Berberine-Containing Herbs and Pregnancy

Berberine-containing herbs, such as goldenseal (*Hydrastis canadensis*) and barberry (*Berberis vulgaris*), are traditionally said to be contraindicated in pregnancy. The *British Herbal Pharmacopoeia 1983* is one such source of this information. In most earlier texts or articles, it is not always clear as to why this contraindication might exist. Certainly, in the case of goldenseal, the concern was that its reputed oxytocic effect might induce premature labor. But since this activity was largely attributed to hydrastine, which is not found in barberry, it is difficult to understand why the contraindication also existed for barberry. The Chinese herb Huang Lian (*Coptis chinensis*) is rich in berberine, but is commonly used during pregnancy (see below).

Berberine has caused uterine contraction in both non-pregnant and pregnant experimental models. In another study that investigated ten berberine-containing plant extracts, stimulation or relaxation of isolated uterus occurred, depending upon the extract tested. Results did not correlate with berberine content. This suggests that a berberine-containing herb will not necessarily produce uterine contractions merely because of the presence of berberine.

A different concern over berberine has arisen in the recent literature. The incidence of kernicterus in premature Chinese infants with neonatal jaundice has been reported to be associated, in some cases, with exposure to Huang Lian either by direct administration, transplacental absorption, or via breast milk. It is thought that the berberine is displacing bilirubin from its protein carrier, leading to a substantial increase in unbound bilirubin and associated adverse consequences. Such a finding would argue against the use of berberine-containing herbs in late pregnancy.

Recent concerns also exist over potential teratogenic or maternal toxic effects from berberine. The maternal lowest observed adverse effect level (LOAEL) for mated rats fed berberine chloride dihydrate from gestational day 6 to day 20 was measured at 531 mg/kg/day. The maternal no observed adverse effect level (NOAEL) was 282 mg/kg/day. In contrast, the developmental LOAEL was 1313 mg/kg/day, and the NOAEL was at 531 mg/kg/day. A follow-up study using the same protocol found similar results, but there was an absence of a significant effect for berberine on developmental toxicity, meaning the developmental toxicity NOAEL could be raised to approximately 1100 mg/kg/day berberine. This indicates that doses less than 1 g/kg of berberine chloride dihydrate to the mother had no observable effect on offspring.

Goldenseal also appears to lack teratogenic activity at normal doses. Reduction in average fetal body weight per litter was observed in the offspring of mated mice fed goldenseal root powder (7.7 g/kg/day) from days 6-17. However, no significant developmental toxicity was observed below this dosage. Maternal liver weights were increased at doses greater than 2 g/kg/day, but histopathological lesions were absent.

At a high oral dosage of 1.86 g/kg, goldenseal did not have an adverse effect on reproductive outcome in rats. Fetal weights were slightly increased when the herb was administered from days 1-8 and days 8-15 of gestation. There was no difference in placental weight or the number of resorptions or litter size, and there were no externally visible malformations. The herb was administered as an ethanol extract, and the dose administered was the highest possible for which ethanol remained below the teratogenic threshold.

However, the same research team published a subsequent study that compared these *in vivo* results with an *in vitro* whole embryo culture study. In this study, goldenseal was found to have a teratogenic effect in the *in vitro* assay at the highest dose tested, while no such effect was observed in the *in vivo* study. This suggests that the *in vivo* and *in vitro* results may not be directly comparable.

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model, treated embryos were exposed to 0.5 to 6.0 mL of goldenseal extract for 26 hours in the culture medium, which represents high levels of exposure. Toxic effects were clearly evident for the goldenseal from this in vitro model. Higher levels of exposure also caused developmental abnormalities, whereas there were no adverse effects from the goldenseal for the lowest level (0.5 mL/mL), either toxic or developmental. The authors attributed these marked differences between the in vivo and in vitro models to the poor absorption of goldenseal (especially the alkaloids) from the digestive tract. They concluded that, at the normal human oral dose, goldenseal is unlikely to be absorbed to an extent to be unsafe to use in pregnancy, despite the apparent toxic effects in vitro.

However, an analysis of a total of 14,551 live births in Taiwan from 1984 to 1987 (but only recently published) has raised a concern for Huang Lian and hence possibly for other berberine-containing herbs. After adjustment for confounding factors, taking Huang Lian during the first trimester of pregnancy was found to be associated with an increased risk of congenital malformations of the nervous system (adjusted odds ratio 8.62, 95% confidence interval 2.54 to 29.24). The exact nature of these malformations was not specified, but it excluded neural tube defects. The absolute incidence of these defects in the whole population assessed was 0.2%. 

Commentary

On the basis of the above information, a cautious approach would suggest that berberine-containing herbs are best avoided in the first trimester of pregnancy, due to potential teratogenic concerns, and in late pregnancy, because of an increased risk of kernicterus. At other times during pregnancy, it is quite likely that their short-term use will be safe, notwithstanding the reputed oxtic effects of goldenseal. An appropriate evaluation or risk versus benefit should dictate therapeutic use during this window.


Blue Cohosh in Pregnancy

Maternal ingestion of blue cohosh (Caulophyllum thalictroides) in late pregnancy has been associated with four documented cases of perinatal adverse events. The first case occurred after a normal labor, where a female infant was not able to breathe spontaneously and sustained CNS hypoxic-ischemic damage. A midwife had attempted induction of labor using a combination of blue cohosh and black cohosh (Cimicifuga racemosa) given orally (dosage undefined) at around 42 weeks gestation.

In the second case, severe congestive heart failure and myocardial infarction in a newborn male were attributed to maternal consumption of blue cohosh tablets. The woman had been advised to take one tablet per day (dose not specified), but she took three tablets per day for three weeks prior to delivery. Cardiomegaly and mildly reduced left ventricular function were still evident at two years of age. The tablets were not analyzed for their content.

Stroke in an infant was reported as a possible adverse event associated with a blue cohosh-containing dietary supplement in the FDA's Special Nutritionals Adverse Event Monitoring System database (which lists adverse events but is not subject to preconditions, analysis, or peer review). The level of documentation of this case is poor.

Finally, a case report linked stroke in a baby with blue cohosh consumption by the mother. A female infant weighing 3860 g (about eight pounds) was born at just over 40 weeks gestation to a healthy 24-year-old woman. The obstetrician reported that the woman had been advised to drink a tea made from blue cohosh (Caulophyllum thalictroides), because induction of labor was a recognized effect of this herb. A cesarean section was performed after a failed attempt at vaginal delivery. The infant had focal motor seizures of the right arm, which began at 26 hours of age and were controlled with phenobarbital and phenytoin. A computed tomographic (CT) scan obtained when the infant was two days of age showed an evolving infarct in the distribution of the left middle cerebral artery. There were no other apparent causes for the baby's condition.

In a curious development with this fourth case, urine and meconium were positive for the cocaine metabolite benzoylecgonine, and testing of the mother's bottle of blue cohosh and another brand of the same herb were
also positive for this metabolite. Maternal cocaine is a well-known cause of perinatal stroke.

Later, the authors commented that the finding of a cocaine metabolite in blue cohosh should be interpreted with caution. This finding is most likely due to a false-positive reading from the analytical tests used (which did not have a high degree of specificity). In other words, blue cohosh most likely contains a phytochemical that looks like the cocaine metabolite in terms of the tests used, but is not related in any way to cocaine.

Adverse effects have also been documented for a pregnant woman ingesting blue cohosh. Nicotinic toxicity was reported following the attempted use of blue cohosh as an abortifacient. A 21-year-old woman developed tachycardia, sweating, abdominal pain, vomiting, and muscle weakness following the ingestion of a blue cohosh tincture. The authors suggested that these symptoms were consistent with nicotinic toxicity and probably resulted from N-methylcytisine, a phytochemical component of blue cohosh. Symptoms resolved over 24 hours.

The known constituents of blue cohosh root include quinolizidine alkaloids, such as N-methylcytisine (0.033-0.091%), anagyrine (0.012-0.029%), taspine (0.00013%), sparteine (amount unknown), and caulophyllumine (amount unknown).7–11 and saponins, including caulosaponin (0.1%) and caulophyllosaponin.12,13

Blue cohosh is regarded as an oxytocic agent, and uterine stimulant effects have been observed for the liquid extract, hot water extract, and saponin fraction of blue cohosh and isolated caulosaponin in vitro.12–14 Intravenous administration of caulosaponin (5-10 mg/kg) increased uterine tone and rate of contraction in situ and in vivo in the rat.13 However, another in vivo study indicated no effect on the uterus when blue cohosh was administered in high doses.15

The presence of quinolizidine alkaloids, including sparteine, in blue cohosh could explain both its oxytocic activity and its occasional toxicity. Sparteine was once widely used as an oxytocic drug, but it fell out of favor because of the uterine spasm that occurred in women who were unable to metabolize it effectively. About five percent of male and female subjects studied were unable to metabolize sparteine by N-oxidation, and this defect appears to have a genetic basis.17 Perhaps N-methylcytisine, which is a quinolizidine alkaloid with a structure closely related to sparteine, is also poorly metabolized in a percentage of women.

Blue cohosh may be linked to teratogenic effects, but the link is tenuous. High levels of the alkaloid anagyrine have been associated with a congenital deformity in cows called "crooked calf disease," which is caused by maternal ingestion of lupine plants during pregnancy.18,19 Similar malformations in goats, dogs, and a human infant have been reported in one case study. Maternal consumption of goat’s milk contaminated with anagyrine was suspected to be the cause. The level of alkaloids in the milk was not measured.20 The relevance of this report to the use of blue cohosh in pregnancy is unclear. It is thought that anagyrine may need to be metabolized by microflora in ruminants for it to exert a teratogenic effect.8

In support of this last point, anagyrine (500 µg/mL) did not demonstrate teratogenic effects in an in vitro rat embryo culture, but it did inhibit overall growth and development. N-methylcytisine (20 µg/mL) has also demonstrated teratogenic activity.8 An ethyl acetate extract (250 µg/mL) and a butanol extract (500 µg/mL) of blue cohosh, and the constituents taspine (5 µg/mL) and caulophyllumine (5 µg/mL), have demonstrated embryotoxicity in the same test.8,11 However, in the context of the above studies, it should be noted that blue cohosh is not typically used in early pregnancy. It can be used in formulations to promote fertility, but is usually immediately discontinued if a period is missed. A more prudent approach would be to not use it at all for enhancing fertility.

Commentary

In a 1999 survey of certified nurse-midwives in the US, blue cohosh was used by 64% of the 90 respondents who used herbal medicine to stimulate labor. Adverse effects attributed to the use of blue cohosh and black cohosh were nausea, increased meconium-stained fluid, and transient fetal tachycardia.21

Due to possible teratogenic effects, a cautious approach would dictate that blue cohosh is best avoided in women wishing to conceive and in early pregnancy and lactation. Traditional texts, such as the British Herbal Pharmacopoeia 1983, tend to support this by recommending that only small doses are advisable during the first trimester of pregnancy.22 Use in late pregnancy has been linked to the adverse events listed above and should only be undertaken by clinicians experienced with the use of blue cohosh for this application, if at all.

Black Cohosh and Breast Cancer Risk: Benefit Shown

Controversy exists over the use of black cohosh (Cimicifuga racemosa or Actaea racemosa) in the context of breast cancer. There are basically two concerns. The first is whether a woman with an existing oestrogen-sensitive breast carcinoma can safely use black cohosh. The second concern is whether the regular use of black cohosh by a healthy woman will increase her risk of subsequently developing breast cancer. Both issues received considerable publicity in 2003 after the American Association for Cancer Research released the findings of an animal study. This controversial study was conducted by Dr. Davis and coworkers from Duquesne University and presented at the 94th annual meeting of the American Association for Cancer Research held in Washington, DC, in July 2003. The media release quoted Dr. Davis as saying: "Although it is unfortunate to be eliminating another option for women needing therapies to relieve menopausal symptoms, our findings suggest that women who may be at high risk of having an undetected breast tumor and certainly those who do have breast cancer should proceed with great caution - or simply avoid - taking black cohosh until we learn if there are ways to circumvent these adverse effects." These statements were inappropriate and far exceeded the scope of the study (see below).

The scientists used a transgenic (genetically engineered) mouse model in which female mice spontaneously develop mammary tumors through the insertion and activation of an oncogene common in human breast cancer. There are several such mouse models in existence. The sexually mature female mice were fed a black cohosh extract (at amounts said to reflect the normal human dose) for 12 months (basically their whole adult life). While the incidence of mammary tumors was not increased, there was an increase in the number of tumors that spread to the lungs (27.1% of black-cohosh-treated mice vs. 10.9% of the control mice).

Fundamentally, the relevance of using a highly artificial mouse model to assess the safety of a treatment that is already widely used in the community is highly questionable. It could well be that this isolated study (which has never been published and hence never been subject to peer review) was nothing more than an irrelevant scientific curiosity. Surely the best way to assess any risks associated with black cohosh consumption is to study the health of women already taking it.

Such a study has now been published. The association between a range of "hormone-related supplements" (including black cohosh) containing "phytoestrogens" and breast cancer incidence was recently assessed in a retrospective case-control epidemiological study. The US study examined 949 cases of women with breast cancer and 1524 controls and specifically targeted use of black cohosh, American ginseng (Panax quinquefolius), red clover (Trifolium pratense), dong quai (Angelica sinensis), and yam products (Dioscorea species). After adjusting for variables such as age, education, age at full-term pregnancy, menopause status, family history of breast cancer, and use of hormone replacement therapy (HRT), intake of the above herbal products (as a group) was associated with a reduced incidence of breast cancer (adjusted odds ratio [OR] 0.65, 95% confidence interval [CI]: 0.49-0.87). However, it was only black cohosh that demonstrated a highly significant breast cancer protective effect (adjusted OR 0.39, 95% CI: 0.22-0.70). The authors concluded that additional confirmatory studies are required to determine whether black cohosh could be used as a treatment to prevent breast cancer. It would certainly appear from this study that use of black cohosh is not associated with an increased incidence of breast cancer.

However, the question remains as to whether black cohosh can be safely used by women with pre-existing breast cancer. While more information is required, findings from a recent clinical study strongly imply that black cohosh lacks any estrogenic activity in breast or endometrial tissue. This was a prospective, open, uncontrolled safety study in which baseline status was compared by blinded observers with status after six months of treatment. A total of 74 women were treated...
with 40 mg black cohosh extract daily (approximately 200 mg dried root), and 65 women completed the study. Mammograms were performed, and breast cells were collected by percutaneous fine needle aspiration biopsies at baseline and after six months. Breast cell proliferation was assessed using the Ki-67/MIB-1 monoclonal antibody (cells positive for this marker are in a state of active proliferation). Safety was monitored by adverse event reporting, laboratory assessments, and measurement of the endometrium by vaginal ultrasound.

None of the women showed any increase in mammographic breast density. Furthermore, there was no increase in breast cell proliferation. The mean change in the proportion of Ki-67-positive cells was -0.5% ± 2.4% for paired samples. The mean change in endometrial thickness was 0.0 ± 0.9 mm. A modest number of adverse events were possibly related to treatment, but none of these was serious. Laboratory findings and vital signs were normal. The findings suggest that the isopropanolic extract of black cohosh tested does not cause adverse effects on breast tissue. Furthermore, the data did not indicate any endometrial or general safety concerns during six months of treatment.

Commentary

Despite the sometimes-intense media and scientific scrutiny, concerns over the use of black cohosh in the context of breast cancer risk appear to be unwarranted. In fact, the herb may even reduce the risk of developing this common cancer. This observation is in stark contrast with the data emerging in the aftermath of a declining use of HRT. Results from a recent analysis demonstrate a strong association between use of HRT and breast cancer incidence. In the study, published in the prestigious and conservative New England Journal of Medicine, investigators assert that the reduced use of HRT that began in mid-2002 (following the release of the findings of the Women’s Health Initiative Study) correlates with a sharp decline in new breast cancer diagnoses.

Analysis of data from the National Cancer Institute’s registries shows that the age-adjusted incidence of breast cancer in women in the US fell sharply (by 6.7%) in 2003. This is the first time in around 50 years that the rate has actually fallen by a significant amount. Data from 2004 show a levelling off relative to the 2003 rate. A careful analysis of the data revealed that the decrease was only evident in women aged 50 years or more and was mainly

for cancers that were estrogen-receptor positive. Such cancers declined by 14.7% in women aged 50 to 69 years. The authors write: “Discontinuation of hormone-replacement therapy could have caused a decreased incidence of breast cancer by direct hormonal effects on the growth of occult breast cancers, a change that would have been expected to affect predominantly estrogen-receptor-positive tumors... The hypothesis that hormone withdrawal can rapidly influence the growth of breast cancer is supported by anecdotal reports of regression of breast cancer after discontinuation of hormone-replacement therapy.”

According to the authors of the study, stopping HRT may have prevented as many as 14,000 breast cancers in 2003 compared to 2002. Such statistics should hopefully place theoretical concerns over the safety of black cohosh into an appropriate context.
