response from the TCM side] (German). *Chin Med* 2024;39:57-67
4. Liu WJ, Li YM, Xia A, et al. Queries on the article “Maternal traditional Chinese medicine exposure and risk of congenital malformations” and suggestions for teratogenicity research. *Reprod Breed.* 2023;3(4):177–183.
5. *Leitfaden Chinesische Medizin*, Vol. 1: Grundlagen, Section 7.6.15: Schwangerschaft. 7th ed. Elsevier; 2018:1018ff.

Relevance of the European Medicines Agency warning on pseudoephedrine for TCM

In December 2023, the European Pharmacovigilance Risk Assessment Committee (PRAC) called for additional contraindications such as severe hypertension or severe renal insufficiency for the sympathomimetic pseudoephedrine, which is included in combination cold remedies. This action was prompted by rare reports of reversible posterior encephalopathy syndrome (PRES) and reversible cerebral vasoconstriction syndrome (RCVS) associated with these medications, which can reduce cerebral blood flow and lead to potentially life-threatening complications.

Pseudoephedrine is also a constituent of *Ephedrae Herba* (*ma huang*). This raises the question: Does the PRAC warning have relevance for Chinese herbal medicine, and how do the dosages of the corresponding constituents in *Ephedrae Herba* compare with those in conventional cold medications?

Ephedrae Herba contains not only pseudoephedrine but also other ephedra alkaloids, including ephedrine, N-methylephedrine, N-norpseudoephedrine, norephedrine (phenylpropanolamine), and trace amounts of methylpseudoephedrine. These compounds can be roughly considered to have a similar risk profile to pseudoephedrine. Total alkaloid content in *Ephedrae Herba* ranges from 0.8 to 2.0% in most analyses, with rare cases up to 5.7%. According to the Chinese Pharmacopoeia, the combined content of ephedrine and pseudo-

ephedrine must be at least 0.8%. The ratio between these two alkaloids varies widely and differs further among the officinal species *Ephedra sinica*, *E. equisetina*, and *E. intermedia*.

Furthermore, it should be noted that the transfer rate of ephedrine and pseudoephedrine from the herbal pieces into the decoction averages 32.4% (1). Based on a maximal total alkaloid content of 5.7% and a maximal daily dose of 10 g of Ephedrae Herba, this corresponds to a daily intake of 185 mg of ephedra alkaloids.

By comparison, over-the-counter cold medications typically provide up to 180 mg/day of pseudoephedrine (e.g., Aspirin Complex®), while certain sustained-release products, such as Reactine Duo retard tablets®, deliver up to 240 mg/day. Therefore, the exposure from Ephedrae Herba in Chinese medicine only approaches the level of chemically defined over-the-counter medications in the case of the maximum 5.7% alkaloid content. In Germany and Switzerland, Ephedrae Herba is prescription-only.

Under typical conditions, with alkaloid contents of 0.8–2.0%, a standard decoction delivers a daily dose of 26–65 mg of total ephedra alkaloids. The same applies to granules when dosed according to the herb-to-extract ratio. In this calculation, the total ephedra alkaloid content and pseudoephedrine are equated, which, from a risk perspective, does not constitute a significant difference.

Conclusion

The very rare but potentially severe adverse effects reported for pseudoephedrine have relatively lower relevance for Chinese medicine than for over-the-counter conventional medications, but they cannot be entirely ruled out.

Within Chinese medicine, **certain precautions** should apply to Ephedrae Herba (*ma huang*) not only since the warning by the PRAC (aligned with Commission E):

Contraindications:

- Hypertension
- Vascular diseases, particularly of the coronary and cerebral vessels
- Heart failure
- Cardiac arrhythmias
- Pheochromocytoma
- Anxiety and tension states
- Mania, schizophrenic psychosis
- Substance use disorders
- Epilepsy
- Narrow-angle glaucoma
- Prostate adenoma with impaired bladder emptying
- Decompensated thyroid dysfunction
- Pregnancy and breastfeeding
- Concomitant use of monoamine oxidase (MAO) inhibitors or vasoconstrictors

Cautions:

- Children
- Deficiency syndromes, especially with sweating

- Renal insufficiency
- During high-intensity exercise or fasting
- Manifest liver disease or excessive alcohol consumption
- Diabetes mellitus (possible increase in blood glucose)
- Sleep disorders

Discontinuation: Therapy with pseudoephedrine-containing medicines should be stopped immediately if symptoms suggestive of PRES or RCVS occur, including sudden severe headache, nausea, vomiting, confusion, seizures, or visual disturbances (2).

References

1. Tong JY, Chao J, Dai YT, et al. Establishment of a quality evaluation system for standard *Ephedrae Herba* decoction (in Chinese). *Zhongguo Zhongyao Zazhi*. 2017;42(5):823–829.
2. *Arznei-Telegramm*. 2023;54:106.

Please report suspected adverse reactions associated with Chinese Herbal Therapy (CHT) directly to the CTCA at www.ctca.center.

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