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Opinion Piece

A re-analysis of studies regarding the use of *Glycyrrhiza* spp. in women during pregnancy

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ABSTRACT

The use of herbal medicines as a form of primary and adjunctive healthcare continues to grow internationally. It is therefore important that healthcare practitioners stay abreast of potential contraindications that may arise when these medicines are taken together with orthodox treatment or are prescribed during pregnancy.

This article analyses the most popularly cited clinical research concerning the use of *Glycyrrhiza* spp. during pregnancy. It also aims to serve as guidance for healthcare professionals who either prescribe herbal medicines or have cause to advise patients in relation to the use of glycyrrhiza by women during pregnancy.

The value of Medical Herbalists goes beyond mere diagnosis and subsequent prescription to encompass many other important factors such as diet, lifestyle, education and also advice to patients. On this latter issue they are often consulted to opine on whether certain herbs may be taken safely together with conventional medicines or, indeed, whether certain herbs are safe to be taken during pregnancy. Given the millions of people around the world who rely on herbal medicine as a primary source of healthcare and still further, tranches of the population who use it as an adjunct to conventional medicine, it is important that we understand and evaluate the research that is available on the use of herbs in pregnancy.

One such herb that has been the subject of recent research is *Glycyrrhiza* spp. (liquorice) which has a variety of uses both in Western Herbal Medicine (WHM) and also Traditional Oriental Medicine (TOM).

Glycyrrhiza is a robust, erect, hairless perennial native to south east Europe and central and south west Asia (Fisher, 2009).

The root is harvested in autumn and dried before being crushed into a powder or soaked in an ethanol and aqueous solution to form a tincture. The resulting medicine may then be used either externally or internally to treat a wide variety of ailments and has a broad spectrum of activity as an

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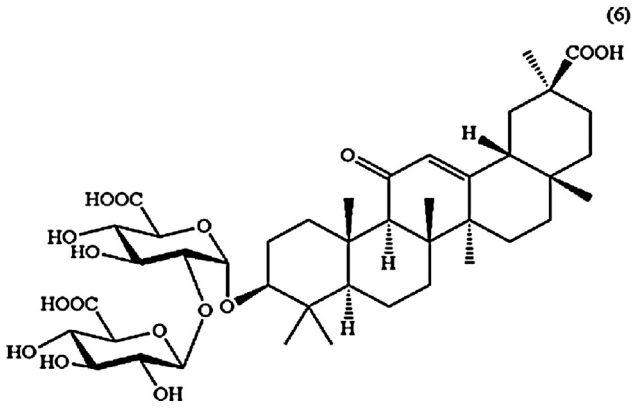

Fig. 1 – Glycyrrhizin.

expectorant, anti-inflammatory, demulcent, antiulcer, mild laxative, adrenocorticotropic and a spasmolytic. In the world of herbal medicines, it is a relatively well researched plant and the main active constituents are recognised to be triterpene saponins, of which there are many, but the main ones appear to be glycyrrhizin (a mixture of calcium and potassium salts of glycyrrhizic acid) (Fig. 1) and glycyrrhetic acid (Sabbioni et al., 2006).

It is used commercially as a sweetener and has been a popular ingredient in confectionary for centuries. Its use in medicine dates back many years in both Western and Eastern cultures. Indeed, the historic use of glycyrrhiza has promoted research into possible future uses of this plant in the treatment of a wide spectrum of viruses where clinical trials have shown that glycyrrhizin and its derivatives demonstrate inter alia the following antiviral activity (Table 1).

In their narrative review of the relevant research on glycyrrhiza, Fiore et al. (2008) listed the possible mechanisms for the apparent antiviral activity of this herb which includes, "*reduced transport to the membrane and sialylation of hepatitis B virus surface antigen, reduction of membrane fluidity leading to inhibition of fusion of the viral membrane of HIV-1 with the cell, induction of interferon gamma in T-cells, inhibition of phosphorylating enzymes in vesicular stomatitis virus infection and reduction of viral latency*."

Interestingly, although there is a wealth of research on the antiviral potential of glycyrrhiza, it is not commonly used in WHM as an antiviral medication but this may change as further research develops.

In TOM, the sweet flavour of glycyrrhiza is believed to 'harmonise' the other constituents in a formulated prescription. In its raw state, glycyrrhiza is believed to rid the body of toxins and clear 'heat'; it is therefore often prescribed in cases of poisoning by either drugs or other potentially harmful substances. In a cross-over with Western uses, TOM also uses glycyrrhiza to clear phlegm and thereby reduce coughing. When baked with honey, it is used to treat 'spleen and stomach weakness',[1] where glycyrrhiza is thought to act therapeutically to stimulate the appetite.

Given the widespread use of this herb as a medicine and its possible future importance as our knowledge of its further application develops, it is important that the safety implications are properly understood in regard to pregnancy. In this article, the authors intend to examine the most popularly cited research which provides guidance to practitioners in the use of *Glycyrrhiza* spp. in pregnant women.

Table 1 – Antiviral activity of glycyrrhizin and its derivatives.

Type of trial	Antiviral activity
Randomised controlled trials	Reduced hepatocellular damage in chronic hepatitis B and C (and act synergistically with interferon in treatment of hepatitis C infections (van Rossum et al., 1999) Reduced risk of hepatocellular carcinoma in hepatitis C induced cirrhosis (Kumada, 2002)
In vivo studies	Reduced mortality and viral activity in herpes simplex virus encephalitis (Sekizawa et al., 2001) and influenza A H5N1 virus (Michaelis et al., 2011)
In vitro studies	Antiviral activity against HIV-1 (Hirabayashi et al., 1991), hepatitis C (Ashfaq et al., 2011), SARS related coronavirus (Cinatl et al., 2003), respiratory syncytial virus (Wang et al., 2006), arboviruses (Briolant et al., 2004), vaccinia virus and vesicular stomatitis virus (Pompei et al., 1979)

1. Study selection

In order to select the relevant research for analysis in this paper, the authors searched PubMed until December 2013 to identify the most appropriate and commonly cited studies. The terms used in the search were [glycyrrhiza, glycyrrhizin, licorice, liquorice] AND [pregnan*, fet*, child*]. Of 90 citations retrieved under these search terms, we will discuss the four most high-profile clinical studies.

2. Discussion

In 2001, Strandberg et al. (2001) conducted a cross-sectional study that aimed to investigate whether 'heavy' glycyrrhiza intake during pregnancy affected birth weight. Questionnaires were distributed to midwives between March and November 1998. However, they were received primarily by women who gave birth in the spring and autumn months of the same year, as midwives were often on vacation during the summer months. The authors argued that there was no possibility of selection bias (where errors are present in the selection of study participants and may skew trial data). The study found no significant effect on birth weight following pre-natal consumption of glycyrrhiza. However, it was noted instead that heavy glycyrrhiza use correlated strongly with lower gestational ages. When gestational age of 38 weeks

[1] In TOM this equates to tiredness and lack of strength, maybe what Western medicine might term chronic fatigue.

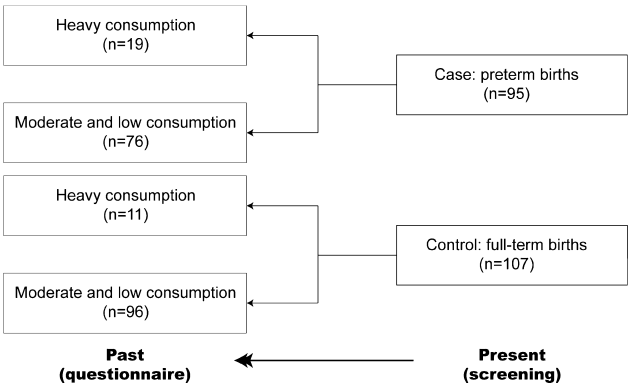

Fig. 2 – Outline of trial flow (Strandberg et al., 2002).

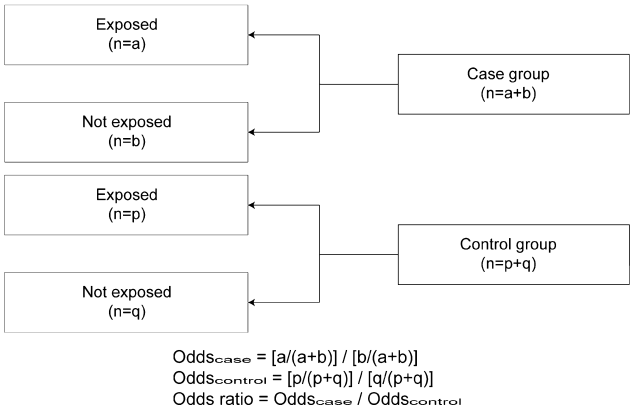

Fig. 3 – Calculation of odds ratio in a case-control study.

was considered as a cut-off point, odds ratio for preterm delivery associated with heavy glycyrrhiza intake was 2.5 (95% confidence interval: 1.1–5.5, $p = 0.03$).

Because the 2001 study was not designed specifically to investigate this association, the authors wanted to confirm their findings in a further case-control study. Consequently, in a subsequent study published in 2002 (Strandberg et al., 2002) by the same authors, the effect of glycyrrhiza on pregnant women was examined. This study involved a sample of 95 Finnish women who delivered preterm births and were then compared with women who delivered babies of normal gestational age in the same hospital. To establish glycyrrhizin intake, questionnaires were issued to each of the women to ascertain their liquorice consumption. Glycyrrhizin consumption was graded in three strata: low (<250 mg/week), moderate (250–499 mg/week), and heavy (≥500 mg/week). The results showed that heavy consumption versus a lower level of consumption was associated with, in excess of a twofold increased risk of preterm (<37 weeks) delivery, with a borderline significance. The association was more apparent in the fully adjusted model when only the 40 births classified as early preterm delivery (<34 weeks) were included (odds ratio = 3.07, 95% confidence interval: 1.17–8.05). As a result of these studies, WHM recommends caution if prescribing glycyrrhiza to pregnant women.

However, we believe that the conclusion drawn from the study by Strandberg et al. (2002) should be viewed with caution. As illustrated by the trial flow in Fig. 2, this study exhibited several issues. First, because data on liquorice consumption was collected through the use of a retrospective postnatal questionnaire, the actual amount of liquorice consumed by a subject may be different to that reported. Second, in a case-control study, statistical analysis is conventionally based on the 'odds ratio'. The odds ratio is defined as the ratio of odds in the case group (i.e. the proportion of people given exposure divided by that of people not given exposure) to the corresponding odds in the control group (Fig. 3). In this study, the odds ratio is 2.18 (95% confidence interval: 0.98–4.86, $p = 0.056$), thus termed as insignificant. Similar issues with this study have been reported by Slattery and Morrison, where they called for further assessment of the role of liquorice in preterm births (Slattery and Morrison, 2003).

In 2009, the American Journal of Epidemiology published an article (Räikkönen et al., 2009) that analysed the mental development of children who had been exposed to heavy consumption (>500 mg/week), moderate ((250–499 mg/week) and low (<250 mg/week) of glycyrrhiza during their mother's pregnancy. When compared with the low dose group, the heavy consumption group was associated with significant decreases in verbal and visuospatial abilities and in narrative memory (range of mean differences in standard deviation units, −0.31 to −0.41; $p < 0.05$) and significant increases in externalising symptoms and inattention, rule-breaking, and aggression problems. The study claimed to establish a dose-related link between glycyrrhiza consumption and reduced cognitive performance.

However, given this study is an extension of the previous study by Strandberg et al. (2001), its value may be questioned for a number of reasons. First, as discussed above, selection bias may have been introduced because subject recruitment took place during spring and autumn months. Second, because the data collection was based on the subjects' memory, the resulting analysis may contain data that is inaccurate. Third, and perhaps most importantly, this is a case controlled study that mainly aims to generate a hypothesis and further investigation is needed to confirm that hypothesis and produce clinical evidence.

More recently, a Korean study published by a team of medical doctors reported a marked increase in the rate of stillbirths where the expectant mother was taking medicine containing glycyrrhiza (Choi et al., 2013). This trial involved *Glycyrrhiza uralensis*, also known as Chinese liquorice and similarly high in the active compound glycyrrhizin.

These are findings that go beyond those discussed in the above research where lower gestation periods and impaired cognitive development were observed in the children of some women who consumed a 'heavy intake' of glycyrrhiza during pregnancy. Obviously, if the result reported by a Korean team is in fact correct, then it is very important that clinicians are increasingly cautious in the prescription of glycyrrhiza to pregnant women. Indeed the results of this study

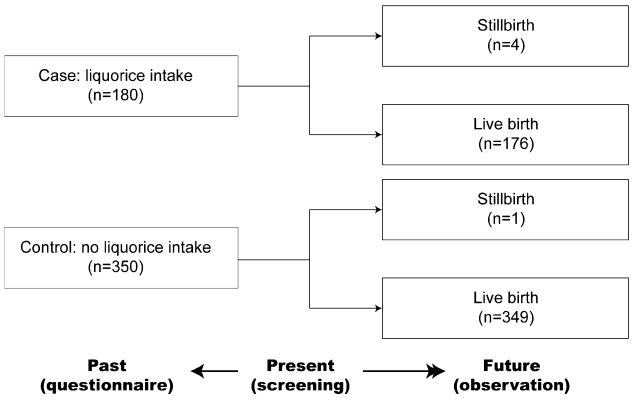

Fig. 4 – Outline of trial flow (Choi et al., 2013).

attracted a notable level of media attention when publicized in Korea.[2]

This trial was a prospective cohort study involving pregnant women who, upon having their pregnancy confirmed, were asked to enrol in the trial. Based upon whether the women took herbal medication or not, they were then split into two groups, an experiment group and a control group. As a result, 185 pregnant women who took herbal medication including glycyrrhiza were compared with 370 age-matched pregnant women who were not exposed to herbal medications. According to this trial, all foetal outcomes assessed at delivery were similar between the groups, except a rate of stillbirths. The rate of stillbirths was significantly higher in women who took glycyrrhiza than in those who did not ($p = 0.048$).

From the point of view of TOM and the customary practice of Korean medicine doctors in day-to-day clinical practice, this result was unexpected. It contradicts a rich history of traditional knowledge and modern practice. For example, according to *Donguibogam*,[3] a landmark in traditional Korean medicine, pregnant women showing signs of miscarriage are recommended to take a liquorice containing herbal medication called *Antaeeum*.

On closer analysis, however, the Korean clinical trial appears to contain a number of critical flaws. For a summary of the authors' thoughts, please see Fig. 4.

First, the data collection method used in this trial was reliant on the trial subjects' memory. Once a subject's pregnancy had been confirmed by a medical doctor, she was then asked to complete a questionnaire where she provided information regarding her ingestion of herbal medicines. As a result of their answer to these questions, women were assigned to either a control group or the experiment group. This data collection method provides an opportunity for significant errors to appear in the study. The errors that may arise in such a situation are called 'memory bias', where a subject may, for a number of reasons, alter the content of what they recall remembering. This therefore reduces the control parameters in the data gathering process allowing the subject to introduce factors that skew the study results.

Second, it is possible that the presence of an acute illness in early gestation influenced the data of the women in the experiment group. According to the study, more than half of the pregnant women received medication containing glycyrrhiza to treat acute illness, including influenza. Infection is an important cause of stillbirths (Goldenberg et al., 2010). Maternal infection might lead to systemic illness in the mother and thus cause the foetus to die because of high maternal fever, respiratory distress or other systemic reactions. Alternatively, if infection occurs early in gestation, the foetus might not die immediately but development of a congenital anomaly could cause foetal death at a later stage.

Third, it is uncertain whether all the women in the experiment group actually received medication containing glycyrrhiza. There was no protocol prescription given to each woman in the experiment group, rather it was reported that women in the experiment group took a commercially available substance or a prescribed herbal medicine. It should be understood that, in Korea, patients do not generally know the ingredients contained in their prescription because Korean medicine doctors often modify original herbal medications according to their examination. Additionally, there are many Korean medicine doctors who prescribe herbal medications based on the principles of 'Four-Constitution' medicine. These principles represent a branch of traditional Korean medicine in which patients are assumed to consist of four types (i.e. greater yang, lesser yang, greater yin, and lesser yin person). According to these principles, glycyrrhiza can be prescribed to only 'lesser yin' patients, although the majority of Korean people are known to be 'greater yin' in nature. Hence, not all women in the experiment group might have taken herbal medicine that included glycyrrhiza.

Fourth, it is of concern to the authors that the analysis of the data collected in the study was incorrect. To explain further, this study determined significance by calculating the 'odds ratio'. There were four stillbirths amongst 180 women in the experiment group and one stillbirth amongst 350 women in the control group. The study therefore reported the odds ratio to be 7.9 (95% confidence interval: 0.9–71.5), with $p = 0.048$. However, on closer analysis, the result should be insignificant because the 95% confidence interval includes value one. If one alternatively calculates the odds ratio using two commonly employed statistical programs,[4] it is revealed that whereas the point estimate and its 95% confidence interval were the same with the original study, p value in this instance was 0.065, thus indicating that there was no statistical difference between two groups.

Following the publication of this study, several Korean newspapers reported that herbal medication in general, and not just that containing glycyrrhiza extract, is of substantial

[2] http://news.kukinews.com/article/view.asp?page=1&gCode=cul&arcid=0006997009&cp=nv. Accessed 5 April 2013. http://www.doctorsnews.co.kr/news/articleView.html?idxno=86469. Accessed 5 April 2013. http://health.joseilbo.com/html/news/?f=read&code=1349931359&seq=3233. Accessed 5 April 2013.

[3] Meaning "Mirror of Eastern Medicine", this is a classical Korean medical text published in 1613 and remains a key reference text to this day.

[4] STATA 11.0 and CMA.

risk to pregnant women.[5] It is the authors' wish to correct this misapprehension by highlighting the weaknesses in the methodology of the clinical trial and also the statistical analysis of the data it produced.

3. Conclusion

If one considers the historical body of research on the use of glycyrrhiza in pregnancy, it is clear that the prudent practitioner may recommend that some caution is exercised. However, it is wrong for practitioners to be expected to continue to exercise such caution predicated on the basis of flawed clinical trials and skewed data analysis. The authors believe that, at present, there is insufficient information to categorically state whether or not glycyrrhiza may be used safely in pregnancy. It is the authors' opinion that there is a need for a systematic and unbiased evaluation of the evidence relating to the use of glycyrrhiza during pregnancy.

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[5] http://dailymedi.com/news/view.html?section=1&category=131&no=765131. Accessed 5 April 2013. http://www.ibabynews.com/news/newsview.aspx?categorycode=0004&newscode=201303281745370312501857. Accessed 5 April 2013.