

# SAFETY AND EFFICACY OF BLUE COHOSH (*Caulophyllum Thalictroides*) DURING PREGNANCY AND LACTATION

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## ABSTRACT

### Background

There is a lack of basic knowledge on the part of both clinicians and patients as to the indications for use and safety of herbal medicines in pregnancy and lactation. This is one article in a series that systematically reviews the evidence for commonly used herbs during pregnancy and lactation.

### Objectives

To systematically review the literature for evidence on the use, safety and pharmacology of blue cohosh, focusing on issues pertaining to pregnancy and lactation.

### Methods

We searched 7 electronic databases and compiled data according to the grade of evidence found.

### Results

According to a survey of midwives in the United States, approximately 64% of midwives reported using blue cohosh as a labour-inducing aid. There are three case reports in the scientific literature that blue cohosh taken at the time of delivery may cause; 1) perinatal stroke, 2) acute myocardial infarction, profound congestive heart failure and shock and 3) severe multi-organ hypoxic injury. There is one case report that blue cohosh possesses abortifacient properties. There is *in vitro* evidence that blue cohosh may have teratogenic, embryotoxic and oxytoxic effects. In lactation, the safety of blue cohosh is unknown.

### Conclusions

Based on the available scientific information, blue cohosh should; 1) be used with extreme caution during pregnancy, 2) be used only under medical professional supervision and 3) not be available to the public as an over-the-counter product. There is an urgent need to conduct a retrospective or prospective cohort study of midwives using blue cohosh in order to determine its safety.

**Key words:** *Blue cohosh, caulophyllum thalictroides, pregnancy, lactation, breastfeeding, systematic review*

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**B**lue Cohosh (*Caulophyllum thalictroides*) is a small woodland perennial plant with large blue berries that is native to the American north-east. Although they are named similarly, blue cohosh should not be confused with black cohosh (*Actea racemosa*), which is actually from a

separate botanical genus. The medicinal effects of blue cohosh are derived from its root and rhizomes. Blue cohosh is also referred to as “papoose root” or “squaw root”, which reflects the use of this herbal medicine by Native American women who brewed blue cohosh as a tea to

relieve menstrual cramps and to ease the pains associated with childbirth.

Between 1882 and 1905, blue cohosh was listed in the *United States Pharmacopoeia* as a labour inducer<sup>1</sup>. Blue cohosh is often part of a combination of herbal medicines that have been traditionally used in the third trimester to prepare a woman for delivery; this preparation is called “mother’s cordial” or “partus preparatus”. In a 1999 survey of Certified Nurse Midwives in the United States, 64% claimed to use blue cohosh during labour.<sup>1</sup> Currently, blue cohosh is used to induce labour, to help speed the process of labour, and generally, to help the mother through labour as quickly and painlessly as possible.<sup>1-3</sup>

Given the historical and modern use of blue cohosh, we conducted a systematic review of the literature to assess the efficacy of blue cohosh and its potential for harm to both mother and fetus during pregnancy, labour and lactation.

#### Synonyms/Common Names/Related Substances

Blue ginseng, caulophyllum, papoose root, squaw root, yellow ginseng<sup>4</sup>

#### Constituents

Triterpene saponins<sup>5,6</sup>: caulophyllogenin, hederagenin, caulosaponin

Alkaloids<sup>7</sup>: thalictroidine, taspine, magnoflorine, anagryne, baptifoline, 5,6-dehydro-alpha-isolupanine, alpha-isolupanine, lupanine, N-methylcytisine, sparteine

#### Parts Used<sup>4</sup>

Rhizome and root

### METHODS

In keeping with the principles of evidence-based practice, we endeavoured to identify and analyze all the relevant scientific medical literature that provided information as to the safety, efficacy and pharmacology of blue cohosh in pregnancy and lactation. We searched the following databases from inception to March 2007: AMED, CINAHL, Cochrane Database of Systematic Reviews, Cochrane CENTRAL Controlled Trials Database, MedLine, E-Psyche, AltHealthWatch and DARE. The MeSH terms used for searching included the

common and Latin name of the herb along with “pregnancy”, “lactation” and “breastfeeding”. In the case of a well-known active constituent of the herb, this term was also used in the search. To ensure that reports, trials and other forms of evidence were not overlooked, the following additional databases were consulted: Complete German Commission E Monographs by the American Botanical Council, Natural Database and Natural Standard.

Each relevant journal article was collected and referenced in our database. The nature of the findings and the grade of evidence were then abstracted and compiled in our final report. The efficacy of blue cohosh was evaluated according to the grade of evidence for indications presented in Table 1. The safety in pregnancy and lactation of blue cohosh was evaluated according to the evidence level for harm presented in Table 2.

### RESULTS

#### Indications for Use

	Evidence Grade
Induction of labour <sup>1</sup>	E

A survey of midwives in the United States found that 64% of midwives use blue cohosh to induce labour<sup>1</sup>. Blue cohosh is part of a combination of herbal medicines that have been traditionally used in the third trimester to prepare a woman for delivery; this preparation is called “mother’s cordial” or “partus preparatus”. In addition to blue cohosh, mother’s cordial may contain: squaw vine (*Mitchella ripens*), raspberry (*Rubus idaeus*), black cohosh (*Cimicifuga racemosa*) and false unicorn (*Chamaelirium luteum*).

Blue cohosh was identified by the midwives surveyed as the herbal medicine used in pregnancy with the lowest comfort level, as based on a scale from 0 to 10.<sup>1</sup> The midwives reported adverse effects that are usually attributed to blue and black cohosh as nausea, increased meconium-stained fluid and transient fetal tachycardia.<sup>1</sup> When inducing labour, the midwives also reported that blue cohosh was typically administered as a tincture at the following dosage: 5 drops every 4 hours or 10 drops in hot water every 2 hours.<sup>1</sup>

## Use and Safety during Pregnancy

### Herbal Preparation

	Level of evidence for potential harm
Unclear if causal relationship - Perinatal stroke	3b
Acute myocardial infarction, profound congestive heart failure and shock <sup>8</sup>	3b
Severe multi-organ hypoxic injury <sup>3</sup>	3b
Abortifacient <sup>7, 9, 10</sup>	3b
Uterine stimulant <sup>7, 9, 10</sup>	3b
May induce nicotinic toxicity <sup>7</sup>	3b
Potentially teratogenic (contains anagyrine) <sup>11-13</sup>	3b
Embryotoxic <sup>12</sup>	4
Induces labour <sup>1</sup>	5
Emmenagogue <sup>10</sup>	5
Oxytoxic <sup>5</sup>	5

Finkel & Zarlengo (2004) reported a case in the *New England Journal of Medicine (NEJM)* of a healthy 24-year-old woman (gravida 2, para 0) who was advised by her obstetrician to drink a tea made from blue cohosh to induce labour.<sup>14</sup> Following a failed vaginal delivery leading to a caesarean section at 40 weeks, a female infant was born weighing 3860g with focal motor seizures of the right arm, which began at 26 hours of age, and which were controlled with phenobarbital and phenytoin.<sup>14</sup> A computed tomography (CT) scan of the infant at two days of age showed an evolving infarct in the distribution of the left middle cerebral artery.<sup>14</sup> After thrombophilia studies and medical history, the newborn showed no evidence of innate tendency nor family history of excessive blood clotting.<sup>14</sup> Urine and meconium samples, however, were positive for the cocaine metabolite benzoylecgonine on screening by immunoassay and were confirmed by gas chromatography-mass spectrometry.<sup>14</sup> The presence of benzoylecgonine was confirmed in the mother's bottle of blue cohosh and in a sealed bottle of a different preparation of the tea administered.<sup>14</sup>

In letters to the *NEJM* Editor, a number of issues were raised as to the validity of a causal relationship between blue cohosh and the cocaine metabolite benzoylecgonine. Potterton (2004) reported that the suggestion that blue cohosh might produce cocaine metabolites is not plausible, given what is known about the plant's

chemistry.<sup>15</sup> Chan & Nelson (2004) reported that there is no published evidence that blue cohosh contains benzoylecgonine or a product that is metabolized to benzoylecgonine; they suggest that the presence of benzoylecgonine in the newborn most likely represents either exposure to a tea containing coca leaves (*Erythroxylon coca*) or to cocaine use by the mother.<sup>15</sup>

In their response, Finkel & Zarlengo (2004) agreed that blue cohosh is not known to contain benzoylecgonine or to be metabolized to this cocaine metabolite, and stated that neither adulteration of benzoylecgonine by cocaine or Inca tea nor maternal cocaine use was supported for this case.<sup>15</sup> They reported that the results may have reflected detection of a cross-reacting substance by an insensitive immunoassay, an incorrect interpretation of the gas chromatography-mass spectrometry data by the reference laboratory, or both.<sup>15</sup> Although benzoylecgonine has direct vasoactive properties, presenting another plausible pathophysiologic mechanism for stroke, it is unclear if the positive toxicologic finding of benzoylecgonine was the sole potential explanation for the neonate's stroke, but rather a confounding issue.<sup>15</sup>

One case was reported of an infant born with acute myocardial infarction, profound congestive heart failure and shock as a result of the mother ingesting blue cohosh to promote uterine contractions.<sup>8</sup> The infant remained critically ill for several weeks and eventually recovered.<sup>8</sup> The

authors reported that all other causes of myocardial infarction were carefully excluded.<sup>8</sup> The authors believed that these observed effects were due to the vasoactive glycosides and an alkaloid of blue cohosh known to produce toxic effects on the myocardium.<sup>8</sup>

Another case was reported of severe multi-organ hypoxic injury in a child delivered "naturally" with the aid of both blue and black cohosh who was not breathing at the time of birth.<sup>3</sup> The child survived with permanent central nervous system damage.<sup>3</sup> Blue cohosh, which possesses a vasoconstrictive glycoside, and not black cohosh, was believed to be responsible for the adverse effects<sup>3</sup>.

A 21-year-old female developed signs of nicotinic toxicity, i.e., tachycardia, diaphoresis, abdominal pain, vomiting and muscle weakness and fasciculations, after using blue cohosh in an attempt to induce an abortion.<sup>7</sup> The saponins in blue cohosh are believed to be responsible for the uterine stimulant effect.<sup>11</sup> A review article on the potential value of plants as sources of anti-fertility agents also reported that blue cohosh was a potential abortifacient, emmenagogue and uterine stimulant.<sup>10</sup> The alkaloid anagryne, which is found in the root of blue cohosh, has been held responsible for the congenital deformity "crooked calf disease".<sup>13</sup> This disease is found in bovine stock, but could not be reproduced in sheep or hamsters.<sup>13</sup> The severity of the deformity was found to be directly related to the concentration of anagryne in the extracts used.<sup>13</sup> There is also a case report of a similar human congenital malformation (marked anaemia, skeletal dysplasia and vascular anomaly) in an infant, which could have been due to maternal exposure to anagryne contamination of goat milk in early pregnancy.<sup>16</sup>

The alkaloid methylcytisine, a constituent of blue cohosh, was shown to be teratogenic in rats.<sup>11,12</sup> The alkaloid taspine, a constituent of blue cohosh, was shown to be highly embryotoxic in rats.<sup>12</sup> A compendium for medicinal plants reported that blue cohosh may have oxytoxic effects.<sup>5</sup>

#### Homeopathic Blue Cohosh (*Caulophyllum*)

	Level of evidence for potential harm
Does not induce labour <sup>17, 18</sup>	1

A systematic review concluded that there is insufficient evidence to recommend the use of homeopathic blue cohosh as a method of inducing labour.<sup>17,18</sup> Although *caulophyllum* is a commonly used homeopathic therapy to induce labour, the treatment strategy used in this review may not reflect routine practice of homeopathy. A homeopathic preparation of *Caulophyllum thalictroides*, called *Caulophyllum*, beyond the potency (dilution) of 12C, does not contain any molecules of the original substance.

#### Use and Safety during Lactation

	Level of evidence for potential harm
Possible cardiotoxic effects <sup>8</sup>	4

Blue cohosh contains vasoactive glycosides and an alkaloid known to produce toxic effects on the myocardium of laboratory animals.<sup>8</sup> Blue cohosh is not reported in the evidence-based medicine literature as being either contraindicated or safe in lactation.

#### Toxicity and Adverse Effects

Blue cohosh contains vasoactive glycosides and an alkaloid known to produce toxic effects on the myocardium of laboratory animals.<sup>8</sup> Blue cohosh may constrict coronary arteries and decrease the flow of oxygen to the heart.<sup>19</sup> The alkaloid methylcytisine was shown to cause symptoms of nicotinic toxicity and teratogenic in rats.<sup>7</sup> The alkaloid taspine was shown to be embryotoxic in rats.<sup>7</sup>

#### Pharmacology

Blue cohosh enhances estradiol binding to estrogen receptors and increases estradiol-induced transcription activity in estrogen-responsive cells.<sup>4</sup> Blue cohosh decreases luteinizing hormone (LH) levels and increases serum ceruloplasmin oxidase activity, which are measures of estrogenic activity in the liver.<sup>4</sup>

On the excised uteri of guinea pigs, blue cohosh was found to contain the only active oxytocic responsible for increasing uterine tone.<sup>20</sup> Blue cohosh frequently initiated contractions in non-active strips of uterine tissue but also increased tone with cessation of contractions, which the authors described as tetanus.<sup>20</sup> Although

a decrease in blood pressure of 30–50 mm with a “fairly prompt” return to normal was observed when blue cohosh was administered to dogs in large doses, a subsequent *in vivo* study, also on dogs, indicated no effect on the uterus when blue cohosh was administered in high doses.<sup>21</sup>

### Drug Interactions

Anti-diabetic Drugs<sup>4</sup>  
Cardiovascular Drugs<sup>5,8</sup>  
Nicotine<sup>7</sup>

## DISCUSSION

In the evidence-based literature, the main, if not only, therapeutic indication of blue cohosh is as an agent to stimulate labour. Unfortunately, this therapeutic indication is based on low quality evidence from a survey of midwives in the United States, where approximately 64% of the respondents reported that they use blue cohosh as a labour-inducing aid, and on a few *in vitro* studies where blue cohosh has demonstrated a uterine stimulating effect on animal uteri. Homeopathic blue cohosh, however, was not shown to be a conclusive method of inducing labour according to a systematic review.

There are three case reports that blue cohosh taken at the time of delivery may cause; 1) perinatal stroke, 2) acute myocardial infarction, profound congestive heart failure and shock and 3) severe multi-organ hypoxic injury. As blue cohosh can have a toxic effect on cardiac muscle, probably due to its vasoconstrictive activity on coronary vessels<sup>22-24</sup>, it is plausible that blue cohosh may have been the causative factor for these observed cardiovascular birth defects. In both case reports of acute myocardial infarction, profound congestive heart failure, shock and severe multi-organ hypoxic injury, the authors imply a causative relationship between blue cohosh intake by the mother and their cardiac toxicity findings. In the case report of perinatal stroke, however, a causal relationship was unclear due to the confounding presence of benzoylgonine, a cocaine metabolite, in urine and meconium samples. In their correspondence with the editor, the authors of this case appeared to have ruled out cocaine use by the mother and adulteration of the blue cohosh product used; rather, they attributed their findings to a

laboratory instrument or analysis error, which is being further investigated. Nonetheless, blue cohosh remains a suspect as the causative factor in perinatal stroke. Lastly, further evidence of cardiac toxicity was observed in the midwife survey where it was reported that one of the most common adverse effect associated with blue and black cohosh administration at delivery was fetal tachycardia; as black cohosh has not been documented as having cardiac effects or as containing cardiac glycosides, it would appear that blue cohosh would be responsible for this adverse effect.

On the other hand, 64% of surveyed midwives reported using blue cohosh during delivery. It would seem likely that these licensed and trained medical professionals would not be administering a therapeutic agent that may cause severe cardiac adverse events to their patients or patients' newborns. Unfortunately, there is no evidence in the scientific literature on the safe use of blue cohosh by midwives during pregnancy. Of interest, however, and as evidence that blue cohosh is perhaps used with caution by midwives, is the report that blue cohosh was the herbal medicine used in pregnancy with the lowest comfort level.

Perhaps the cases reported above are due to blue cohosh being administered outside of its therapeutic window? Evidence to support a dose-dependant relationship was reported in the midwife survey where there was a wide variation in doses and number of doses for administering blue cohosh at delivery. As midwives reported learning about the use of herbal therapies by “word-of-mouth” from other midwives and not from research or specific texts, it may be plausible that whenever they use blue cohosh, they administer it at dosages within its therapeutic window.

There is fair evidence based on a case report that blue cohosh possesses abortifacient properties. Theoretical and/or expert opinion evidence lends support to this observation, as blue cohosh is also listed as a potential abortifacient, emmenagogue and uterine stimulant. Of concern, however, is a report of nicotinic toxicity associated with the use of blue cohosh to induce abortion.

Although it appears that blue cohosh was administered outside of its therapeutic window in

this case, clinicians should be made aware of the potential of blue cohosh to cause nicotinic toxicity.

Based on *in vitro* evidence, blue cohosh may have teratogenic, embryotoxic and oxytoxic effects. Of concern is the presence of anagryne in blue cohosh, which is believed to be responsible for the congenital deformity “crooked calf disease” in bovine animals. Although this teratogenic effect was not observed in sheep or hamsters, a case was documented of a human infant with similar congenital malformations (marked anaemia, skeletal dysplasia and vascular anomaly) following maternal exposure to anagryne-contaminated goat milk in early pregnancy.

In lactation, the safety of blue cohosh is unknown. It is unclear if the cardiac glycosides would cross into breast milk and potentially cause cardiovascular adverse effects in the newborn. It should be noted, however, that blue cohosh is mostly used to stimulate labour and would most likely be discontinued after delivery; thereby, it would appear unlikely that lactating mothers would consume this herb. Nonetheless, blue cohosh should be avoided in lactation until further high quality research is conducted.

Based on case reports of cardiac toxicity, abortive effects, nicotinic toxicity and potential teratogenicity, blue cohosh should; 1) be used with extreme caution during pregnancy, 2) be used only under medical professional supervision and 3) not be available to the public as an over-the-counter product. Blue cohosh should be avoided, particularly during the first trimester, due to case reports of abortifacient and teratogenic properties. The use of blue cohosh should be restricted to medical professionals trained in its administration at delivery, such as obstetricians, midwives, naturopathic doctors and medical herbalists, to name a few. As natural health products are frequently unregulated, governmental agencies should take immediate steps to limit public access to blue cohosh to prevent the administration of this herb without the supervision of a licensed and trained medical professional. There is an urgent need to conduct a retrospective or prospective cohort study of midwives using blue cohosh to determine its safety at the time of delivery, as any scientific evidence of safety or harm is more likely to be in the files of the midwifery practices than in governmental databases or hospitals.

**TABLE 1** Levels of Evidence for Efficacy

<b>GRADE</b>	<b>LEVEL OF EVIDENCE</b>
A	<b>VERY STRONG SCIENTIFIC EVIDENCE</b> Statistically significant evidence of benefit from one or more systematic reviews/ meta-analysis.
B1	<b>STRONG SCIENTIFIC EVIDENCE</b> Statistically significant evidence of benefit from one or more properly conducted random control trials (RCTs).
B2	<b>GOOD SCIENTIFIC EVIDENCE</b> Statistically significant evidence of benefit from one or more RCTs. The RCTs, however, are either of small sample size OR have discrepancies in their methodologies.
C	<b>WEAK SCIENTIFIC EVIDENCE</b> Statistically significant evidence of benefit from one or more cohort studies OR case control studies.
D	<b>VERY WEAK SCIENTIFIC EVIDENCE</b> Evidence from case series OR case reports.
E	<b>INDIRECT EVIDENCE</b> Expert opinion OR laboratory studies.
F	<b>HISTORICAL OR TRADITIONAL EVIDENCE</b> Historical or traditional use by medical professionals, herbalists, scientists or aboriginal groups.

**TABLE 2** Levels of Evidence for Harm

LEVEL	EVIDENCE
1	<b>STRONG SCIENTIFIC EVIDENCE</b> Statistically significant evidence from one or more systematic reviews or RCTs.
2	<b>ACCEPTABLE SCIENTIFIC EVIDENCE</b> Statistically significant evidence from one or more well designed cohort studies OR case control studies.
3a	<b>WEAK SCIENTIFIC EVIDENCE</b> Evidence from one or more case series.
3b	<b>VERY WEAK SCIENTIFIC EVIDENCE</b> Evidence based on case reports.
4	<b>INDIRECT SCIENTIFIC EVIDENCE</b> Evidence based on scientific studies conducted on animals, insects or microorganisms OR laboratory studies on human cells.
5	<b>THEORETICAL EVIDENCE</b> Evidence based on scientific theory OR expert opinion.
6	<b>UNKNOWN</b> No available information.

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