

Safe Use of Herbs in Pregnancy - Phytotherapy Review & Commentary

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The safe use of herbal medicines during pregnancy is becoming an increasingly contentious issue. On the one hand, regulatory authorities appear to be adopting the policy that if there is no clear evidence of safety from controlled clinical trials, then an herb should not be recommended during pregnancy. This was well illustrated by some recent deliberations of the Complementary Medicines Evaluation Committee (CMEC) of the Australian Therapeutic Goods Administration (TGA). CMEC was assessing the safe use of over-the-counter products containing kava (*Piper methysticum*) and came to the conclusion, despite the lack of evidence for harm from kava during pregnancy, that kava products should carry the following warning: "Not for prolonged use. If symptoms persist seek advice from a health care practitioner. Those who are pregnant or nursing are not recommended to use Kava." The American Herbal Products Association also suggests that professional advice should be sought before using kava during pregnancy.

If this condition is applied to all commonly used herbs, then probably only ginger, which has been trialled for hyperemesis gravidarum, and senna and ginseng would not need to carry such a warning. Ironically, some herbal and scientific authors believe that these three herbs are contraindicated in pregnancy.

On the other hand, some scientists with little clinical experience in prescribing herbs have speculated about harmful effects which might ensue from the use of herbs during pregnancy. They appear to adopt the stance that even if a negative effect from an herb is only remotely possible (I would add, highly unlikely), then that herb should not be taken during pregnancy. The unspoken assumption here is that herbs are only marginally efficacious, if at all, so even the remotest risk during pregnancy is unacceptable. This approach is exemplified by the list provided in the book by Newall and co-authors. (1) According to these authors, the following innocuous herbs are contraindicated in pregnancy (their reasons are provided in parentheses):

- * Agnus castus (hormonal action)
- * Burdock (uterine stimulant in vivo)
- * Calendula (reputed to affect menstrual cycle, uterine stimulant in vivo)
- * German chamomile (reputed to affect menstrual cycle, uterine stimulant with excessive use)
- * Corn silk (uterine stimulant in vitro)
- * Damiana (risk of cyanide toxicity in high doses)
- * Fenugreek (oxytotic, uterine stimulant in vitro)
- * Gentian (reputed to affect menstrual cycle)
- * Ginseng (hormonal activity)
- * Hawthorn (uterine activity)
- * Nettle (reputed abortifacient etc)

And so the list goes on. Much of this list was compiled by extrapolating from pharmacological experiments where the herb is injected in very high doses, or from experiments where the herb in very high concentrations is infused through isolated organs. Clearly these types of experiments are of little relevance in a careful assessment of safety.

Even some herbalists have adopted a conservative stance. In his book entitled *Herb Contraindications and Drug Interactions*, Francis

Brinker suggests that the following relatively innocuous herbs are unsafe to take during pregnancy: alfalfa, lemon balm, basil, black pepper, burdock, calendula, catnip, chamomile, dill, fennel, fenugreek, flaxseed, garlic, gotu kola, lavender, licorice, passionflower, and St John's wort. (2) Ironically, many of these herbs are enjoyed as foods, teas or spices by the general populace, including pregnant women. How is it that an herb which is regarded as completely safe by herbalists, the general public and regulatory authorities, suddenly becomes so dangerous when a woman is pregnant?

Essentially, the list of herbs which are safe to take during pregnancy is determined by the stance which is taken. If you require evidence of safety from controlled clinical trials in pregnant women, then that list is very short. If you wish to take a speculative approach, then you should not use many herbs during pregnancy, because it is very likely that most plants will contain some compound which, when given in massive doses under highly artificial conditions, will show some effect which could be construed to be detrimental during pregnancy. To be consistent, you would also recommend that your patients refrain from taking most plant foods during their pregnancy as well.

The stance which is adopted in this article is neither of the above. Instead, the traditional knowledge about the safe use of herbs during pregnancy is combined with a meaningful interpretation of modern pharmacological data to provide an approach which is cautious, but rational.

Types of Risks

The following risks could be associated with use of an herb during pregnancy:

1. Toxicity to the mother, which might also indirectly impair the health or development of the child.
2. Toxicity to the child.
3. Developmental malformations (teratogenesis).
4. Increased risk of miscarriage.
5. Poor postnatal health of the child.

With herbal medicines, if known toxic herbs are avoided, then toxicity effects should not occur (apart from idiosyncratic reactions). Teratogenicity, with a few notable exceptions, does not appear to be caused by herbs, although this area is poorly studied. Increased risk of miscarriage is the area of most concern for herbal medicine. One reason for this is that herbalists have promoted the concept of "emmenagogue." Emmenagogues are often abortifacients. The usefulness of this concept will be examined later. Many of the herbs which are listed not to use in pregnancy are emmenagogues. (This contrasts with conventional drugs where abortifacient effects are of the least concern).

Sometimes an herb traditionally comes with a caution for pregnancy and it is difficult to understand why. One reason could be that the herb adversely affects the postnatal health of the child. For example, berberine-containing herbs such as Hydrastis and Berberis are not recommended for use during pregnancy. (3) A Chinese study investigating the effect of berberine on protein binding of bilirubin in vitro found that berberine exerted a 10-fold effect in comparison to phenylbutazone, a potent displacer of bilirubin. (3) Hence, chronic use of berberine-containing herbs during pregnancy might increase the risk of neonatal jaundice by decreasing the clearance of bilirubin from the body.

Safety During Pregnancy

Although, in general, it is safe to prescribe certain herbs in pregnancy, this should only be done if they are necessary. All medication should be especially kept to a minimum in the first three months of pregnancy, although it is quite acceptable to judiciously use herbs to treat morning sickness and threatened miscarriage during this period.

Caution with the use of herbs should be particularly exercised where there is a past history of miscarriage or difficult conception. A recent history of low back pain with bearing down abdominal pain, or vaginal discharge or bleeding, should be regarded as a potential

miscarriage and treated very cautiously.

There is not a great deal of consensus about which herbs are safe during pregnancy. Hence some authorities may dispute some of the advice contained here. As outlined above, many concerns have arisen from coincidence or from the use of inherently dangerous doses which have little relevance to normal therapy. A number of commonly accepted "truths" are open to question. For example, old pharmacopeias carry warnings about the use of Aloes resin, an anthraquinone-based laxative, during pregnancy. It was said to cause miscarriage. However a well-documented case history of a woman who took large quantities of Aloes revealed that it resulted in little more than slight vaginal bleeding. (4) Similarly there is no evidence that senna (*Cassia senna*) is unsafe during pregnancy. (5) In fact there is evidence to the contrary. Nonetheless it is preferable to allow a large margin for safety, and the following guidelines are best observed:

- * Do not prescribe an herb to a pregnant woman unless you are both familiar and experienced with its use.

- * Known toxic or poisonous plants (such as those with a poison classification) should be avoided. These include *Bryonia* (bryony), *Aconitum* (aconite), *Sanguinaria* (blood root), *Ephedra* and *Phytolacca* (poke root). Some herbs, such as *Lobelia* and *Gelsemium* may be used during childbirth. See the appendix for the list of potentially toxic herbs which in addition should not be used in pregnancy. (There might be some overlap between this appendix and the list given below.)

- * Pure herbal volatile (essential) oils should not be taken internally during pregnancy. This is because volatile oils are a highly concentrated dosage form and the risk of excessive doses is accordingly much greater, e.g. *Matricaria* (chamomile) contains only 0.5% volatile oil, so the pure oil is 200 times stronger than the dried herb. The exception here is low quantities of oils used in flavouring such as spearmint, peppermint, aniseed, orange etc.

- * Any herb which is described as an emmenagogue should not be given in high doses (more than 1 g a day). Most of these herbs are best avoided.

- * Additional herbs (to the list of potentially toxic herbs) not to be used in pregnancy (or to be used with caution) are listed below. Suggested classification according to the Australian TGA system has been provided (see the table for explanation). Category A means that the treatment is considered safe to use by pregnant women. This system allows for discretionary use of treatments in categories B, C and D provided it is felt that there is sufficient benefit from the treatment. A high dose as defined in the list is more than 1 g per day or its equivalent, e.g. 2 mL of a 1:2 extract, 5 mL of a 1:5 tincture etc. No list can be totally comprehensive. The focus during the compilation of this list was on commonly used herbs. If in doubt, consult authoritative texts and journals.

- * Laxative herbs in high doses should be avoided, although as noted above these are probably safe even in high amounts. They include *Aloe barbadensis* (Aloes resin), *Rhamnus purshiana* (cascara), *Cassia* species (senna) and *Rheum officinale* (rhubarb). The Commission E (an expert German government committee) is of the opinion that all these herbs containing anthraquinone-type laxative agents are contraindicated in pregnancy.

- * Apart from this consideration with laxative herbs, the above list is in general agreement with the Commission E recommendations. (6) However, the Commission E additionally cautions against ginger, kava and parsley leaf during pregnancy at any dose. These cautions appear to have little basis in fact, although excessive intake of these herbs should be avoided.

- * Some misinformation exists about the safety of herbs in pregnancy. *Apium* (celery seed) is thought by many to be unsafe because it contains apiol. However, the level of apiol in *Apium* is negligible. In contrast, some chemotypes of *Petroselinum* (parsley) contain high levels of apiol. The name apiol was derived from an old botanical name for parsley, not celery.

- * Sometimes substitution of an herb makes it unsafe during pregnancy. For example *Teucrium* (germander) substituted for *Scutellaria* (skullcap) would be a safety concern. Also buchu is often listed as unsafe in pregnancy. At doses less than 2 g per day this is not so, provided that the species used is *Barosma betulina*. Only other species of *Barosma*, which are used as substitutes, contain high levels of the toxic compound pulegone in their essential oil.

- * *Rubus idaeus* (raspberry leaf) and to a lesser extent *Mitchella* (squaw vine) have a special role to play in pregnancy. However it is

best to avoid their use in the first trimester. This is because they have a reputation as uterine stimulants, which is probably doubtful, except near term. However in the event of a miscarriage they may be blamed, so a prudent approach should apply.

Emmenagogues

In herbal medicine, the term emmenagogue is often used to describe herbs reputed to "bring on the menses" or "stimulate menstrual flow." They are indicated for "delayed menstruation" and are contraindicated in pregnancy. It is no coincidence that many emmenagogue herbs are also abortifacients. In other words, emmenagogues "brought on the menses" when they were delayed by pregnancy. The term was a convenient euphemism for times not as liberal as these. Clearly, in any pharmacological sense, there is no justification for the use of a substance which will terminate pregnancy for the correction of secondary amenorrhea from other causes.

In the context of herbs containing essential oils, the term emmenagogue often causes confusion. The logic which creates this confusion is something like the following:

- a. Essential-oil-containing, emmenagogue herbs such as tansy, thuja and pennyroyal cause abortion in high doses by stimulating uterine contraction.
- b. Hence these are agents which pharmacologically stimulate the uterus to contract.
- c. Therefore, in a susceptible pregnant woman, even a low dose might stimulate uterine contraction and cause an abortion.
- d. Hence even low doses of these herbs must be avoided during pregnancy because there is a risk of abortion.

While statement a) is correct, b), c) and d) are not. Pharmacological studies (admittedly rather old) show that low doses of these oils have no effect on uterine muscle, and in large doses cause uterine relaxation. (7,8) One group of authors concluded the following: (8) "It would seem that the emmenagogue oils in very small amounts have no action at all on the uterus. In higher concentrations such as could never be reached in the blood without producing dangerous, probably fatal, poisoning, they inhibit the uterine movements.

"When abortion occurs after their use, it is probably an indirect result of the severe irritation and inflammation of the bowel and kidney. This may induce congestion and reflex movements of the uterus which may in some cases result in abortion.

"The absence of specific stimulant action of these oils on the uterus renders them all the more dangerous poisons, as, after their failure in ordinary doses, large doses are sometimes taken, resulting in frequent poisoning in a large proportion of cases without the production of abortion."

In other words, the abortifacient effect is an indirect toxic activity rather than a direct pharmacological one. The above conclusions are borne out by published case studies on pennyroyal oil which showed that single doses of about 10 g often did not induce abortion, but resulted in severe liver damage. (9,10) However, it still holds that even small doses of these oils or the herbs which contain them should be avoided in pregnancy, but because they are toxic and not because there is a risk of abortion. The corollary is also true that these essential oils are very uncertain and dangerous abortifacients and should never be used in this context.

Other emmenagogue herbs may be progesterone antagonists and should also be avoided during pregnancy.

The Issue of Phytoestrogens

The medical world still lives in fear of another diethylstilbestrol (DES). This was a potent synthetic non-steroidal estrogen, liberally used in the 1940-1960 period for the purpose of treating threatened abortion, toxemia of pregnancy and gestational diabetes.

In the 1970s there was a noticeable increase in the incidence of a very rare clear cell adenocarcinoma of the vagina. These tumours were found to occur in women whose mothers had been treated with DES during pregnancy. The female embryos were thus exposed to DES during organogenesis. Other anomalies of the female reproductive tract have been reported.

Many plants contain substances which are weakly estrogenic, known as phytoestrogens. The phytoestrogens can be divided into five main chemical classes:

1. flavonoids, especially isoflavonoids
2. lignans
3. saponins
4. sterols
5. some essential oils are also estrogenic e.g. fennel, clary sage

Moreover, one of the richest sources of phytoestrogens is the soy bean. If phytoestrogen intake did represent a real risk during pregnancy, then problems similar to those caused by DES should be higher in countries where soy is a staple. These have not been reliably observed.

There is a concern in some circles that phytoestrogens may act like DES and cause toxic effects on the female tract in utero. In fact a Brisbane, Australia gynecologist carries the warning in his surgery that "Herbal Medicines May Harm Your Unborn Child." However, the important consideration is that phytoestrogens are weakly estrogenic, whereas DES is so powerful that it depresses serum gonadotropin levels and induces uterine growth in relatively small doses. A sheep living on *Trifolium* spp. (which contain isoflavonoid phytoestrogens) might show these effects, but they do not occur with normal human consumption of phytoestrogens from either food or herbal medicine.

Nonetheless, it is best to take a cautious stance until further research is carried out. Therefore herbs containing phytoestrogens should not be prescribed during pregnancy unless there is a clear benefit from their use. Also, intake of foods rich in phytoestrogens such as soy products, flaxseeds, alfalfa and red clover tea and some seed oils such as pumpkin seed oil, should not be excessive during pregnancy.

Teratogenic Plants

Knowledge about teratogenicity usually comes from animal studies under controlled experimental conditions. Very few herbal medicines have been studied under these conditions. The following gives a review of the most pertinent studies to date.

The teratogenicity of *Scutellaria baicalensis* (Baical skullcap) was studied in rats. Three dosages were used -- 0.25 g/kg (group I), 12.49 g/kg (group II) and 24.98 g/kg (group III). There was an increase in the incidence of skeletal variations (lumbar rib). This was only marked for groups II and III. There was also a dose-dependent increase in dilation of the ureter. There were no significant differences for the other parameters tested. (11) The normal human dose for Baical skullcap is about 0.05 g/kg. Given the above results it would be prudent not to use Baical skullcap for extended periods during early pregnancy, however, more studies are needed to draw definitive conclusions about any teratogenic effect from Baical skullcap.

The Ayurvedic herb *Boerhaavia diffusa* had no teratogenic effect on rats at 0.25 g/kg. (12)

Anti-teratogenic effects have been demonstrated for herbs. For example, *Eleutherococcus* (Siberian ginseng) abolished the embryotoxic and teratogenic effects of ethanol manifested against the background of iron deficit in pregnant female rats. (13) A Japanese herbal formula containing *Paeonia lactiflora*, *Bupleurum*, *Zingiber*, *Glycyrrhiza*, *Panax*, *Scutellaria baicalensis* and other herbs abolished the teratogenicity of sodium valproate in rats. (14)

One human use of an herbal product has been linked to a suspected teratogenic effect. *Podophyllum* resin (American mandrake) was applied 5 times for a duration of 4 hours from the 23rd to the 29th week of pregnancy. At birth, a simian crease on the left hand and a preauricular skin tag were noted. (15)

Knowledge about teratogenic effects from leaves, bark and fruits of plants has come from the observation of grazing animals. It should be kept in mind that in these circumstances the intake of the herb by the animal can be quite large and the animals are consuming parts of the plant which may not be used by humans. In fact several of these plants are known poisons and human intake is specifically avoided. On the basis of these observations and resultant experiments, three categories have been assigned: (16-18)

1. Known teratogens in known teratogenic plants -- Lupinus, Veratrum, Conium and Solanum species
2. Known teratogenic plants with unidentified teratogens -- Astragalus, Nicotiana, Ferula and Trachymene species
3. Suspected teratogenic plants -- Datura, Prunus, Sorghum and Senecio species.

Although solanine and other compounds found in potatoes are teratogens in animals, pregnant women are not advised to avoid potatoes!

It is unlikely that the root of Astragalus used in herbal medicine is teratogenic since the species of Astragalus which induce teratogenic effects are known to be toxic. Moreover, a formula containing Astragalus and Rehmannia (Man-Shen-Ling) did not exhibit teratogenic effects. (19)

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Australian TGA Classification for Risk During Pregnancy

Category A: Drugs used by a large number of pregnant women without detrimental effects to the fetus

Category B1: Drugs taken by only a limited number of pregnant women without apparent harm and no evidence of harm from animal studies

Category B2: As for B1 but animal studies are inadequate or lacking, but do not indicate harm

Category B3: As for B1 but animal studies have shown evidence of fetal damage, the significance of which is considered uncertain in humans

Category C: Drugs which because of their pharmacological properties have caused, or might be expected of causing, harmful effects on the human fetus or neonate, without causing malformations. Effects may be reversible.

Category D: Drugs which have caused or suspected to cause an increased frequency of malformation or irreversible damage

Category X: Drugs which have a high risk of causing permanent damage to the fetus

Note:

* For drugs in B1, B2 or B3 documented human data are lacking or inadequate and subcategorization is based on available animal data.

* The allocation of a B category does not imply greater safety than C.

Achillea millefolium (yarrow) - thujone-containing varieties in high doses	D for high doses
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Adhatoda vasica is contraindicated in pregnancy except at birth	D
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Aesculus hippocastanum (horsechestnut) in high doses	C for high doses
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Andrographis paniculata is contraindicated in pregnancy	B3
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Angelica sinensis (dong quai) is contraindicated in first trimester of pregnancy and tendency to spontaneous abortions	C
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Angelica archangelica (angelica) in high doses	C for high doses
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Arctostaphylos uva-ursi (bearberry)	C
Artemisia species except in doses less than 500 mg per day or equivalent	D for high doses
Berberis species (barberry) in high doses	C for high doses
Caulophyllum thalictroides (blue cohosh)	D
Chelidonium majus (greater celandine) except in doses less than 1 g per day or equivalent	C for high doses
Cinnamomum species (cinnamon) except in low doses as spices	C
Corydalis ambigua	C
Crocus sativus (saffron) except in low doses as a spice	C
Embelia ribes	C
Glycyrrhiza glabra (licorice) in doses higher than 3 g per day	C for high doses
Hydrastis canadensis (golden seal) in high doses	C for high doses
Juniperus communis (juniper)	C
Lycopus species (bugleweed or gypsywort)	C
Mentha pulegium (pennyroyal)	D
Myristica fragrans (nutmeg) except in low doses as a spice	D
Panax notoginseng	C
Petroselinum crispum (parsley) root or seed	D

<i>Peumus boldus</i> (boldo)	X
<i>Pulsatilla vulgaris</i> (pasque flower)	D
<i>Ruta graveolens</i> (rue)	D
<i>Salvia miltiorrhiza</i>	C
<i>Salvia officinalis</i> (sage) -- thujone-containing varieties	D
<i>Sarothamnus scoparius</i> (broom tops)	D
<i>Schisandra chinensis</i> except in last 6 weeks to assist with birth	C
<i>Solanum</i> species	X
<i>Tanacetum parthenium</i> (feverfew) except in doses less than 500 mg per day or equivalent	C
<i>Tanacetum vulgare</i> (tansy)	D
<i>Thuja occidentalis</i>	D
<i>Tribulus terrestris</i>	C
<i>Tylophora indica</i>	D
<i>Urginea</i> species (squill)	C
<i>Vinca</i> species (periwinkles) in high doses	D
<i>Viscum album</i> (mistletoe) except in last 6 weeks to assist with birth	C
<i>Zingiber officinale</i> (ginger) except in doses less than 2 g per day or equivalent of dried rhizome	C in high doses

Appendix: Toxic or Potentially Toxic Herbs -- Not to be taken during pregnancy

(Categories D or X - see table for explanation of categories)

Abrus precatorius seed and root	Jequirity
Aconitum species	Aconite
Acorus calamus	Sweet Flag
Adonis vernalis	
Ammi visnaga	
Apocynum	
Aristolochia (all or any species)	Snakeroot, Birthwort
Arnica (all or any species), other than for external use	Arnica
Arum maculatum	Cuckoopint, Lords-and-Ladies
	Deadly nightshade
Belladonna	
Brugmansia	
Brunfelsia uniflora	Manaca, Mercury
Calotropis	
Catha edulis	Khat
Chenopodium ambrosioides	Wormseed oil
Cicuta virosa	Cowbane
Cinchona	Quinine Bark
Colchicum	
Convallaria	Lily of the Valley
Coronilla	
Crotalaria (all or any species)	
Croton (all or any species)	Cascarilla, Croton
Cynoglossum officinale	Hounds tongue
Daphne mezereum	Mezereum
Datura	Jimson weed
Digitalis	Foxgloves
Dryopteris filix-mas	Male fern
Duboisia	
Echium vulgare	Viper's bugloss
Ephedra (ephedrine)	Ma Huang
Erysimum	
Euonymus europaeus	European spindle tree
Galanthus	Snowdrop
Gelsemium	
Heliotropium (all or any species)	Heliotrope
Helleborus (all or any species)	Hellebore
Hyoscyamus	Henbane
Lantana camara	Lantana
Larrea species	Chaparral
Lathyrus sativus, other than the cooked seed	Grass pea
Lithospermum (all or any species)	
Lobelia	
Mandragora	Mandrake
Menispermum canadense	Yellow parilla

Mentha pulegium	Pennyroyal
Oleander	
Opuntia cylindrica	San Pedro cactus
Papaver somniferum	Opium poppy
Peganum harmala	Wild rue
Petasites (all or any species)	Butterbur
Peumus boldus	Boldo oil
Phytolacca decandra (P. americana)	Poke root, Pokeweed
Podophyllum resin	
Pteridium aquilinum	Bracken fern
Rauwolfia	
Ricinus communis, other than the fixed oil of the seed	Castor tree
Robinia pseudoacacia, other than the leaf and flower	False acacia
Schoenocaulon officinale (Sabadilla officinarum, Veratrum officinale)	Sabadilla
Scopolia carniolica	
Semecarpus anacardium (Anacardium orientale), other than the seed	Marking nut tree
Senecio (all or any species)	
Solanum (all or any species) except stems of Solanum dulcamara (Bittersweet) and potatoes	
Sophora secundiflora	Mescal bean
Spigelia marilandica	Pink root, Worm grass
Staphisagria	
Strophanthus	
Strychnos	Nux vomica
Strychnos gaulthieriana	
Strychnos ignatii (Ignatia amara)	Ignatious bean
Symphytum (all or any species)	Comfrey
Tamus communis fruit and root	Black bryony
Tanacetum vulgare (except in preparations containing 0.8% or less of oil of Tansy)	Tansy
Teucrium (all or any species)	Germander
Thevetia	
Toxicodendron radicans (Rhus toxicodendron)	Poison Ivy
Tussilago farfara	Coltsfoot
Viola sebifera	Cuajo negro, Camaticaro
Yohimbe (yohimbine)	