

A Research on the Erupted Fetal Diseases Caused by Traditional Chinese Drugs — Discussion from the Issue that Chinese Goldthread Rhizome is Prohibited in Singapore

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Chinese Goldthread Rhizome is prohibited in Singapore since it is thought to induce neonatal jaundice. In literatures of traditional Chinese medicine, this drug was never treated as a contraindication for pregnancy, and there were no records and reports on it inducing neonatal jaundice. The results of the authors's experiments showed that Chinese Goldthread Rhizome and berberine had no induction of neonatal jaundice in pregnant rats and mice and newly born rats, and had no influence either on the activity of glucose-6-phosphate dehydrogenase of mice red blood cells. Fetal toxicity of traditional Chinese drugs including Chinese Goldthread Rhizome should be further studied in order to promote the development of traditional Chinese medicine.

Modern medicine has already proved that physical and chemical factors such as radiation and drugs can change biological heredity direction of living beings by changing gene recombination or induce intra-uterine death, malformation and function damage by interfering with normal development procedures of embryo. During embryonic development period, the effect of drugs inducing intrauterine death, malformation, fetal growth retardation, insufficiency of function, and injuries of nerve system, immunity, endocrine system and enzymatic system are regarded as fetal toxicity of drugs. Now fetal toxicity of drugs has become one of the important fields of contemporary researches of drugs. In China, researches of erupted fetal diseases caused by traditional Chinese drugs have very important theoretical and practical significance.

Knowledge of Traditional Chinese Medicine on Erupted Fetal Diseases and Records of Contraindication Chinese Drugs of Pregnancy in Materia Medica Books of Past Dynasties

Erupted fetal diseases have long been recognized by TCM and there are many records of etiological

factors, manifestations and prevention and cure methods of them in literatures. In *General Treatise on the Etiology and Symptomology of Diseases* (诸病源候论), it is recorded that "if the weather appears in the season it should not do, it will hurt all people. Although the old and the young are different in age, they are all diseased, same from poison. For pregnant women, fetuses may be hurt in severe cases". *Key to Therapeutics of Children's Diseases* (小儿药证直诀) says: "Fetus stays 10 months in the uterus and eats blood and dirty of five viscera, after born, the poison should be discharged". *A Complete Work on Paediatrics* (幼幼集成): "Erupted fetal diseases include sarcoptidosis and erysipelas, moist sore, carbuncle and tubercle, congenital deformity of swollen tongue and rigid tongue, thrush, fetal fever, fetal cold, fetal spasms and pregnant jaundice."

The above expressions indicate that the disease, called erupted fetal diseases in TCM, is the sum of poison taken in uterus. Neonatal jaundice is only a manifestation of erupted fetal diseases, causes of which are no more than biological factors (such as intrauterine infection, hereditary factors), physical

and chemical factors (including drugs), and comprehensive environment factors which have effect on fetus or mother to cause abnormal fetal development. In this text, the authors mainly investigate fetal toxicity caused by traditional Chinese drugs.

Those Chinese drugs having adverse effect on pregnant mothers and fetus are called contraindicant drugs of pregnancy. As early as in *Shen Nong's Herbal Classic* (神农本草经), there were records of abortifacient. And the supplements were added by medical scientists of later generations. In *Compendium of Materia Medica* (本草纲目) written by Li Shizhen of Ming Dynasty, 87 kinds of contraindicant drugs of pregnancy were compiled as a chapter, and it became one of the important parts of theories of TCM. In modern *China Pharmacopeia* (中国药典), more than 50 Chinese drugs are recorded, which should be prohibited or cautiously taken by pregnant women. Gao Xiaoshan of the Institute of Chinese Materia Medica collected 38 records of contraindicant Chinese drugs of pregnancy from TCM books, after repetitions removed, there were 264 Chinese herbal medicines in all, 38 of which, such as Huai Jiao (槐角 Fructus Sophorae), Yuan Hua (芫花 Flos Genkwa), Ba Dou (巴豆 Fructus Crotonis), and Ban Mao (斑蝥 Mylabris), were recorded in more than half of the literatures.¹

Arguments Aroused from Singapore's Prohibition of Chinese Goldthread Rhizome

Under the suggestions of Professor Huang who was the chairman of Drug Advisory Council of Singapore, Ministry of Public Health of Singapore announced on October 6, 1978 that Chinese Goldthread Rhizome and drugs containing berberine were prohibited in the whole country of Singapore. Up to now, more than 20 years have passed and the drugs are still prohibited, arousing extensive attention in medicine circles of the world. Those people supporting the prohibition think that no matter taken during pregnancy or taken by lactating mothers and infants directly, Chinese Goldthread Rhizome and berberine can all cause serious jaundice of infants.

Their thinking was based on Singapore Nuclear Jaundice Researches, the thesis of Professor Huang

published in 1968:²⁻³ "Of 102 glucose-6-phosphate dehydrogenase (G6PD) defected infants who had administration history of traditional Chinese drugs prior to birth, 22 had serious jaundice (medication group); of 31 G6PD defected infants which didn't have such a history, 2 had serious jaundice (control group) ($P < 0.02$). The statistical result showed that Chinese drugs had the effect to cause serious infant jaundice in the medication group."

In the articles by Professor Huang, morbidity mechanism was cited that after the Second World War those who with inborn G6PD deficiency had hemolytic diseases owing to their red blood cells easily affected by oxidizing agents, such as primaquine. Thus Chinese Goldthread Rhizome and berberine were deemed as oxidizing agents. They seemed to have found theoretical basis. However, it should be pointed out that there lacks enough facts, even Huang's article didn't say that it was Chinese Goldthread Rhizome administrated to "the 102 G6PD defected infants". In addition, many researches carried out on in China elucidated that Chinese Goldthread Rhizome is a drug having antioxidation effect but not oxidizing agent.¹²⁻¹³ Scholars from Taiwan, Liao Changli et al., reported:⁴ 22 neonates in hospital in the Chinese Goldthread Rhizome experimental group, in which there were 3 cases of G6PD deficiency, were fed with decoction of Chinese Goldthread Rhizome 20 hours after born, 2 times each day, each time equivalent to 2.5 fen crude drug, for continuous 3 days. In the control group, 23 neonates, in which there were 4 cases of G6PD deficiency, was given the same amount of plain boiled water. Each day the clinical biochemical index including hemobilirubin was determined for 7 days. The results showed that whether for normal neonates or G6PD deficiency neonates, Chinese Goldthread Rhizome would not cause acute hemolytic jaundice and other adverse reactions. What's more, the mean value of total bilirubin of blood serum of the test group was significantly lower than the control group ($P < 0.01$), which was consistent with reports in literatures.

For more than 20 years, no other countries have

responded to Forbidden Rule of Singapore, and there are many different viewpoints in academic circles.⁴⁻¹² However, Singapore government declared forbidden use of Chinese Goldthread Rhizome and berberine in the form of laws and regulations, exerting an extensive and far-reaching influence.

Tradition and Status of Chinese Goldthread Rhizome Used in Traditional Chinese Medicine

Classified as high-quality drug in *Shen Nong's Herbal Classic* (神农本草经), Chinese Goldthread Rhizome has been used as an important drug with a history of more than two thousand years. In literatures, it is used for heat-clearing and damp-drying and purging fire for removing toxin. In *Materia Medica of Decoction* (汤液本草), there were records of taking Chinese Goldthread Rhizome to treat scabies of neonates. According to *A New Book of Pediatrics* (幼幼新书), *Prescriptions for Universal Relief* (普济方), *Standards of Diagnosis and Treatment* (证治准绳) and so on, the ancients treated neonates with Chinese Goldthread Rhizome Method: "When there is retention of vicious fluid in chest and diaphragm, there produces heat, frightened epilepsy and sore. Sodden the smashed high-quality Chinese Goldthread Rhizome wrapped into the shape of nipple in hot water and drip one or two drops of yellow juice into the mouth of neonate, his anorexia will disappear and he will like to suck milk". Now in some areas of South China, there is still habit to feed "open-mouth berberine" to neonates, which is thought to be able to treat erupted fetal diseases. In literatures, Chinese Goldthread Rhizome was never a contraindication of pregnancy, no records and reports of neonatal jaundice caused by it either. There were in all 50 prescriptions in *Prescriptions for Universal Relief* (普济方) to treat pregnant dysentery, 13 of them contained Chinese Goldthread Rhizome (26.0%). There were 15 formulas of *Complete Effective Prescriptions for Women* (妇人大全良方) treating white and yellow dysentery during pregnancy, 5 of them contained Chinese Goldthread Rhizome (33.3%). Especially now, it is not good to take western medicines during gestational period, if pregnant women have diarrhea, berberine is frequently used.

Rhizoma Coptidis chinensis from Sichuan is the best type of Chinese Goldthread Rhizomes, containing biological active components which are mainly alkaloids such as berberine. Among the alkaloids contained in it, content of berberine is the highest,¹⁰ so it is called berberine. While many Chinese drugs contain berberine, not only Chinese Goldthread Rhizome.

Experimental Studies are Important Routes of Researches on Erupted Fetal Diseases Caused by Traditional Chinese Drugs

Any fetal toxicity tests of any drugs could not be carried out directly on human body, and it only can be deduced to human body by animal experiments or ex vivo tests, which have great difference from human body tests. However, there is an important rule in embryology, which is, ontogenesis is recapitulation of phylogenesis, which means that during the course from a fertilized ovum to an intact organism, the whole evolution course of the animal is sure to be replayed. For mammals, their fetal development course is very close to that of human beings. During the course of a fertilized ovum developing into an intact organism, embryo cells must migrate in a certain direction according to inherent order and time differentiation and concordantly implement great quality and quantity changes of reciprocal induction. The whole fetal development course can be deemed as a live precision instrument, which has certain sensitivity to drugs, thus constitutes the basis of experimental studies of those drugs with fetal toxicity. After the malformation accidents of Thalidomide, it was reused in animal tests, which could repeat fetal toxicity happened clinically — abnormal embryo like seal.

Responses to toxicity of drugs during different phases of fetal development were not the same. The development process from fertilized ovum to neonate can be divided into four phases, i.e. prenidation phase, organogenetic phase, foetal phase and neonate phase. The prenidation phase includes the process from fertilized ovum to gastrulation and implantation into uterus. For rats and mice, it is only in the first 6 days of pregnancy, if embryos are influenced by drugs,

there may be intrauterine death, so no nidation. During organogenesis, embryo cells form into organs after vigorous roaming and integration. In this period, if embryos are influenced by drugs, fetus malformation and intrauterine death may happen. In foetal period, organs are shaped on the whole, effect of drugs mainly causes growth retardation, insufficiency of function and late fetal death. In neonates phase, maturation of structure and function is continued, effect of drugs mainly produces growth retardation and injuries of nerve, immunity, endocrine and enzyme systems. Early intrauterine death may mask the occurrence of fetus malformation, accordingly, fetal toxicity of drugs should be studied with intrauterine death, malformation, fetal growth retardation and insufficiency of function all taken into consideration. During the long-term medical practice of Chinese medicine, the authors have accumulated hard-won clinical data and research clues, which are a precious heritage. The cognitive process of each contraindicant drug of pregnancy will open our thought and is helpful for predicting the links of drugs' action. However, we should also see that our knowledge of erupted fetal diseases caused by Chinese drugs is mainly from literature to literature, lack of in-depth scientific researches. What's more, without enough modern scientific language expression, it is hard for us to communicate with the medicine science of the world, which also prevents TCM from going to the world. Effective constituents of Chinese drug are the basis of its action. If during further separation and extraction, modern research methods for reproductive toxicology can be used to make correct appreciation on these effective constituents, our knowledge of contraindicant drugs of pregnancy will be enriched.

Chinese Goldthread Rhizome Issue is the Best Moment for Pushing Forward the Researches of Erupted Fetal Diseases Caused by Chinese Drugs

China is a big country which products, exports and consumes traditional Chinese drugs such as Chinese Goldthread Rhizome. For the health of descendants and the people of the world, we must have an attitude of carefulness and seeking truth from fact to carry out in-depth scientific researches on Chinese Goldthread

Rhizome aiming directly at questions people raised and push forward scientific evaluation of the contraindicant Chinese drugs of pregnancy to facilitate development of enterprise of traditional Chinese medicine. We should make it clear whether Chinese Goldthread Rhizome can cause neonatal jaundice. With financial assistance provided by National Nature Science Fund (NO. 39470856), using research methods of modern reproductive toxicology, the authors carried out the "experimental studies on whether Chinese Goldthread Rhizome and berberine can cause neonatal jaundice" for the first step. Main contents of the studies and findings were as follows:

1. Comparative research on acute toxicity and content of alkaloids of several domestic Chinese Goldthread Rhizomes

Through determination, it was found that content of alkaloids of *Rhizoma Coptidis chinensis* was the highest, acute toxicity was significantly higher than *Rhizoma Coptidis deltoidea* and *Rhizoma Coptidis teetoides*. What the authors used in studies was *Rhizoma Coptidis chinensis* all produced in Kai county of Sichuan Province, and berberine hydrochloride was 98% in purity.¹⁰ LD₅₀ of decoction of single *Rhizoma Coptidis Chinensis* intragastrically administrated to mice was 6.0 g/kg, when intra-venously administrated, LD₅₀ was 251.9 mg/kg; LD₅₀ of berberine hydrochloride, the main alkaloid contained in *Rhizoma Coptidis chinensis*, intra-gastrically administrated to mice was 975.0 mg/kg, when intravenously administrated, LD₅₀ was 168.8 mg/kg.

2. Research on influence of Chinese Goldthread Rhizome and berberine on enzymatic activity of G6PD of mice red blood cells

Acetylphenylhydrazine is a powerful oxidizing agent, which can induce anaemia of animals (being used as positive control drug). Test of positive control drug indicated that 30 mg/kg acetylphenylhydrazine could decrease significantly enzymatic activity of G6PD of mice red blood cells ($P < 0.001$), enlarge spleen ($P < 0.01$), increase total bilirubin of blood serum ($P < 0.05$) and lower hemoglobin compared with blank control group. For the other medication groups, there

was no statistical significant deviation of enzymatic activity of G6PD of mice red blood cells, total bilirubin of blood serum, hemoglobin and spleen weight compared with the blank control group after intragastric administration of 0.60, 0.20 and 0.067g/kg decoction of single Chinese Goldthread Rhizome and 97.5, 32.5 and 10.8 mg/kg berberine which were 1/10, 1/30 and 1/90 LD₅₀ respectively to mice. Especially, after administration of acetylphenylhydrazine which decrease significantly enzymatic activity of G6PD, there was no changes of enzymatic activity of G6PD of mice red blood cells caused by Chinese Goldthread Rhizome or berberine in groups in which 0.20 g/kg Chinese Goldthread Rhizome or 32.5 mg/kg of berberine was added compared to the group in which only acetylphenylhydrazine was used. The result indicated that there was no addition, synergism or antagonism effect between Chinese Goldthread Rhizome and berberine and the strong oxidizing agent, acetylphenylhydrazine, thus it was proved that Chinese Goldthread Rhizome and berberine had no influence on enzymatic activity of G6PD.

3. Research on fetal toxicity of Chinese Goldthread Rhizome and berberine

Decoction of single Chinese Goldthread Rhizome 0.6g/kg/d and berberine 97.5 mg/kg/d (both dosages were 1/10 of LD₅₀ for mice) were continuously intragastrically administrated to rats and mice with pregnancy 6 to 15 days, and the total dosages were both one LD₅₀. There were no increase of vaginal bleeding and intrauterine death of pregnant rats, indicating that Chinese Goldthread Rhizomes and berberine would not cause abortion. Compared with the control group, there was no malformation of live fetus and no significant deviation of body weight in the test group, and no significant increase of total bilirubin of blood serum of live fetus, liver function (GPT) and hemoglobin, indicating that during pregnancy, taking certain dosage of Chinese Goldthread Rhizome and berberine wouldn't cause neonatal jaundice and other fetal toxicity.⁷⁻⁸ Experimental results of rats and mice were the same, while there was significant fetal toxicity in the

positive control drug group (N'N-methylene-bis).

4. Research on effect of administration of Chinese Goldthread Rhizome and berberine to lactating mother rats on newly born mice

Intragastric administration of 0.6 g/kg/d and 97.5mg/kg/d decoction of single Chinese Goldthread Rhizome and berberine respectively was carried out on neonatal lactating mother rats, total dosages of both drugs were equivalent to 2/3 LD₅₀. The results showed that there were no statistical significant changes in body weight, liver function, hemoglobin and total bilirubin of blood serum of lactating mother and newly born rats in the test group compared with the control group, meaning that administration of Chinese Goldthread Rhizome and berberine to lactating mother rats wouldn't cause jaundice in newly born rats.

5. Experimental studies on effect of Chinese Goldthread Rhizome and berberine on neonatal jaundice of rats

Six percent of the decoction of single Chinese Goldthread Rhizome and 0.975 percent of berberine were smeared on the nipples of mother rats, thus oral administration of both drugs were carried out on neonatal rats, besides, a subcutaneous injection group of newly born rats with 200mg/kg Chinese Goldthread Rhizome and 32.5mg/kg berberine was set up for observation as well. The results showed that no matter Chinese Goldthread Rhizome and berberine were administrated by oral taking or subcutaneous injection, there were no significant increase of total bilirubin of blood serum or significant decrease of G6PD of red blood cells of newly born rats. The experimental results of newly born rats and mice were coincident, indicating that taking certain dosage of Chinese Goldthread Rhizome and berberine would not cause neonatal jaundice. While in positive control drug (acetylphenylhydrazine) group, there were significant changes in blood serum total bilirubin and G6PD of red blood cells of newly born rats. The results of experiment showed that Chinese Goldthread Rhizome and berberine had no influence on the activity of G6PD of mice red blood cells, and they

had no evocation effect of neonatal jaundice for pregnant mice and rats and newly born rats. Findings of the studies have been written into eight papers which have been published.⁵⁻¹² However, in recent years, in-depth studies of G6PD deficiency showed that there were many mutation types of human G6PD, which displayed great difference of enzymatic activity. Not all patients of G6PD deficiency had haemolysis after taking oxidizing agents, meaning that there were other factors causing the morbidity.¹² Except for further experimental studies, a great deal of scientific clinical researches should be carried out.

TCM has its intact and independent theoretical system. We must understand that Chinese drugs are used under theoretical direction of TCM. For example, different processing, compatibility, dispensing, preparation and routes of administration of Chinese drugs are all important measures to decrease toxicity and boost their curative effects. In the studies of evaluating fetal toxicity of Chinese drugs, attention should also be paid to characteristics of TCM. Besides, we should also know that except for drugs, there are many other causes for intrauterine death, fetus malformation, growth retardation and dysfunction, the mechanism of which are not yet clear. Therefore, cautiousness should be especially taken when evaluating the fetal toxicity of drugs.

In the seventies and the eighties of the last century, basic investigations of G6PD deficiency were carried out in a large area of our country. Now it has been ascertained that the inborn G6PD deficiency heredity disease is widely distributed in South China, especially in Guangdong, Guangxi, Yunnan, Guizhou and Sichuan provinces, where are the main production areas of Chinese Goldthread Rhizome. And China has a history of using traditional Chinese drugs for more than two thousand years. Thus we have every advantage to carry out large scope of social survey for researching on issues whether Chinese drugs such as Chinese Goldthread Rhizome and berberine can cause/worsen neonatal jaundice of inborn G6PD deficiency patients. "Perform Family Planning to Control the Population Size and Improve

the Health of People" is the fundamental state policy of China. Researches on erupted fetal diseases caused by Chinese drugs are very significant for the health of our descendants and the development of TCM.

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