# Herbal Medicines and Pregnancy

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## ABSTRACT

The prevalence of herbal medicine use during pregnancy is between 7% and 55%, depending upon the geographic area surveyed and the surveyed group's socio-cultural aspects and ethnicity. Why are women taking natural health products (NHPs) in pregnancy? Women who learn they are pregnant are concerned about the safety of their fetus and may turn to NHPs rather than prescription medication. Use of NHPs in pregnancy is an area where more research is needed. The importance of knowing about these products is to understand their potential dangers in women of childbearing age, particularly when it is known that they are trying to conceive. Information on select NHPs is provided in this presentation.

## Introduction

Use of natural health products in pregnancy is a very interesting area where more research is definitely needed. The prevalence of herbal medicine use during pregnancy is between 7% and 55%.[1] These percentages depend upon the geographic area surveyed and the surveyed group's socio-cultural aspects and ethnicity. In Canada we have one study reporting that approximately 9% of pregnant women in Quebec use natural health products (NHPs) in pregnancy.[2] In the U.S., a survey of midwives found that 45% to 93% of them had prescribed or administered a herbal or NHP to women during their pregnancy.[3] The products they used most commonly were castor oil, evening primrose oil, black cohosh, and blue cohosh.

The question is, "Why are women taking NHPs in pregnancy?" In a study on pharmaceutical drug use by 295 pregnant women, 37% reported non-compliance with their existing medication regimen due to hesitation to use drugs during pregnancy.[4] Women who learn they are pregnant are concerned about the safety of their fetus and may turn to NHPs rather than prescription medication. In 2006, 75 systematic reviews were published in the book "Herbal Medicines in Pregnancy and Lactation: An Evidence-Based Approach".[5] Included in the book is a quick reference table, a portion of which is shown as Table 1. The safety for use of each of the herbs in pregnancy is designated by colour: red means NO and green means GO. For example, Pennyroyal and Parsley have traditionally been used as abortefacients, so are shaded in red; foxglove is the plant from which digitalis was originally extracted; Juniper can be teratogenic; and obviously, something called "Deadly Nightshade" can't be good in pregnancy. Some of these herbs will be addressed in this presentation.

For the text, supplements, such as glucosamine sulphate, and vitamins were also reviewed (*see* Table 2 and Table 3). At the time of this work, there was no data on the safety of Vitamin E. However, recent data have shown that when given in the first trimester, Vitamin E may increase the risk for cardiovascular defects in newborns. Adverse events were not seen when the vitamin was taken in the second or third trimesters. The risk of birth defects when taking NHPs, or virtually any intervention in pregnancy depends upon the timing. Risk of malformation varies among the periods of embryonic and fetal growth, according to the stages of organ, body part and system development.

**TABLE 1** Herbs in Pregnancy*[5]

| | | |
|---|---|---|
| **Barberry** | **Feverfew** | **Parsley** |
| **Black Cohosh** | **Flax** | **Passionflower** |
| **Blazing Star** | **Foxglove** | **Pennyroyal** |
| **Blue cohosh** | **Garlic** | **Peppermint** |
| **Borage** | **Gentian** | **Raspberry** |
| **Deadly nightshade** | **Juniper** | **Valerian** |

*Selected and adapted from: Mills E, Dugoua J-J, Perri D, Koren G. Herbal Medicines in Pregnancy and Lactation: An Evidence-Based Approach. Toronto: Taylor & Francis, 2006.

**TABLE 2** Supplements in Pregnancy*[5]

| Pregnancy Safety Scale | | Lactation Safety Scale |
|---|---|---|
| **Safe** | | **Safe** |
| **Caution** | | **Caution** |
| **Unsafe** | | **Unsafe** |
| **Unknown** | | **Unknown** |
| | | |
| **Glucosamine sulphate** | | **Glucosamine sulphate** |
| **Soy isoflavones** | | **Soy isoflavones** |
| **Lactobacillus sp.** | | **Lactobacillus sp.** |

*Selected and adapted from: Mills E, Dugoua J-J, Perri D, Koren G. Herbal Medicines in Pregnancy and Lactation: An Evidence-Based Approach. Toronto: Taylor & Francis, 2006.

**TABLE 3** Vitamins in Pregnancy*[5]

| Pregnancy Safety Scale | Lactation Safety Scale |
|---|---|
| **Safe** | **Safe** |
| **Caution** | **Caution** |
| **Unsafe** | **Unsafe** |
| **Unknown** | **Unknown** |
| | |
| **Vitamin A** | **Vitamin A** |
| **Vitamin E** | **Vitamin E** |

*Selected and adapted from: Mills E, Dugoua J-J, Perri D, Koren G. Herbal Medicines in Pregnancy and Lactation: An Evidence-Based Approach. Toronto: Taylor & Francis, 2006.

As already noted by previous speakers, about half of all pregnancies are unplanned and women of childbearing age may be taking herbal medicines as general treatment. They may be taking Evening Primrose oil, Cramp Bark or Black Cohosh to regulate periods or to help with menstrual cramping. In an unplanned pregnancy, what can typically happen is that by 4 weeks' gestation there is no period; by 5 weeks the woman begins to worry; by 6 weeks she does a home pregnancy test; it takes a week to see her doctor; and by 8 weeks she is confirmed pregnant. By this time, at 8 or 9 weeks, she has already passed through the time when there is the most risk of major malformations.

The importance of knowing about NHPs is to understand their potential dangers in women of childbearing age, particularly when it is known that they are trying to conceive. Provided below, is information on select NHPs, sorted by category.

**Pregnancy-Induced Nausea**

**GINGER**

Ginger is commonly used to treat nausea, including post-chemotherapy, and for motion sickness. For the treatment of nausea and vomiting in pregnancy, about 7 clinical studies have been published.

Willetts et al. conducted a randomized clinical trial in a population of 120 women at less than 20 weeks' gestation having symptoms of morning sickness.[7] The women were given Ginger extract equivalent to 1,500 mg daily for 4 days. After 4 days, there was an improvement in nausea and retching. In follow-up of birth outcomes, infants post-delivery had normal birth weight, gestational age, and APGAR scores, and the frequency of malformations was compatible with the normal population.

In other studies there have been variations in the dose. Fisher-Rasmussen et al. in 1990 gave a dose of 1000 mg,[8] as did Vutyavanish et al. (as dried Ginger) in a randomized controlled trial in 70 women, published in 2001.[9] Nausea and vomiting decreased significantly, and there were no adverse events on

pregnancy or pregnancy outcome. Keating and Chez published a trial in 2002 where they used ginger syrup.[10] Sripramote et al. gave 500 mg Ginger or 10 mg of Vitamin B6.[11] Nausea and vomiting were decreased significantly, with no adverse effects on pregnancy and pregnancy outcome.

Additional studies include those published by Portnoi et al. in 2003,[12] and by Smith et al. in 2004.[13]

Women suffering from nausea and vomiting of pregnancy commonly have difficulty swallowing capsules, therefore Ginger taken as a tea seems to work well.

### VITAMIN B6

In 2004 the American College of Obstetrics and Gynecology recommended Vitamin B6 as first-line treatment for nausea and vomiting of pregnancy, based chiefly on two clinical trials, Sahakian et al.[14] and Vutyavanich et al.[15] The first randomized controlled trial included 59 pregnant women. The dose of 25 mg given every 8 hours was found effective at reducing nausea and vomiting. The second trial was also randomized and controlled, with 342 pregnant women, investigated 10 mg Vitamin B6 given every 8 hours. They found that nausea was improved, but there was no effect on vomiting.

## Labour Aid

In midwifery and traditional herbal practice, there are herbal medicines used to prepare the uterus for labour, *partus preparatus*. Among these are Red Raspberry, Blue Cohosh, and Black Cohosh, which are often administered by nurse midwives, naturopaths or herbalists. They can be given as single ingredients or as a mixture of agents.

### RASPBERRY

Red Raspberry, commonly taken as a tea, is traditionally used for fertility. Some women take it as a labour aid during the last two months before delivery, whereas others take it throughout the pregnancy.

In a controlled clinical trial, 192 women were randomized at 32 weeks' gestation to receive 1.2 grams of Raspberry leaf tablets twice daily.[16] No adverse effects to mothers or infants were reported. The active treatment shortened the second stage of labour and lowered the rate of forceps delivery.

In a retrospective observational study of 108 pregnancies, the 57 women who ingested Raspberry leaf were less likely to receive an artificial rupture of their membranes, or to require caesarean section (C-section), forceps or vacuum birth (vs. 51 controls).[17]

The mechanism of action of Red Raspberry is unclear. Human data show it to have either stimulatory or spasmolytic effects on the uterus, possibly being dose- and tissue-dependent. For example, in low doses Raspberry leaf might cause more contraction, while higher doses might have spasmolytic effects and decrease contraction. Red Raspberry might decrease contraction of tonic tissues and increase contraction of relaxed tissues. Animal data where raspberry was applied directly to rat uteruses did not show any direct effect.

### CASTOR OIL

Castor oil is commonly used as an potent laxative. It is used by midwives and pregnant women to initiate labour.

In a prospective cohort of 100 women with intact membranes at 40-42 weeks' gestation, 52 women received a 60 mL oral dose of Castor oil and 48 controls received no treatment.[18] In the treated group, 30/52 women (57.7%) went into active labour within 24 hours as compared to 2/48 in control group (4.2%). When Castor oil was successful at initiating labour, 83.3% of women delivered vaginally. The

study authors concluded that women receiving Castor oil have in increased likelihood of initiating labour within 24 hours.

Castor oil does not contain the deadly poison, ricin. Castor oil is hydrolyzed in the duodenum to ricinoleic acid by pancreatic lipase. Ricinoleic acid may have stimulant laxative effects, the exact mechanism of which are unknown. Possible mechanisms are that it has an osmotic effect in the large bowel, increasing fluid secretion, or has a direct irritant effect on the smooth muscle of the small intestine. Onset of bowel evacuation is in 2-6 hours.

In pregnancy, Castor oil induces labour by producing hyperemia in the intestinal tract, which causes reflex stimulation of the uterus.[19] It may increase prostaglandin production (prostaglandin F2 alpha (PGF2 alpha)), which in turn stimulates uterine activity.[18]

#### BLUE COHOSH

The NHP that is most commonly used to induce labour, and that is of most concern, is Blue Cohosh. There have been 3 reports in the literature of cardiovascular side effects resulting from women using Blue Cohosh in pregnancy. These were all cases of unsupervised use of the agent, and it appears that use was beyond the therapeutic dose. One neonate experienced acute myocardial infarction, profound congestive heart failure and shock.[20] In another, there was severe multi-organ hypoxic injury.[21] And in the third case the adverse event was perinatal stroke.[22] There is a fourth case report of abortifacient and nicotinic toxicity.[23] When surveyed in 1999, 64% of Certified Nurse Midwives in the United States claimed to use Blue Cohosh during labour.[3] They also reported that this herb is one that worries them most and which they use with the least amount of confidence.

Blue Cohosh's mechanism of action involves the glycosides caulosaponin and caulophyllosaponin and the chemical sparteine to induce labour contractions.[24] Blue Cohosh causes constriction of coronary arteries, seems to decrease flow of oxygen to the heart and to be toxic to the myocardium, thus explaining the cardiovascular effects.[25]

Furthermore, other alkaloids, such as anagyrine and N-methylcytosine, may be teratogenic, and yet others (e.g., taspine), embryotoxic. However, given the timing of use, these latter effects may not be relevant.

### Cervical Ripening

#### EVENING PRIMROSE OIL

Evening Primrose oil is a fatty acid commonly given by midwives to trigger cervical ripening.

In a parallel group retrospective study of quasi-experimental design, it was not shown that Evening Primrose oil actually induced cervical ripening. In two groups of 54 women at 37 weeks' gestation, one cohort took Evening Primrose oil and the other acted as a control. The findings indicated that the product did not shorten gestation or decrease the overall length of labour; rather, it increased the incidence of prolonged rupture of membranes, oxytocin augmentation, arrest of descent, and vacuum extraction.[26]

There has also been a case report of petechiae and ecchymoses in a newborn infant whose mother drank raspberry leaf tea and took 6.5 g of primrose oil (as 500 mg capsules, vaginally and orally) one week before giving birth.[27]

## Atopic Disease Prevention

### PROBIOTICS

A meta-analysis of trials using probiotics during pregnancy was completed in 2008.[28] Eleven randomized controlled trials were reviewed with a total of 1,505 patients. A number of strains of bacilli, when given to women during the last few weeks of gestation and then during the period of breastfeeding and/or given to the breastfeeding child, resulted in some improvement in the prevention of atopic disease (mostly eczema) in the children followed for 2 to 4 years. There was no evidence that probiotics affected C-section incidence, birth weight or pre-term delivery. There was a non-significant increase in birth weight by 45 grams ($p = 0.699$) and a non-significant increase in gestational age by 0.4 weeks (approx. 3 days) ($p = 0.336$). The following are some of the studies and their findings.

Kalliomaki et al. published a trial of *Lactobacillus rhamnosus GG* (LGG) $1 \times 10^{10}$ CFU given daily from 2-4 weeks pre-delivery.[29] At 2 years of age, the frequency of atopic eczema in the LGG group was half that of the placebo group. At 4 years of age, the frequency of atopic disease remained lower in the LGG group versus placebo. Kukkonen and colleagues published two separate studies in 2006 and 2007.[30,31] In the earlier trial, *LGG, L. rhamnosus, B. breve* and *Propionibacterium freudenreichii* subsp. *shermanii* were given to women at 2-4 weeks pre-delivery and to infants postnatally to determine whether the probiotics could affect the immune response to vaccination. There was no difference in antibody responses to diphtheria, tetanus or *Haemophilus influenzae* type b (Hib) vaccination versus placebo.

In the latter, Kukkonen et al. trial, 1,223 pregnant women with a family history of atopic disease were given either placebo or the same probiotics - *LGG* ($5 \times 10^9$ CFU), *L. rhamnosus* ($5 \times 10^9$ CFU), *B. breve* ($2 \times 10^8$ CFU) and *Propionibacterium freudenreichii* subsp. *shermanii* ($2 \times 10^9$ CFU) - plus galacto-oligosaccharides daily at 2-4 weeks pre-delivery and to infants postnatally.[31] Infants of the actively treated mothers were more frequently colonized with *Lactobacillus* and *Bifidobacterium spp* at 3 to 6 months. At 2 years of age, they had a significant decrease in eczema and atopic eczema versus the placebo group.

Other studies of interest include those by Abrahamsson et al.,[32] Kaplas et al.,[33] Gueimonde et al.,[34] and Neri et al.[35]

## Upper Respiratory Tract Infection

### ECHINACEA

Echinacea is commonly given to treat upper respiratory tract infections.

A prospective study involved a cohort of 206 women using Echinacea in the 1st trimester vs. 206 controls.[36] In the Echinacea group, there were 195 live births, 13 spontaneous abortions, 1 therapeutic abortion, and 6 major malformations. In the control group, there were 198 live births, 7 spontaneous abortions, 1 therapeutic abortion, and 7 major malformations. There were no statistically significant differences between the groups (the rates of spontaneous abortion were not significantly different), therefore, it was concluded that Echinacea did not pose an increased risk of malformations during pregnancy.

### BERBERINE-CONTAINING HERBS

Herbs often given as immune stimulants during upper respiratory tract infections are those that contain berberine, such as Goldenseal (*Hydrastis canadensis*), Barberry (*Berberis vulgaris*), and Oregon Grape (*Berberis aquifolium*). There is some concern that berberine given around the time of birth can displace albumin-bound bilirubin. This is based on animal data, where it has been shown in rats that berberine displaces bilirubin bound to albumin and may aggravate newborn jaundice (kernicterus). In that study, berberine was administered to rats daily (intraperitoneally) for one week.[37] After the week, there was a

significant decrease in bilirubin albumin binding and persistent elevated serum unbound and total bilirubin were observed.

## Depression

### ST. JOHN'S WORT

The entire evidence regarding the safety of St. John's Wort in pregnancy seems to have rested on one case report up until about one year ago. The case regards a 38-year-old woman who started taking St. John's Wort at 24 weeks gestation.[38] Her pregnancy was unremarkable, with the exception of late onset thrombocytopenia, which the author did not attribute to St. John's Wort. The offspring was born healthy, had a normal birth weight, normal Apgar score, and physical examination and laboratory results were normal. The infant's behavioural assessment at 4 and 23 days was within normal limits.

In 2009 a prospective cohort study was conducted by Motherisk.[39] They followed 54 pregnant women exposed to St. John's Wort during their pregnancy, 54 pregnant women on anti-depressant medications during pregnancy, and 54 healthy pregnant women with no teratogenic exposure during pregnancy as controls. It was found that the rates of major malformations were similar across the 3 groups (5%, 4% and 0%), keeping in mind that the major malformation rate in the general population is 3-5%.

## Conclusion

In summary, there is some evidence regarding the safety of select NHPs, as well as some evidence of harm. For approximately 60% of NHPs, safety in pregnancy is unknown - nonetheless some women continue or initiate taking these products during pregnancy. To provide best care, clinicians and pharmacists must screen their patients for use of complementary and alternative medicines and stay up-to-date on research regarding such agents. Here are a few resources to turn to: Mills, Dugoua, Perri & Koren (2006)[6] www.naturaldatabase.com,[40] and www.naturalstandard.com.[41] The on-line sites offer good evidence-based reviews of much of the NHP information available. More research is needed on NHPs. Regulatory intervention may be necessary for products that may be contraindicated in certain conditions or that should have dosing restrictions. We met with Health Canada regarding NHPs last year through Pregmedic, and hope to do more work with them in the future.

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