A Systematic Literature Review to Assess the Safety of Using Chinese Herbal Medicines in Pregnancy

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Index

Glossary of Terms

AAs	-	Aristolochic acids
CAM	-	Complementary and Alternative Medicine
CHM	-	Chinese herbal medicine
D&B	-	Downs and Black
FAS	-	Foetal Alcohol Syndrome
FBE	-	Fugh-Berman and Ernst
MeSH	-	Medical Subject Headings
MH	-	McHarm
WPP	-	Western pharmaceutical products

Abstract

Background: A systematic literature review was carried out to find out if Chinese herbal medicine (CHM) is safe to use in pregnancy.

Methods: The Cochrane database, Pubmed, CINAHL, MEDLINE, AMED and ALT Healthwatch were searched and 123 papers were found, 7 of which met the inclusion criteria. Of these 7, 3 were cohort studies and 4 were case studies.

Results: After quality assessment was carried out, 3 of the case studies were not deemed of good enough quality, or did not have good enough evidence to be considered for discussion. Of the remaining papers, there were conflicting results. A cohort study showed that in comparison to Western pharmaceutical medicine, CHM intake in pregnancy did not carry any significant risk of congenital abnormalities. Conversely, in a different cohort study, it was shown that Huang Lian *(Rhizoma coptidis)* and An Tai Yin *(Calm Foetus Drink)* use in pregnancy was associated with congenital malformation of the nervous system, and of the musculoskeletal and connective tissues and eye respectively. Interestingly, in a separate study, Huang Lian intake during pregnancy was not shown to have any adverse effect on birth weight. Ci Wu Jia *(Eutherococcus sentincosus)* was described in a case study to be associated with neonatal androgenisation.

Conclusion: This was a small, scoping study used to assess any current information about the teratogenicity of CHM. Due to the lack of information about the safety of CHM in pregnancy, it should be used with caution and only prescribed by qualified practitioners. Until more information is available Huang Lian and An Tai Yin should be avoided during the first trimester of pregnancy, and Ci Wu Jia should be avoided in pregnancy.

Introduction

The use of complementary and alternative medicine (CAM) in the United Kingdom is about 10% of the population per year and one of the most commonly used therapies is herbal medicine (Thomas and Coleman, 2004). Of those that use CAM, more than half do not tell their general practitioner (Thomas and Coleman, 2004). A cross-sectional survey by Gibson *et al.* (2001) in America showed that almost 10% of pregnant women used herbal supplements during their pregnancy. Dugoua (2010) found that pregnant women used herbal medicine instead of prescription medications because they were worried about the safety of their foetus. However, herbal remedies are not without risk; some herbs have been shown to adversely affect the foetus, pregnancy or labour and others can interact with pharmaceutical medication (Pinn and Pallett, 2002). Therefore, it is of upmost importance to have safety information on any herbal remedies that are prescribed to pregnant women.

At present, safety information on CHMs is very limited and this lack of information about potential toxicity can even encourage its use in disease treatment and prevention (Tian *et al.,* 2009). Many pregnant women do not realise that naturally occurring chemicals in herbal medicines can be toxic and can trigger foetal malformations (Tiran, 2003), and most clinicians have a basic lack of knowledge about the safety of the use of herbal remedies in pregnancy and breast feeding (Seely *et al.,* 2008). To further confound this problem, adverse effects from herbal medicines are rarely reported or recognised (Ernst, 2002a). Moreover, many midwives and complementary therapists are recommending herbal medicines to their pregnant patients (Ernst, 2002a).

Although there have been several studies and systematic reviews looking at the safety of using herbal medicines in pregnancy, there have not been any systematic reviews in English to determine the safety of using CHMs in pregnancy. This was established by searching the Cochrane Pregnancy and Childbirth Group (2013), the Cochrane Database of Systematic Reviews (Cochrane Collaboration, 2013a) and on the Database of Abstracts of Reviews of Effects (Cochrane Collaboration, 2013b) to check for existing, new, upcoming and/or unpublished systematic reviews on the safety of using CHMs in pregnancy. Therefore, this research will be the first of its kind in English. It is in the interest of the author to find out what safety information exists on the use of CHMs in pregnancy as she has a particular interest in treating infertility and pregnancy-related conditions.

Aims and Objectives

The aim of this systematic literature review is to evaluate published research to determine the incidence and characteristics of adverse effects associated with using CHMs in pregnancy. There are 4 main objectives within this aim:

- Is there any research which shows serious risks associated with using CHM in pregnancy?
- If so, which herbs or herbal formulas should not be used in pregnancy?
- What other adverse events/side effects are associated with using CHM in pregnancy and are they considered an acceptable risk?
- Is CHM safe to use in pregnancy?

Critical Evaluation of Literature

Prevalence of Use

In Taiwan, Yeh *et al.* (2009) found that over a fifth of women were shown to be using CHM in pregnancy for problems such as hypertension, nausea and vomiting. Another similar study showed that over one third of the population of Taiwan were using CHM in pregnancy and almost 90% used it in the postpartum period (Chuang *et al.,* 2009a). Thomas and Coleman (2004) found that in 2004, in England, Scotland and Wales, 0.5% of the population used CHM. In 2011, this equates to 280,000 people in England and Wales (Office for National Statistics, 2011).

Yeh *et al.* (2009) and Broussard *et al.* (2010) found that more women used CHMs in their first trimester, which is the most vulnerable time for the rapidly growing embryo (Chung, 2004). However, Nordeng and Havnen (2004) found that herbal drug use increased throughout the pregnancy. Furthermore, according to Dugoua (2010), around 50% of all pregnancies are not planned and because of this many women won't be aware that they are pregnant until week 5 or 6 of gestation. As the first 10 weeks carry the greatest risk of major malformations through teratogenicity, the mother may have already taken substances that are harmful to her embryo before realising she is pregnant (Dugoua, 2010).

Studies from Taiwan have shown that women are most likely to use CHMs in pregnancy if they have threatened abortion (pain, cramping or bleeding), or have a history of miscarriage or stillbirth (Chuang *et al.,* 2005; Chuang *et al.,* 2007).

However, in Western culture women are more likely to seek herbal treatment for: nausea, labour aid, cervical ripening, respiratory tract infections and depression (Dugoua, 2010).

Herbal Formulae Used in Pregnancy

According to Chuang et al., (2009a), the most commonly used Chinese herbal formulae in pregnancy are: An Tai Yin *(Calm Foetus Drink)* and Si Wu Tang *(Four Substance Decoction)* (table 1, appendix i shows list of ingredients), whereas, the most commonly used herbs in pregnancy are: Pearl Powder *(Margarita),* Huang Lian *(Rhizoma coptidis)* and Ginseng *(Radix ginseng).* However, this differs slightly from the most 20 commonly used Chinese herbs in pregnancy listed by Wang *et al.,* (2012) as shown in table 2, appendix i.

Teratogens and Pregnancy

A teratogen is any environmental factor that either causes death of an embryo or foetus, or results in congenital malformations or birth defects (Gilbert-Barness, 2010). These environmental factors are comprised of: certain medications or drugs, exposure to specific chemicals or radiation, genetic factors and maternal diseases or conditions such as diabetes (Chung, 2004, Gilbert-Barness, 2010). Teratogens cause around 7% of congenital malformations, with drugs and medications accounting for less than 1%; whereas 65-75% of causes are unknown and 20-25% are caused by genetic factors (Chung, 2004). The most vulnerable time for exposure is at the time of the most rapid cell division, weeks 5 – 10 of gestation, whereas exposure in the first 2 weeks of development (week 2 – 4 of gestation) will usually result in the death of the embryo rather than in malformation (Chung, 2004). Exposure during the foetal period (week 10 – 40 of

gestation) causes more minor structural defects and can restrict foetal growth (Chung, 2004). For this reason, it is strongly recommended that women avoid all types of medication during the first 10 weeks of pregnancy (Chung, 2004).

The thalidomide disaster in the 1960s stands as an example to practitioners of the importance of using extreme caution when prescribing medications in pregnancy. An estimated 20% of all mothers who took thalidomide whilst pregnant delivered infants with 'thalidomide syndrome', characterised by: limb, cardiac and genital defects, and dental and ear anomalies (Chung, 2004, Gilbert-Barness, 2010). The drug was marketed worldwide as extremely safe and was used for common symptoms experienced in early pregnancy (The Thalidomide Trust, 2011).

Chinese Herbs

Little is known of the teratogenicity of CHMs (Broussard *et al.,* 2010), but their use in pregnancy ranges from 9% - 35% depending on location (Fok, 2001; Nordeng and Havnen, 2004; Chuang *et al.,* 2009a; Yeh *et al.,* 2009). This potential risk is further confounded by the reality that as many as 58% of women do not tell their health care providers that they are taking herbal medicines (Broussard *et al.,* 2010). Furthermore, with around 3.5 million people affected in the United Kingdom by infertility (Human Fertilisation and Embryology Authority, 2011) and the trend towards seeking CAM therapies such as herbal therapy (Thomas and Coleman, 2004), it is very likely that women will be using CHMs in the very early stages of pregnancy before they know that they are pregnant. A recent systematic review involving 1851 women showed that CHM treatment was twice as effective as Western medical fertility treatments for helping women to become pregnant (Ried and Stuart, 2011). This shows the encouraging potential that CHM has in

the treatment of fertility; however, the risks associated with taking CHMs in the first few weeks of development have not been rigorously and systematically ascertained (Nordeng and Havnen, 2004; Broussard *et al.,* 2010). For example, Broussard *et al.* (2010) found that *Ephedra* (known as Ma Huang in CHM) was used in 0.6% of the first trimester of pregnancies in the United States between 1998 and 2004. In 2004, this herb was taken off the American market because of its adverse affect on the cardiovascular system, which could have implications for foetal risk, but at the time of taking the herb these women would have had no idea of its potential risk to them or their unborn baby (Broussard *et al.,* 2010).

Leung (2006) argues that there is sufficient toxicity information on CHMs and that this information has been accumulated from human studies over the last 3000 years. However, Ernst (2010) contends that just because CHM has been used over a long period of time doesn't render it safe. He points out that adverse affects could be long term and therefore not associated with particular Chinese herbs or formulae. This happened with Chinese herbs containing aristolochic acids (AAs), they were deemed safe until the 1993 Belgium case whereby over 100 women treated with pharmaceutical medication and a Chinese herb containing AAs developed kidney failure (Wu *et al.,* 2007; Jordan *et al.,* 2010). This example of doctors' misuse of CHMs actually brought to light the previously unknown dangers of AAs and the delayed reaction that can occur with their ingestion (Wu *et al.,* 2007).

There are some key differences between modern pharmaceutical medicine and CHM shown in the table below, and these have a great impact on how toxicity is measured and understood.

Pharmaceutical Medicines	Chinese Herbal Medicines
Mostly uses one drug for a specific use	Uses decoctions of herbs often to treat many different complaints at once
Tested for toxicity in animals, and then on humans	Traditionally only tested for toxicity in humans
Individual mechanisms of actions of chemicals properly understood	Collective data over thousands of years informs the user of the toxicity of herbs and formulae
Mostly have less than 75 years of human use	Have around 3000 years of human use
Information readily available in English	Only a fraction of the safety data has been translated into English

(Leung, 2006)

One of the biggest issues facing the identification of toxicity of CHMs is the fact that the modern scientific methods used usually rely on isolating certain chemical constituents within one herb (Leung, 2006). This is impractical for CHM as multiple herbs are used in each decoction (Leung, 2006; Lan *et al.,* 2011). Lan *et al.* (2011) propose a system of using a metabolomics approach to understand the pharmacokinetics of herbal formulae and the complexity of the interactions between herbs within a formula. This is important because combinations of herbs can diminish each other's reactions, or lead to harmful interactions or unforeseen toxicity (Zhu, 2006). However, at present, modern, scientific data on the toxicity of Chinese herbs and formulae is limited (Ernst, 2010) which may indicate that mostly the teratogenicity of an herb or formula is unknown.

With the increasing use of CHMs, the growing number of women using them for fertility treatment, and the potential benefit that CHM can have on an individual's health and fertility prospects, it is important to know that the herbs we are using are safe. This systematic literature review aims to evaluate what we know about the safe use of CHMs in pregnancy, in order to allow practitioners and pregnant women alike to make safer, more informed decisions about treatment.

Methodology and Study Design

Search Strategy

As recommended by the Centre for Reviews and Dissemination (2008), relevant medical subject headings (MeSH) should be assigned for each database searched. These are shown in full in appendix ii. The following databases were searched from inception to February 2013:

- CINAHL
- Cochrane library
- MEDLINE
- Pubmed
- ALT Healthwatch
- AMED

The literature search was carried out using the following terms (with relevant MeSH headings):

safety OR adverse effects OR embryotoxity OR teratogens OR teratogenicity AND

pregnancy OR pregnancy complications AND

Chinese herb* OR Chinese herbal medicine

This search strategy was developed using the population, intervention, comparator and outcomes method (Centre for Reviews and Dissemination, 2008). As recommended by White and Schmidt (2005), reference lists of included papers were searched and relevant documents were included in the review.

Inclusion Criteria

Primary research that reports adverse events associated with the use of Chinese herbal medicine in pregnancy, and to any medical problems suffered during pregnancy will be included. Although it is best to include research in all languages (White and Schmidt, 2005), it is beyond the scope of this project to include published literature in any language other than English. All literature published before February 2013 in peer reviewed journals will be evaluated to gain a full understanding of any safety implications. As data on safety can be found in different types of studies, it is important to include a range of relevant types (Pilkington and Boshnakova 2011). Therefore, the following studies will be included: randomised controlled trials, controlled trials, quasi-experimental studies, and observational studies - case–control, case reports and cohort studies.

Exclusion Criteria

Primary research relating to the safety of using Chinese herbal medicine in conditions other than those in pregnancy will be excluded. Epidemiological studies will not be included because they measure how often diseases occur and why (British Medical Journal, 2013). Herbs that are not used in CHM will not be reviewed, as the focus of this review is specifically about CHMs. Furthermore, animal studies evaluating the safety of CHMs in pregnancy will be excluded for the following reasons. The Food and Drug Administration (2004, p9) discuss the inability of animal trials to '...assess and predict product safety...' and this is further shown in the alarming statistics that 92% of drugs that are deemed safe for testing in humans never make it to the market. Of those that do, over half have to be withdrawn or relabelled due to lethal or serious side effects in humans (Food and

Drug Administration, 1990). Archibald and Clotworthy (2007) describe the track record of animal testing to predict drug safety as 'abysmal'. Perel *et al.,* (2007) found that animal experiments were as effective at predicting human response to a drug as flipping a coin. Therefore, if the safety of CHMs were established in animal models, this would not necessarily be a good indication that they would be safe to use in humans. As pregnancy is such a delicate human state of being and the repercussions of incorrect treatment are potentially serious, as with congenital malformations or miscarriage, animal models should not be relied on for safety assurance. Moreover, Goodyear (2006, p677) points out, 'Relative lack of severe toxicity in animal models should never be construed as a guarantee of safety in man, as the story of thalidomide taught us.'

Limitations

Due to limited resources and time constraints there are certain limitations with this review. Firstly, it is not possible to search books or conference proceedings, or to hand search relevant journals. This will lead to an element of publication bias due to the restriction of only searching for published literature in peer reviewed journals (Centre for Reviews and Dissemination, 2008). Secondly, as Chinese herbal medicine is practised so widely in countries such as China, Taiwan and Japan, it is likely that there are a number of studies about this subject that have not been published in English. Therefore, this will lead to a strong language bias. This will be in part overcome by showing all the Chinese language studies excluded in appendix iii. Thirdly, it is best practice to have at least 2 authors carrying out the review, to increase reliability of the decisions made to include/exclude papers (Centre for Reviews and Dissemination, 2008).

Data Analysis and Results

In this study statistical meta-analysis of the findings will not be possible as not all of the studies will be randomised controlled trials, therefore, a narrative synthesis of the data will be undertaken. This will be carried out using a systematic approach to the synthesis process by using the Narrative Synthesis in Systematic Reviews guidelines (Popay *et al.,* 2006).

Ethical Considerations

There are no ethical considerations for this systematic review.

Search Details

Figure 1 in appendix iii shows the details of the systematic search process as well as the details of the excluded papers.

Data Extraction and Quality Assessment

The data from the seven studies is displayed in tables 1 and 2 below. A data extraction form was designed using recommendations from the Centre for Reviews and Dissemination (2008). The McHarm (MH) scale was used to assess the studies because it has been designed specifically to evaluate adverse events and the potential for error or bias when reporting and assessing them (Cochrane Bias Methods Group, 2013). It is used mostly as a checklist rather than using the final number as an indication of quality. Despite the value of this scale, the Downs and Black (D&B) (1998) scale was highly recommended by Saunders *et al.,* (2003) after they had thoroughly appraised 18 instruments used to assess the quality of non-randomized studies. Furthermore, they recommended using the

scale as a checklist. For this reason, both scales were used to assess the cohort studies and were used as checklists for indication of quality, validity and reliability.

The case studies and data extraction were assessed and handled differently, because of the nature of how they are reported. For this reason, data extraction was based on a form designed by Ernst (2002b) and the Fugh-Berman and Ernst (FBE) (2001) scale was used, alongside the MH scale to assess quality, validity and reliability. The former scale is interpreted by using the final number as an indication of the likelihood of the adverse event being caused by the intervention. Full details of the assessments are in appendix iv.

Table 1: Case Studies Data

Record Number	Authors	Article Title	Study Design; Country; Setting	Patient Information	
				Mother	**Baby/Embryo**
Pub 3	Cayan et al., 2009	Use of Chinese Herbal Medicine 'Meizintanc' in Pregnancy: Report of Three Cases	Case studies; Turkey; Antenatal hospital visit patients;	28 years old: gravida 1, parity 0, BMI 25	Born at 38 weeks. Healthy at birth and at 8 month check up
				25 years old: gravida 1, parity 0, abortus 0, BMI 30	Study is unclear as to exact age of embryo at missed abortion
				29 years old: gravida 3, parity 2, abortus 0, BMI 22	Study is unclear as to exact age of embryo at missed abortion
Pub 10	Takei *et al.,* 1997	Meningoencephalocele Associated with *Tripterygium wilfordii* Treatment	Case Study; Japan; Showa University Fujigaoka Hospital Departments of Neurosurgery and Pediatric Surgery	Study is unclear as to mother's age. She suffered with rheumatoid arthritis	Born at 38 weeks.
Pub 11	Pradeepkumar *et al.,* 1996	Is 'Herbal Health Tonic' Safe in Pregnancy; Fetal Alcohol Syndrome Revisited	Case Study; Singapore; Department of Neonatology 3 year follow up visit	29 years old: Chinese, gravida 2, parity 2	Born at 41 weeks by caesarean section
Pub 13	Koren *et al.,* 1990	Maternal Ginseng Use Associated with Neonatal Androgenization	Case Study; Canada; Hospital for Sick Children	30 years old: gravida 3, parity 2	Born at full term

Table 1 (continued) - Case Studies Data and Scoring

Record Number	Herbal Medicine Ingested By Mother; Daily Dosage	Timing and Time Period Medication Was Taken	Other Interventions Used	Adverse Event	Diagnosed By	Diagnostic Method(s)	Fugh-Berman & Ernst Score	Mc-Harm Score
Pub 3	LiDa Dai Dai Hua Jiao Nang; 350mg	3 months, up to 7th week of gestation	Not Stated	none	Unknown - presumed doctors at the hospital	none		
	LiDa Dai Dai Hua Jiao Nang; 350mg	5 months, up to 6th week of gestation	Not Stated	Miscarriage	Unknown - presumed doctors at the hospital	Ultrasonographic examination and blood tests - serum B HCG levels	4 = Adverse event possibly caused by the herbs	7
	LiDa Dai Dai Hua Jiao Nang; 350mg	6 months, up to 7th week of gestation	Not Stated	Miscarriage	Unknown - presumed doctors at the hospital	Ultrasonographic examination and blood tests - serum B HCG levels		
Pub 10	Lei Gong Teng; unknown	Early in pregnancy' - 8th week of gestation	Not Stated	Occipital meningoencephalocele	Unknown - presumed doctors at the hospital	Observation, roentgenogram and MRI	3 = Unable to evaluate if herbs caused the adverse event	8
Pub 11	Herbal Health Tonic; 2 ounces	First 2 months of gestation	None	Fetal alcohol syndrome, or foetal alcohol effects	Unknown-presumed doctors at the hospital	Observation: dysmorphic features, growth, motor and mental milestones at 3 year follow up	7 = Adverse event possibly caused by the herbs	9
Pub 13	Ci Wu Jia *(Eutherococcus sentincosus)*; 1300mg	1.5 years, throughout entire pregnancy and during 2 weeks of breastfeeding	None	Neonatal Androgenization	Medical doctors at the hospital	Observation: inappropriate hair growth, enlarged testes. Various serum concentration tests	8 = Adverse event was likely to have been caused by the herbs	10

Table 2 - Cohort Studies Data

Record Number	Authors	Article Title	Study Design; Country; Setting and Time Period	Study Inclusion and Exclusion Criteria	Recruitment Procedures Used: details of randomisation/blinding
MED 2	Leung *et al.,* 2002	Are Herbal Medicinal Products Less Teratogenic than Western Pharmaceutical Products?	Retrospective; Hong Kong; antenatal hospital visit patients; Jan 1995 - Dec 2001	Included: Pregnant women who had taken CHMs or Western medicines	Women taking both CHM and Western pharmaceutical products (WPPs) were assigned to whichever group they were most worried about
MED 7	Chuang *et al.,* 2006b	Herbal Medicines Used During the First Trimester and Major Congenital Malformations: An Analysis of Data from a Pregnancy Cohort Study	Cross Sectional Analysis of Cohort Study; Taiwan; prenatal hospital visit patients at Taipei Municipal Maternal and Child Hospital; September 1984 - June 1987	Included: Pregnant women > 26 weeks gestation	Around 80% of all women coming to the hospital were included in the study
PUB 8	Chuang *et al.,* 2006a	Use of Coptidis Rhizoma and Foetal Growth: A Follow-Up Study of 9895 Pregnancies	Cohort Study; Taiwan; antenatal hospital visit Taipei Municipal Maternal and Child Hospital; 1995-1987	Included: Every pregnant woman with 26 or more weeks gestation	Women were assigned to 5 groups: no herbal medicine use, only used Huang Lian (2 groups), used other herbs, used Huang Lian and other herbs

Table 2 (continued) - Cohort Studies Data

Record Number	No of Participants	Age	Chinese Herbs or Formulae Used
MED 2	Total: 433 CHM: 61 WPP: 372	CHM: 30.5 ± 5.1 WPP: 30 ± 4.8	Various unknown and known: Xuan Shen *(Radix scrophulariae),* Zhi Shi *(Fructus aurantii immaturus),* Tian Hua Fen *(Radix trichosanthis)*, Da Zao *(Fructus ziziphi),* Hou Po *(Cortex magnoliae officinalis),* Sheng Di Huang *(Radix rehmanniae),* Yu Li Ren *(Semen pruni),* Zhi Mu *(Rhizome anemarrhenae),* Gan Cao *(Radix glycyrrhizae),* Ji Nei Jin *(Endothelium corneum gigeriae galli), Mai Men Dong (Radix ophipogonis),* Huang Qi *(Radix astragali seu hedysari),* Chai Hu *(Radix bupleuri),* Huang Qin *(Radix scutellariae).*
MED 7	14, 551	Majority of parents were 20-34 years old	**Herbs: Huang Lian** *(Rhizoma coptidis recens)*; **Ren Shen** *(Radix ginseng)*; **Formulae: An Tai Yin** (Bai Shao *(Paeonia radix),* Dang Gui *(Angelica sinesnsis),* Chuang Xiong *(Ligusticum rhizoma),* Tu Si Zi *(Cuscuta semen),* Chuan Bei Mu *(Fritillaria bulbus),* Huang Qi *(Astragalus radix),* Hou Pu *(Magnolia cortex),* Ai Ye *(Artemisia folium),* Sheng Jiang *(Zingiber officinale),* Zhi Ke *(Citrus aurantium fructus),* Gan Cao *(Glycyrrhiza radix),* Qiang Huo *(Notopterygium radix)*); **Ba Zhen Tang** (Ren Shen, Fu Ling *(Sclerotium poriae cocos),* Bai Zhu *(Rhizomaatractylodis macrocephalae),* Zhi Gan Cao *(Radix glycyrrhizae uralensis)* Shu Di Huang *(Radix rehmanniae glutinosae praeparata),* Dang Gui *(Radix angelicae sinensis),* Bai Shao Yao *(Radix paeoniae lactiflorae),* Chuan Xiong, Sheng Jiang *(Rhizoma zingiberis officinalis recens),* Da Zao *(Fructus Jujubae)*); **Si Wu Tang** (Dang Gui, Chuan Xiong, Bai Shao Yao, Shu Di Huang); **Dang Gui Shao Yao San** (Dang Gui, Bai Shao Yao, Fu Ling, Bai Zhu, Chuan Xiong, Ze Xie *(Rhizoma alismatis orientalis)*).
PUB 8	9895	Mostly 20-34 years old. Exact ages not given	Huang Lian *(Coptidis Rhizoma)* NB: Other herbs were used but those women who used herbs other than Huang Lian were not included in the study.

Table 2 (continued) - Cohort Studies Data

Record Number	Other Interventions Used	Dosages; Length of Treatment; Gestation Age When Taking Medication	Statistical Techniques Used	Safety Issues/Adverse Events	Length of Follow Up
MED 2	WPPs	Dosages unknown. Mean duration of use: CHM - 11 days WPP - 48 days. Mean gestation age: CHM - 5 weeks WPP - 3 weeks	SPSS 10.1 Student's *t*-test and *Chi*-square test	CHM: 1 - Megacystitis and umbilical cord cyst, 1 - Body stalk anomaly. WPP: 3 - Cleft lip and palate	n/a
MED 7	WPPs and supplements	Dosages unknown; length of treatment unknown; First trimester	SPSS 11.0	Increased risk of congenital malformation of the nervous system and possibly with external genital organs with Huang Lian. Increased risk of congenital malformations of the musculoskeletal and connective tissues and eye with An Tai Yin	To live birth. National Health Insurance data searched to 2000 and national death register searched up to 2003.
PUB 8	Unspecified WPPs, and other types of CHMs	Most commonly 0.3-0.5g daily; any duration; any gestation age	SPSS 11.0 Multiple logistic regressions and multiple linear regression analysis	None reported. A non-significant decreased birth weight was recorded in users of Huang Lian	Followed up to time of birth

Table 2 (continued) - Cohort Studies Data and Scoring

Record Number	Number of Participants Enrolled	Number of Participants Included in Analysis	Number of Withdrawals; Exclusions; Lost to Follow Up	Quality Score - Downs and Black: Quality; External Validity; Internal Validity Bias; Internal Validity Confounding; Power = Total Score	McHarm Score
MED 2	433	433	n/a	9; 3; 5; 2; 0 = 19/32	10
MED 7	unclear	14551	16% of births were not at the hospital, so were not followed up. However, as National health insurance data and national death register were searched, an extra 55 additional cases were found.	10; 3; 5; 3; 0 = 21/32	12

PUB 8	9895	9895 (1565 specifically for Huang Lian use)	no loss to follow up due to checking the national birth registration data	11; 3; 5; 4; 5 = 28/32	12

Discussion

Case Studies

The data from the case studies, displayed in Table 1, shows the variety of the cases discussed. The case studies are reported from Turkey, Japan, Singapore and Canada, they involve pregnant women from 25-30 years old (and one unknown age), all taking different CHMs apart from one case which discusses 3 women taking the same CHM. All babies were born within a normal range 38-41 weeks, apart from 2 that miscarried at an earlier stage. The timing of ingestion of CHMs varied from: before conception into early pregnancy and the first trimester to throughout the entire pregnancy and postpartum. Some cases were well reported whereas others were quite poorly reported as discussed below.

LiDa Dai Dai Hua Jiao Nang 'Meizintanc'

Three cases were discussed in this report of pregnant women ingesting 'Meizintanc' at various stages of their pregnancies. The woman who had taken the formula for the least amount of time was the only one who delivered a healthy baby. The other two women miscarried at earlier stages of their pregnancies. This was a patent CHM remedy, with unknown ingredients used for weight loss. It was recalled by both the Australian and Canadian governments as it was considered unsafe for use due to the levels of sibutramine, a prescription only western medication that was found within the remedy (Department of Health and Ageing, 2007 and Government of Canada, 2008). According to the Government of Canada (2008), 'Use of sibutramine may cause headaches, increased heart rate and blood pressure, chest pain and stroke.' This was not mentioned in the case report. There was no record of who diagnosed these women, at what point

they miscarried, if they were taking any other medications or if other explanations were investigated. As the chance of miscarriage is around 25% in pregnancy, more likely in the first trimester and is often of unknown cause (American Pregnancy Association, 2011), it is very difficult to link these miscarriages to the patent formula. The FBE scale showed that there was a low possibility that the adverse event was caused by the herbs and the MH scale showed that less than 50% of the criteria were met. Furthermore, as the patent formula was not tested for sibutramine, until proven otherwise, this case cannot be considered as evidence of harm from ingestion of CHMs in pregnancy, as there is a strong likelihood that the formula was contaminated with pharmaceutical medication.

Lei Gong Teng (Tripterygium wilfordii)

This case was also poorly reported. A woman of unknown age and medical history gave birth at 38 weeks to a baby boy with a meningoencephalocele. She took Lei Gong Teng from what was described as 'early in pregnancy' to the 8th week of gestation. There wasn't adequate information about other medications or relevant medical history, other than the mother having rheumatoid arthritis, which was her reason for taking the medication. No alternative explanations were investigated and it was unclear who diagnosed the baby's condition and what their background was. However, Lei Gong Teng is known for its toxicity (Tao and Lipsky, 2000), which would suggest that it should not be taken in pregnancy.

Meningoencephalocele is a neural tube defect and most neural tube defects can be prevented by adequate folic acid intake before and during pregnancy (National Institute of Child Health and Human Development, 2013). Despite there being so many factors that affect the likelihood of congenital abnormalities, such as: socio-

economic, genetic and environmental factors as well as maternal infections and nutritional state, around 50% of all congenital abnormalities are from unknown causes (World Health Organisation, 2012). Without knowing the age and nutritional, environmental and genetic status of the mother, it is a very tenuous link between Lei Gong Teng and the meningoencephalocele. Furthermore, this is shown in the FBE score, which defined the case as unable to evaluate if the CHM was the cause of the adverse event.

Herbal Health Tonic

This case involved a woman who took 2 ounces (59ml) of an 'herbal health tonic' daily, in the first 2 months of gestation. She had a caesarean section at 41 weeks and gave birth to a baby with suspected foetal alcohol syndrome (FAS). At a 3 year follow up visit, FAS or foetal alcohol effects was the most likely cause of the child's dysmorphic features and delayed: speech, language, motor and mental skills. Standard checklists and scales were used to test for the syndrome, but it was unclear exactly who carried out these tests and what their medical background was. On the FBE scale, it scored quite high, suggesting that the adverse event could have been caused by the tonic. It must be taken into account that the suspected FAS would have been caused by the alcohol content of the tonic (as FAS can only be caused by alcohol), rather than any of the herbs contained within it. Furthermore, it was unclear exactly which herbs constitued the tonic. Therefore, although there is a reasonable link between the ingestion of the tonic in early pregnancy and FAS, there is no association of adverse effects with CHM that are discussed or implied.

Ci Wu Jia (Eutherococcus sentincosus)

A 30 year old woman took Ci Wu Jia for 1½ years, before pregnancy, during her whole gestation and for 2 weeks of breast feeding. Her baby boy was born at full term and was diagnosed with neonatal androgenisation by medical doctors at the hospital. The mother also experienced increased hair growth. When the baby ceased to be given Ci Wu Jia (via breast milk), his excess hair fell out, suggesting a probable link. Other causes of neonatal androgenisation are thought to be: genetic, spontaneous mutation or adrenal tumour (New Zealand Dermatological Society Incorporated, 2013). There was no information about the mother's medical history and whether there would be any genetic link to this type of disorder. However, despite this, there have only ever been 50 reported cases worldwide that were due to genetic links or spontaneous mutations (New Zealand Dermatological Society Incorporated, 2013). Adrenal tumour was tested for in this case and ruled out. According to the FBE scale, the Ci Wu Jia was likely to have been the cause of this disorder. This case had the highest MH score, showing that the level of reporting was more comprehensive. Although it is impossible to make an indisputable link between Ci Wu Jia intake and neonatal androgenisation, there is a strong likelihood that this Chinese herb was the cause of the adverse event.

Cohort Studies

The data from the cohort studies is shown in table 2. It shows 3 studies that all scored well on the D&B scale (19-28/32) and the MH scale (10-12/15). They all analysed large groups of participants (433 – 14,551) and used statistical analysis to interpret the results. According to the D&B scale, they were all of high external

validity whereas internal validity, or risk of bias, was compromised by lack of blinding and randomisation. The studies will be discussed individually below.

Leung et al., (2002) – CHM vs. Pharmaceutical medicine

The authors wanted to find out if CHMs were less teratogenic than Western pharmaceutical products (WPPs). They analysed 433 women from a hospital in Hong Kong who took a wide variety of CHMs of unknown dosages. Although there were a higher percentage of congenital anomalies in the CHM group, there was no significant difference between CHM and WPP. There are several points to consider. Firstly, they didn't carry out adequate adjustments for confounding in the analyses which would affect the internal validity of the study, putting it at greater risk of bias (Downs and Black, 1998). Secondly, the women taking the CHMs were of lower socioeconomic status than those taking WPP, and this is associated with a higher number of congenital abnormalities (Vrijheid *et al.,* 2000). Thirdly, herbal medicine use is often under reported (Thomas and Coleman, 2004), so it is possible that the women in the WPP group were also taking CHMs. Furthermore, the women in the study who took both WPP and CHM were not put in a separate group for dual medication types, they were instead assigned to either group depending on which type of medicine (WPP or CHM) they were most concerned about taking. It is unclear how many women were taking both products, which makes it difficult to make any kind of clear comparison between the two types of medicine. Nevertheless, it does appear that this has not had an impact on the final results, as of the 5 women who had babies with congenital abnormalities, all of them took either CHM or WPP, not a combination of the two.

Chuang et al, (2006b) – CHM Use in the First Trimester and Congenital Malformations

The authors of this study looked at 14,551 women, their use of CHMs in the first trimester of pregnancy and whether or not this increased the risk of congenital abnormalities. The study was carried out in the Taipei Municipal Maternal and Child Hospital in Taiwan. A wide variety of CHMs were taken, but the dosages and duration of ingestion were unknown. They found that Huang Lian was associated with an increased risk of congenital malformation of the nervous system and possibly with the external genital organs. An Tai Yin was associated with an increased risk of congenital malformations of the musculoskeletal and connective tissues, and the eye. They found no risks associated with Ren Shen *(Radix Ginseng)*, Si Wu Tang *(Four Substance Decoction)*, or Dang Gui Shao Yao San *(Angelica and Peony Powder)*.

There are a few points to take into consideration. Firstly, the authors found that 95% and 40% of the women who used Huang Lian and An Tai Yin respectively, bought it from either their family or from a shop. It is possible therefore, to assume that most of these women did not have a proper consultation or diagnosis from a trained professional. This type of self-prescribing could potentially have dangerous consequences as untrained professionals would most likely be unaware of any safety implications of CHMs.

Secondly, as the CHMs were bought and prescribed from a variety of sources, it is unknown if there was any contamination of the CHMs with western pharmaceuticals, heavy metals, or incorrect herb substitutions, which makes it difficult to be certain about the apparent teratogenicity of Huang Lian or An Tai

Yin. Overall, the study was very well reported and designed. However, the authors didn't state the exact number of women in the study who took CHMs, only a percentage. There was a small number lost to follow up but this was partially covered by searching national registers of health insurance and death, which found an extra 55 cases for analysis.

Chuang et al, (2006a) – Huang Lian and Foetal Growth

This study analysed 9895 women in Taiwan and looked at the impact of Huang Lian on foetal growth and birth weight. The most common dosage was 0.3-0.5g daily taken at various stages of gestation. There was no significant adverse effect on foetal growth or birth weight. However, there was a non-significant decreased birth weight and 'small for gestational age' associated with Huang Lian use of more than 56 times, suggesting that a higher cumulative intake could pose a possible risk. This study was very well reported and scored the highest on both the D&B scale - 28/32 and the MH scale - 12/15. It was the only study to detect a clinically important effect with the probability of the difference being due to chance being less than 5%. There was no loss to follow up as data about the newborns was retrieved from the national birth register. Other than lack of blinding and randomisation, this study can be considered of high validity (Downs and Black, 1998).

Objectives

From these studies the main objectives can now be answered:

- **Is there any research which shows serious risks associated with using CHM in pregnancy?** Yes

- **If so, which herbs or herbal formulas should not be used in pregnancy?** Huang Lian and An Tai Yin in the first trimester, and Ci Wu Jia should be avoided completely until further information is obtained.
- **What other adverse events/side effects are associated with using CHM in pregnancy and are they considered an acceptable risk?** No other adverse events were recorded other than the serious ones associated with the above mentioned formulae and Chinese herb.
- **Is CHM safe to use in pregnancy?** Caution should be used with all untested CHMs until further research proves them to be safe. Ren Shen, Si Wu Tang and Dang Gui Shao Yao San have been shown to be safe for use in pregnancy.

Conclusion

The cases of LiDa Dai Dai Hua Jiao Nang, Lei Gong Teng and Herbal Health Tonic cannot be used as reliable information about the safety of CHM in pregnancy. In the former case, the patent medication is widely known to be contaminated with pharmaceutical drugs that are potentially life threatening (Department of Health and Ageing, 2007 and Government of Canada, 2008). Contamination was not tested for which means that meaningful conclusions cannot be drawn from this case. Furthermore, missed miscarriages are often of unknown cause, and are more common in the first trimester (American Pregnancy Association, 2011).

With the case of Lei Gong Teng, there are many possible causes for meningoencephalocele, none of which were even discussed by the authors, or

ruled out. Interestingly, a well known cause of this congenital abnormality is lack of folic acid intake, both before and during pregnancy (World Health Organisation, 2012). As we have no knowledge of the nutritional status of the mother, it is reasonable to speculate that this could have been the cause of the abnormality. Furthermore, as drugs and medications account for less than 1% of teratogens (Chung, 2004), it is almost impossible to implicate Lei Gong Teng as the cause without further information. Moreover, the case didn't score a high enough FBE score to show any possibility of a link between the herb and the adverse reaction.

The Herbal Health Tonic was likely to be the cause of the FAS, however it was not CHM that was to blame, it was the alcohol content of the product. Therefore, this does not give any new or further information about CHM and adverse effects in pregnancy. For these reasons, the first 3 case studies cannot be considered as evidence of adverse reactions as the link between the CHM and the adverse event is too tenuous or non-existent. However, despite this, it would be advisable and common sense for women to avoid slimming medications, excessive alcohol intake and CHMs with known toxicity during pregnancy and if they are trying to conceive.

It is highly likely that Ci Wu Jia intake during pregnancy can cause neonatal androgenisation. As this information has been derived from single case study, the likelihood of pregnant women taking Ci Wu Jia to experience this adverse reaction is unknown. It could be a rare or a common occurrence. Therefore, until further research has been carried out, it would be advisable to avoid this remedy in pregnancy.

According to Leung *et al.,* (2002) there is no significant increase in risk of congenital abnormalities with women taking CHMs or WPP. Conversely, Chuang *et al.,* (2006b) found an increased risk of malformation of the nervous system, and possibly the external genital organs, in babies whose mothers had taken Huang Lian. An Tai Yin intake was also associated with congenital malformations of the musculoskeletal and connective tissues, and of the eye. Interestingly, there was no associated risk of congenital abnormalities with Ren Shen, Si Wu Tang or Dang Gui Shao Yao San ingestion in pregnancy. Furthermore, Chuang *et al*., (2006a) found that there was no significant adverse effect on foetal growth or birth weight in women taking Huang Lian in pregnancy. However, there was a non-significant decreased birth weight and 'small for gestational age' associated with Huang Lian use of more than 56 times, suggesting that a higher cumulative intake could pose a possible risk. Therefore, it can be concluded that until further research has been carried out, pregnant women should avoid Huang Lian and An Tai Yin in the first trimester, and avoid Ci Wu Jia in all stages of pregnancy. They should also be advised to seek professional advice before taking any type of medication and be urged not to self-prescribe. CHM is not without risk and until more is known about the safety of it in pregnancy, great care should be taken.

As discussed previously, toxicity testing for pharmaceutical medicine relies on isolating one chemical component and testing that for safety (Leung, 2006). This is not possible with CHM because the majority of usage is with decoctions, and not only is this a mixture of herbs, each with their own active component/s, but as they are cooked together, the interactions that occur are complex (Zhu, 2006). This complex interaction often reduces the toxicity of certain herbs and is often

intended to have that function (Lan *et al.,* 2011). Therefore, even if one herb is tested and proven teratogenic, when cooked in a decoction it may be safe.

In CHM practice, individual decoctions are often given to patients, therefore it is impossible to test CHMs in the same way that western pharmaceutical medicine is tested. There are a vast number of possible herbal combinations and dosages, further confounded by different preparation methods. Although the research outlined in this review is very informative, as it represents such a small amount of the available CHMs, no firm conclusions can be drawn as to whether or not CHM is safe to use in pregnancy. Therefore, it should only be prescribed with great caution and care, by qualified practitioners. Nevertheless, as argued by Leung (2006) it must not be ignored that there is 3000 years of clinical evidence of the safety and efficacy of CHM, and by utilising this information, practitioners can make informed decisions about which herbs can be safely prescribed in pregnancy.

Words: 7608

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Zhu, Y.P., (2006). *Safety of Chinese Herbal Medicine: Information and Risk Management of Adverse Events.* [online] Amsterdam: European Chamber of Commerce for Traditional Chinese Medicine. Available from: <www.congress.mtc.es/ponencies/Dr.%20ZHU%20You%20Ping.pdf> [Accessed 2 January 2013].

Appendix i – Commonly Used Herbs and Formulae in Pregnancy

Table 1 – Commonly Used Formulae in Pregnancy

Herbal Formula	Ingredients
An Tai Yin *(Calm Foetus Drink)*	Chuan Bei Mu *(Bulbus fritiliariae cirrhosae),* Dang Gui *(Radix angelicae sinensis),* Gan Cao *(Radix glycyrrhize uralensis),* Chuan Xiong *(Radix ligustici wallichii),* Bai Shao Yao *(Radix paeoniae lactiflorae),* Gan Jiang *(Rhizoma ziniberis officinalis),* Qiang Huo *(Radix et rhizoma notopterygii),* Hou Po *(Cortex magnoliae officinalis),* Jing Jie *(Herba seu flos schizonepetae tenuifoliae),* Huang Qi *(Radix astragali membranacei),* Chen Pi *(Pericarpium citri reticulatae),* Ai Ye *(Folium artemisiae argyi),* Tu Si Zi *(Semen cuscutae chinensis)*
Si Wu Tang *(Four Substance Decoction)*	Shu Di Huang *(Radix rehmanniae glutinosae praeparata)*, Bai Shao Yao *(Radix paeoniae lactiflorae),* Dang Gui *(Radix angelicae sinensis),* Chuan Xiong *(Radix ligustici wallichii)*

Chuang *et al.,* 2007

Table 2 – Commonly Used Herbs in Pregnancy

Author	Commonly Used Herbs
Chuang *et al.*, 2007	Pearl Powder *(Margarita),* Huang Lian *(Rhizoma coptidis recens),* Ginseng *(Radix ginseng)*
Wang *et al.,* 2012	Chuan Xiong *(Radix ligustici wallichii),* Chen Pi *(Pericarpium citri reticulatae),* Yi Mu Cao *(Herba leonuri heterophylli),* Bai Zhu *(Rhizoma atractylodis macrocephalae),* Sha Ren *(Fructus amomi),* Xu Duan *(Radix dipsaci asperi),* Tu Su Zi *(Semen cuscutae Chinensis),* Ai Ye *(Folium artemisiae argyi),* Dang Shen *(Radix dodonopsis pilosulae),* Sheng Di Huang *(Radix rehmanniae Glutinosae),* Sang Ji Sheng *(Ramulus loranthi),* Huang Qi *(Radix astragali membranacei),* E Jiao *(Gelatinum corii asini),* Gan Cao *(Radix glycyrrhizae uralensis),* Bai Shao Yao *(Radix paeoniae lactiflorae),* Dang Gui *(Radix angelicae sinensis),* Huang Qin *(Radix scutellariae baicalensis),* Du Zhong *(Cortex eucommiae ulmoidis),* Shu Di Huang *(Radix rehmanniae glutinosae praeparata),* Shan Yao *(Radix dioscoreae oppositae)*

Appendix ii – Full Search Details

Database Searched	Date Searched	Searched From	Search Terms
Medical Literature Analysis and Retrieval System (**MEDLINE**), Alternative Health Research Database (**ALT Healthwatch**) and Allied and Complementary Medicine Database (**AMED**) were searched via EBSCO	14/02/13	Inception to February 2013	(MH "Safety") OR (MH "Teratogens") OR "teratogenicity" OR (MH "Drug Toxicity") OR (MH "No-Observed-Adverse-Effect Level") OR embryotoxicity **AND** (MH "Hypertension, Pregnancy-Induced") OR (MH "Pregnancy Complications, Parasitic") OR (MH "Pregnancy Complications, Hematologic") OR (MH "Pregnancy") OR "pregnancy" OR (MH "Pregnancy Complications, Cardiovascular") OR (MH "Pregnancy Complications, Infectious") OR (MH "Pregnancy Complications, Neoplastic") OR (MH "Pregnancy Trimester, First") OR (MH "Pregnancy Trimester, Second") OR (MH "Pregnancy Trimester, Third") **AND** (MH "Medicine, Kampo") OR (MH "Drugs, Chinese Herbal") OR (MH "Medicine, Chinese Traditional") OR (MH "Medicine, East Asian Traditional") OR (MH "Herbal Medicine")
The Cochrane Library	14/02/13	Inception to February 2013	(Safety OR no-observed-adverse-effect level OR teratogens OR embyrotoxicity) **AND** (pregnancy OR pregnancy complications) **AND** (drugs, Chinese herbal OR medicine, Chinese traditional OR plants, medicinal)
PubMed	14/02/13	Inception to February 2013	(Drugs, Chinese herbal) **AND** (pregnancy OR pregnancy complications) **AND** (adverse effects OR toxicity OR abnormalities drug-induced OR teratogens)
Cumulative Index to Nursing and Allied Health Literature (**CINAHL**) was searched via EBSCO	20/02/13	Inception to February 2013	(MH "Safety") OR (MH "Adverse Health Care Event") OR (MH "Prenatal Exposure Delayed Effects") OR (MH "Adverse Drug Event") OR (MH "Teratogens") **AND** (MH "Pregnancy") OR (MH "Pregnancy Complications, Hematologic") OR (MH "Pregnancy Complications, Neoplastic") OR (MH "Pregnancy Complications, Psychiatric") OR (MH "Pregnancy Trimesters") **AND** (MH "Drugs, Chinese Herbal") OR (MH "Medicine, Chinese Traditional") OR (MH "Medicine, Oriental Traditional")

Appendix iii – Details of Search Inclusions and Exclusions

Figure 1 – Flow Chart of Study Selection Process

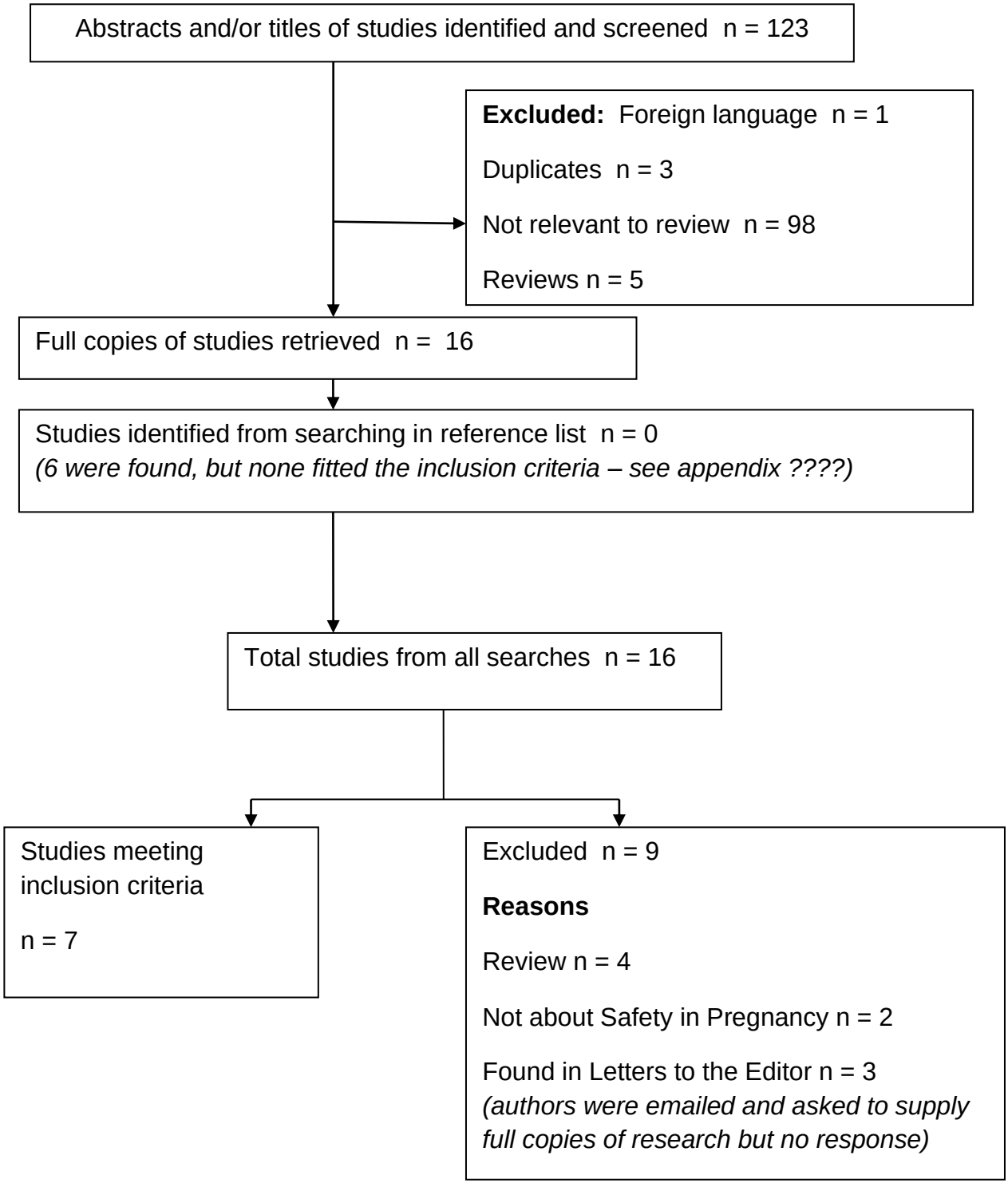

Table 1 – Details of Each Database Search Inclusions and Exclusions

Database Searched	Search Retrieved	Abstracts Immediately Excluded	Total Full Text Papers Sourced	Full Text Papers Excluded and Reasons Why	Full Text Papers Retrieved
MEDLINE, AMED & Alt Healthwatch	16	7 = not relevant	9	4 All reviews	5
CINAHL	1	1 = not relevant	0	0	0
Pubmed	101	94 3 = duplicates 1 = foreign language 90 = not relevant	7	5 2 = Not about safety and pregnancy 3 = Letters to the editor and of the 2 that were research studies, they could not be sourced in full despite emailing the authors	2
Cochrane Library	5	5 = reviews	0	0	0
Totals:	123	107	16	9	7

Excluded Due to Foreign Language:

Shi, J.M., Xu, B.L., Ruan, J.W., Zhang, W.J., (1988). Pharmacological and toxicological effects of compound jimu oral liquid. *Zhong Yao Tong Bao.* **13** (2), 39-41. [online] Available from: Pubmed <http://www.ncbi.nlm.nih.gov/pubmed/3262018> [Accessed 14 February 2013].

Full Text Papers Excluded

Sixteen full text papers were looked at in detail, nine were excluded. Full details of exclusions are given below:

Not Fully Published Research Study/Opinions and Comments Found in Letters to the Editor (3)

Awang, D.V.C., (1991). Maternal Use of Ginseng and Neonatal Androgenization. *Journal of American Medical Association.* **265** (14), 1828. [online] Available from: Pubmed <http://www.ncbi.nlm.nih.gov/pubmed/2056644> [Accessed 2 March 2013].

Chuang, C.H., Lai, J.N., Wang, J.D., Chang, P.J., Chen, P.C., (2007). Use of Traditional Chinese Herbal Medicines During Early Pregnancy in Mainland China. *Pharmacoepidemiology and Drug Safety.* **16,** 942-945. [online] Available from: Wiley Online Library <http://onlinelibrary.wiley.com/doi/10.1002/pds.1413/abstract> [Accessed 25 February 2013].

Chuang, C.H., Doyle, P., Wang, J.D., Chang, P.J., Lai, J.N., Chen, P.C., (2009). Herbal Medicines During Pregnancy and Childhood Cancers: An Analysis of Data from a Pregnancy Cohort Study. *Pharmacoepidemiology and Drug Safety.* **18,** 1119-1120. [online] Available from: Wiley Online Library <http://onlinelibrary.wiley.com/doi/10.1002/pds.1835/pdf> [Accessed 9 March 2013].

Not About Safety in Pregnancy (2)

Chen, X. and Chen, S.L., (2011). A Woman with Premature Ovarian Failure Induced by Tripteryium Wilfordii Hook.f. Gives Birth to a Healthy Child. *Fertility and Sterility.* **96** (1) 19-21. [online] Available from: <http://www.ncbi.nlm.nih.gov/pubmed/21640345> [Accessed 25 February 2013].

Nambiar, S., Schwartz, R.H., Constantino, A., (1999). Hypertension in Mother and Baby Linked to Ingestion of Chinese Herbal Medicine. *Western Journal of Medicine.* **171** (3), 152. [online] Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1305794/> [Accessed 25 February, 2013].

Review – Not Primary Research (4)

Allaire, A.D., (2001). Complementary and Alternative Medicine in the Labor and Delivery Suite. *Clinical Obstetrics and Gynecology.* **44** (4), 681-91. [online] Available from: <http://www.ncbi.nlm.nih.gov/pubmed/11600851> [Accessed 25 February 2013].

Gallow, M., Einarson, A., Koren, G., (2003). Herbal Medicine Use in Pregnancy: A New Frontier in Clinical Teratology. *Birth Defects Research.* **68** (6), 499-500. [online] Available from: <http://www.ncbi.nlm.nih.gov/pubmed/14745986> [Accessed 25 February 2013].

Gossler, S.M., (2010). Use of Complementary and Alternative Therapies During Pregnancy, Postpartum, and Lactation. *Journal of Psychosocial Nursing and Mental Health Services.* **48** (11), 30-6. [online] Available from: <http://www.ncbi.nlm.nih.gov/pubmed/21053788> [Accessed 25 February 2013].

Jurgens,, T.M., (2003). Potential Toxicities of Herbal Therapies in the Developing Fetus. *Birth Defects Research.* **68** (6), 496-8. [online] Available from: <http://www.ncbi.nlm.nih.gov/pubmed/14745985> [Accessed 25 February 2013].

Hand Searching of Reference Lists

Six papers were found, none were included, reasons are given below:

Nothing About Safety of Chinese Herbal Medicine (2)

Chuang, C.H., Chang, P.J., Hsieh, W.S., Tsai, Y.J., Lin, S.J., Chen, P.C., (2009a). Chinese Herbal Medicine Use in Taiwan during Pregnancy and the Postpartum Period: A Population-Based Cohort Study. *International Journal of Nursing Studies.* **46,** 787-795. [online] Available from: <http://ntur.lib.ntu.edu.tw/bitstream/246246/161150/1/28.pdf> [Accessed 25 February 2013].

Yeh, H.Y., Chen, Y.C., Chen, F.P., Chou, L.F., Chen, T.J., Hwang, S.J., (2009). Use of Traditional Chinese Medicine Among Pregnant Women in Taiwan. *International Journal of Gynecology and Obstetrics.* **107** (2), 147-50. [online] Available from: Pubmed <http://www.ncbi.nlm.nih.gov/pubmed/19716133> [Accessed 25 February 2013].

Nothing about Chinese Herbal Medicines (1)

Nordeng, H. and Havnen, G.C., (2004). Use of Herbal Drugs in Pregnancy: A Survey Among 400 Norwegian Women. *Pharmacoepidemiology and Drug Safety.* **13,** 371-380. [online] Available from: Wiley Online Library <onlinelibrary.wiley.com/doi/10.1002/pds.945/pdf> [Accessed 25 February 2013].

Reviews – Not Primary Research (3)

Ernst, E., (2002a). Herbal Medicinal Products During Pregnancy: Are They Safe? *International Journal of Obstetrics and Gynaecology.* **109,** 227-235. [online] Available from: Wiley Online Library < http://onlinelibrary.wiley.com/doi/10.1111/j.1471-0528.2002.t01-1-01009.x/pdf> [Accessed 30 December 2012].

Seeley, D., Dugoua, J.J., Perri, D., Mills, E., Koren, G., (2008). Safety and Efficacy of *Panax Ginseng* During Pregnancy and Lactation. *Canadian Journal of Clinical Pharmacology.* **15** (1), 87-94. [online] Available from:<www.cjcp.ca/cjcp07034reviewf_e87-e94-r101696> [Accessed 25 February 2013].

Tiran, D., (2003). The Use of Herbs by Pregnant and Childbearing Women: A Risk-Benefit Assessment. *Complementary Therapies in Nursing and Midwifery.* **9,** 176-181. [online] Available from: <https://notendur.hi.is/~irv1/5.%C3%A1r/Kvenna/n%C3%A1tt%C3%BAruefni_og_me%C3%B0ganga/The_use_of_herbs_by_pregnant.pdf> [Accessed 26 February 2013].

Appendix iv – Assessment Scales

McHarm Assessment Scale Results

McHarm Question	Record Number						
	MED 2	**MED 7**	**PUB 3**	**PUB 8**	**PUB 10**	**PUB 11**	**PUB 13**
Were the Harms Pre-Defined Using Standardized or Precise Definitions?	Yes	Yes	No	Yes	No	No	No
Were Serious Events Precisely Defined?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were Severe Events Precisely Defined?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were the Number of Deaths in Each Study Group Specified or Were the Reason(s) for Not Specifying Them Given?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Was the Mode of Harms Collection Specified as Active?	Yes	Yes	No	Yes	No	No	No
Was the Mode of Harms Collection Specified as Passive?	No	No	No	No	No	No	No
Did the Study Specify Who Collected the Harms?	No	Yes	No	Yes	Yes	No	Yes
Did the Study Specify the Training or Background of Who Ascertained the Harms?	No	Yes	No	Yes	No	No	Yes
Did the Study specify the Timing and Frequency of Collection of the Harms?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Did the Author(s) Use Standard Scale(s) or Checklist(s) for Harms Collection?	Unsure	Yes	No	Yes	No	Yes	No
Did the Authors Specify if the Harms Reported Encompass All the Events Collected or a Selected Sample?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Was the Number of Participants that Withdrew or Were Lost to Follow-Up Specified for Each Study Group?	No	No	No	Yes	No	No	No
Was the Total Number of Participants Affected by Harms Specified for Each Study Arm?	Yes	No	Yes	No	Yes	Yes	Yes
Did the Author(s) Specify the Number for Each Type of Harmful Event for Each Study Group?	Yes	Yes	Yes	No	Yes	Yes	Yes
Did the Author(s) Specify the Type of Analyses Undertaken for Harms Data?	Yes	Yes	No	Yes	No	Yes	Yes
Total Score: (Yes = 1 No = 0 Unsure = 0)	10	12	7	12	8	9	10

(Cochrane Bias Methods Group, 2013)

Downs & Black Assessment Scale Results

Downs & Black Question	Record Number		
	Pub 8	Med 7	Med 2
Quality			
Is the Hypothesis/Aim/Objective of the Study Clearly Described?	1	1	1
Are the Main Outcomes to be Measured Clearly Described in the Introduction or Methods Section?	1	1	1
Are the Characteristics of the Patients Included in the Study Clearly Described?	1	1	1
Are the Interventions of Interest Clearly Described?	1	1	1
Are the Distributions of Principal Confounders in Each Group of Subjects to be Compared Clearly Described?	2	2	1
Are the Main Findings of the Study Clearly Described?	1	1	1
Does the Study Provide Estimates of the Random Variability in the Data for the Main Outcomes?	1	1	1
Have All Important Adverse Events that May Be a Consequence of the Interventions Been Reported?	1	1	1
Have the Characteristics of Patients Lost to Follow-Up Been Described?	1	0	0
Have Actual Probability Values Been Reported for the Main Outcomes Except Where the Probability Value is Less Than 0.001?	1	1	1
Total:	**11**	**10**	**9**
External Validity			
Were the Subjects Asked to Participate in the Study Representative of the Entire Population from Which They Were Recruited?	1	1	1
Were Those Subjects Who Were Prepared to Participate Representative of the Entire Population from Which They Were Recruited?	1	1	1
Were the Staff, Places and Facilities Where the Patients Were Treated, Representative of the Treatment the Majority of Patients Receive?	1	1	1
Total:	**3**	**3**	**3**
Internal Validity - Bias			
Was an Attempt Made to Blind Study Subjects to the Intervention They Have Received?	0	0	0
Was an Attempt Made to Blind Those Measuring the Main Outcomes of the Interventions?	0	0	0
If Any of the Results of the Study Were Based on "Data Dredging", Was This Made Clear?	1	1	1
In Trials and Cohort Studies, Do the Analyses Adjust for Different Lengths of Follow-up of Patients, or in Case-Control Studies, is the Time Period Between the Intervention and Outcome the Same for Cases and Controls?	1	1	1

Were the Statistical Tests Used to Assess the Main Outcomes Appropriate?	1	1	1
Was Compliance with the Intervention/s Reliable?	1	1	1
Were the Main Outcome Measures Used Accurate (Valid and Reliable)?	1	1	1
Total:	**5**	**5**	**5**
Internal Validity - Confounding (Selection Bias)			
Were the Patients in Different Intervention Groups (Trials and Cohort Studies) or Were the Cases and Controls (Case-Control Studies) Recruited from the Same Population?	1	1	1
Were Study Subjects in Different Intervention Groups (Trials and Cohort Studies) or Were the Cases and Controls (Case-Control Studies) Recruited Over the Same Period of Time?	1	1	1
Were Study Subjects Randomised to Intervention Groups?	0	0	0
Was the Randomised Intervention Assignment Concealed from Both Patients and Health Care Staff Until Recruitment Was Complete and Irrevocable?	0	0	0
Was There Adequate Adjustment for Confounding in the Analyses from Which the Main Findings Were Drawn?	1	1	0
Were Losses of Patients to Follow-Up Taken into Account?	1	0	0
Total:	**4**	**3**	**2**
Power			
Did the Study Have Sufficient Power to Detect a Clinically Important Effect Where the Probability Value for a Difference Being Due to Chance is Less Than 5%?	5	0	0
Total:	**5**	**0**	**0**
Grand Total:	**28/32**	**21/32**	**19/32**

(Downs and Black, 1998)

Fugh-Berman & Ernst Assessment Scale Results

Fugh-Berman & Ernst Scale	Record Number			
	Pub 3	**Pub 10**	**Pub 11**	**Pub 13**
Adequate Patient History (including age, sex, relevant medical conditions)	0	0	0	0
Concurrent Diseases, Conditions, or Medications Associated with an Adverse Event	1	0	1	1
Concomitant Medications are Documented	0	0	1	1
Description of Interactors is Adequate	0	0	1	1
Obvious Alternative Explanations Have Been Excluded	0	0	1	1
Chronology is Complete	1	1	1	1
Time Sequence of Drug Administration to Adverse Event is Reasonable	1	1	1	1
Adverse Event is Adequately Described	1	1	1	1
Event Ceases on Stopping the Drug	0	0	0	1
Event Recurs on Rechallenge	0	0	0	0
Total Score:	4	3	7	8

Scoring:

0-3 = Unevaluable - Report contains inadequate information to assess the likelihood of an interaction

4-7 = Possible - Report provides some evidence for an interaction, but there may be other causes of the event

8-10 = Likely - The report is well documented and appears to provide reliable evidence for an interaction

(Fugh-Berman and Ernst, 2001)