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Blue Cohosh: History, Science, Safety, and Midwife Prescribing of a Potentially Fetotoxic Herb

Aviva Romm

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**Blue Cohosh:
History, Science, Safety, and Midwife Prescribing
of a Potentially Fetotoxic Herb**

**A Thesis Submitted to the
Yale University School of Medicine
in Partial Fulfillment of the Requirements for the
Degree of Doctor of Medicine**

Aviva Jill Romm

2009

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1. Introduction

“So eight days late, huh, you must be getting a little uncomfortable? If you’re anxious there are a few ways to help things along...actually there are things you can do...just some home remedies.... I’ve found that some of them are very effective.... there’s an herbal tea you can drink....”

- Obstetrician in Television Program *Friends*, “The One Where Rachel is Late,” (2002)

Overview: Herb Use by Women in the United States

Herbs have been applied for the treatment of difficulties arising during pregnancy and childbirth since time immemorial, with texts and treatises on the uses of herbs for childbearing problems dating back at least to ancient Egypt. (1, 2) With the advent of modern pharmaceuticals and the transition of the place of birth primarily from home to hospital, their use fell out of common practice in the United States (US) in the early to mid 20th century. Herbal products have since enjoyed renewed popularity in the US, with a revival beginning in the 1980s. Several herbal products, for example, echinacea (*Echinacea* spp.) and St. John’s wort (*Hypericum perforatum*), have achieved nearly household name status for the prevention of colds and the treatment of mild to moderate depression, respectively. Botanical medicines are now officially recognized as a category of complementary and alternative medicines (CAM) by the National Institutes of Health (NIH) National Center for Complementary and Alternative Medicine (NCCAM). (3)

Women are the primary consumers of herbal medicines in the US. Herbs are a particularly attractive natural alternative for women seeking to avoid drugs and invasive treatments during pregnancy and labor. (4) Herbal supplements are commonly used to relieve a variety of normal pregnancy complaints (i.e., nausea, insomnia, heartburn) and are less frequently used for the prevention or treatment of medical problems (threatened miscarriage, post-term pregnancy), the latter either under the guidance of an obstetric professional or by self-prescription with information from friends, relatives, books, magazines, or the Internet.

There is a prevailing belief (and misconception) amongst herb users that “natural is safer,” however, it is well known that many herbal products contain potent, pharmacologically active constituents. (4) A second common belief is that use of an herb for centuries is proof of its safety. (4) However, lack of evidence of harm is not always proof of safety. Further, products available today, and instructions for their dosing and duration of use may differ significantly from traditional and historical practices. Thus, extrapolation of safety in a contemporary context based on what is assumed to have been centuries of safe traditional use is not always reliable. (4) Finally, as analysis of blue cohosh products has demonstrated, there is tremendous variability in the constituents of herbal products between brands and types of products (i.e., dried herb, capsules, liquid extracts) making it impossible, in the current herbal products market, to have any idea of the actual ingested daily dose of the chemical constituents in the herb. (4, 5) This also makes pharmacologic results obtained with one product difficult to apply universally. (4)

Federal regulations support labeling of herbs for uses related to the normal “structure and function” of the body, for example, morning sickness associated with pregnancy, but not for medical problems related to pregnancy. (6) Several clinical trials have established the efficacy and safety of ginger root (*Zingiber officinalis*) to treat mild nausea and vomiting of pregnancy (NVP) and raspberry leaf (*Rubus idaeus*) to slightly reduce operative delivery and postpartum bleeding when taken as a tea regularly during pregnancy. (7-10) However, the safety and efficacy of most herbs used during pregnancy remains unknown, and inherent ethical issues regarding research involving pregnant women as subjects will likely continue to limit clinical trials.

Epidemiologic studies and surveys over the past 10 years estimate a range of approximately 7% to 46% of women using herbs during pregnancy. (11-15) There is considerable evidence of herb prescribing by obstetric health professionals including certified nurse-midwives (CNM) and direct-entry midwives (DEMs), with one survey demonstrating that 90% of CNMs use herbs for their pregnant clients. (16-19, 20-22) No studies have been conducted to evaluate the volume of use of blue cohosh by obstetricians, but at least one case report suggests that such use is occurring. (22) The introductory quote to this thesis suggests

a mainstreaming of herb use, enough so that it would be mentioned by an OB-GYN on a popular television sit-com (*Friends*) when one of the characters is seeking advice for her post-term pregnancy.

Blue Cohosh: What Is It?

A native of the eastern and central woodlands of the United States, blue cohosh (*Caulophyllum thalictroides*) has been used traditionally and historically as a gynecologic aid for the treatment of amenorrhea, dysmenorrhea, and menorrhagia; and most notably, for labor induction, to assure a prompt labor, to reduce the pain of childbirth, and to induce abortion. (28, 29) The use of herbs prophylactically during pregnancy to expedite and ease labor dates to antiquity when herbs used for such purposes were called *partus preparators*. The use of blue cohosh for this purpose was first introduced to white settlers by native inhabitants who referred to it as “squawroot” or “papoose root” and who reportedly used it to facilitate childbirth. (2, 28)

Blue cohosh was officially listed in the *United States Pharmacopoeia* from 1882-1905 for labor induction, and in the *National Formulary* from 1916-1950. (30) The practice of labor induction with blue cohosh remains a popular choice by pregnant self-prescribers seeking natural alternatives to labor induction and by obstetric professionals in the US, especially midwives working in home, birthing center, and hospital settings. (22, 23, 24-27) In one study, 64% of midwives reported using blue cohosh to facilitate childbirth. (24) In addition to its use for labor induction, blue cohosh is popularly taken daily during the last 3-6 weeks of pregnancy as a *partus preparator* in the belief that it can facilitate labor, prevent post-term pregnancy, shorten labor duration, reduce labor pain, and prevent complications such as “failure to progress” and postpartum hemorrhage.

Maternal ingestion of this herb as a *partus preparator* has been associated with a range of fetal and neonatal side-effects and adverse outcomes including tachycardia, increased meconium, and increased need for resuscitation. (24, 31-33) Several case reports in the scientific literature link maternal ingestion of blue cohosh in the weeks prior to labor with perinatal stroke, acute myocardial infarction and congestive heart failure, and multi-organ hypoxic injury. (33, 34, 35) There is also a case report of acute nicotinic toxicity in

a non-smoking woman who took large amounts to induce abortion. (36)

The plant and its extracts contain the alkaloids *N*-methylcytisine, baptifoline, anagryne, and sparteine, among others, some of which are toxic and have been implicated as teratogens in higher animals (5, 23, 35, 36, 37, 38, 39). The pharmacologic actions of several alkaloid and saponin glycoside components in blue cohosh are consistent with possible mechanisms for reported adverse effect. (30, 37, 38) The safety of these products to the fetus is of concern because the use of the herb involves administration to women of reproductive age and pregnant women. (38, 39) In spite of known concerns, the prevalence of use and safety of this herb have not been well-studied. The unevaluated and prevalent use of blue cohosh as a late pregnancy tonic represents a potential maternal-fetal public health concern.

Habitat and Identification

Blue cohosh, a member of the barberry family, is a moist woodland perennial standing 1-2 ft. tall, found in a geographic distribution ranging from New Brunswick (Canada) to South Carolina and from North Dakota to Arkansas (Figure 1). The plant arises from a large rhizome. The leaves are divided into three (occasionally 5) leaflets, each with 2-3 lobes (Figure 4-5). Early in the spring the plant has a waxy bloom of 6-parted, greenish-yellow in terminal clusters (Figure 2). (43)

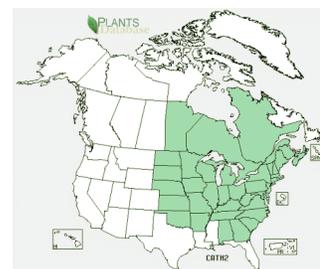


Figure 1: USDA Blue cohosh distribution map



Figure 2: Blue cohosh flower



Figure 3: Blue cohosh fruit



Figures 4-5. Left: Blue cohosh flowering plant (courtesy Martin Wall Botanical Images) Right: Blue cohosh botanical line drawing

The entire plant develops a peculiar bluish-green appearance and, by late August, bears mature blue fruit (Figure 3). The root and rhizome are the medicinally used plant parts. Blue cohosh should not be confused with black cohosh (*Actaea racemosa* syn *Cimicifuga racemosa*). Although the two herbs are often used in combination and both are commonly used for women's gynecologic complaints, they are not from the same genus.

Historical Use

Blue cohosh was a widely used emmenagogic (an agent used to stimulate the menses) and oxytocic (used to stimulate uterine contractions) drug in the US and remained an official medication until 1955. *The Dispensatory of the United States of America*, 24th Edition (1947), states that blue cohosh was used by Native Americans (nations unspecified) to facilitate childbirth, a practice reported to have been brought to the attention of the medical profession by Peter Smith in 1813. (44, 45) Smith was an “Indian doctor,”¹ in whose book, *The Indian Doctor's Dispensatory*, appears the first mention of this herb in Euro-American medical literature. (44, 45)

Most reports credit the Algonquin (Algonkin) people for knowledge of its use. Daniel Moerman, Professor of Anthropology at the University of Michigan and authority on Native American ethnobotany, reports the use of blue cohosh by numerous Eastern tribes, however, amongst these, only the Cherokee and the Potawatomi were reported to use it as an aid to childbirth. (28)

Rafinesque (c.1828), a famed natural scientist who lived amongst Native Americans, brought further attention to blue cohosh in his *Medical Flora*, in which he cites its use by Native Americans, calling it “a powerful emmenaogogue promoting delivery, menstruation, and dropsical discharges.”² (47) It was Rafinesque who is said to have suggested the name blue cohosh, based on the dark blue berry-like structures; the word “cohosh” is attributed to the Algonquin word for “rough” referring to the texture of the roots. (48, 49)

¹ The term ‘Indian doctor’ was a description of an herbalist who used the native North American plants; it did not necessarily denote Native American ancestry nor direct study with Native Americans. (46).

² “Dropsical discharges” refers to profuse watery discharges.

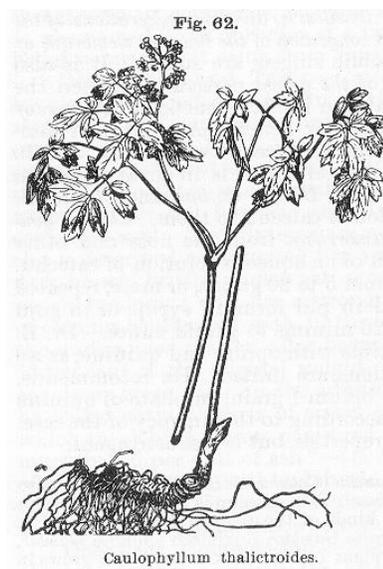


Figure 6. From King's American Dispensatory

Three modern secondary sources on native American ethnobotany (Erichsen-Brown, Moerman, Vogel) reveal only occasional use of the plant for childbirth preparation, however, there is more frequent mention of use during labor to promote delivery, possibly in arrested labor. (28, 46 , 50, 51) It is unclear, based on available historical documents, how universally blue cohosh was used by Native Americans within its geographic distribution range. (46)

In the nineteenth century ergot was the primary pharmaceutical used for labor induction. Introduced to the obstetric profession by a French midwife but in use since as early as 600 BCE, ergot caused extremely strong and uncontrollable contractions, so was not an ideal substance for safely initiating labor. Blue cohosh was widely used as a gentler and safer alternative to ergot by the Eclectic physicians, a branch of American medical doctors popular from the early nineteenth to early twentieth centuries. It was typically administered 2 to 3 weeks prior to labor based on the recommendations published by Smith and Rafinesque. (45) John Uri Lloyd (1849-1936) and Curtis Lloyd (1859-1926), influential American pharmacists and founders of Lloyd Brothers Pharmacists, Inc., describe the use of blue cohosh use in one of their pharmaceutical bulletins, stating that:

...when used by delicate females, or those subject to prolonged and troublesome labors, for several weeks previous to the parturient period, it appears to impart tone and normal action to all the powers engaged in this important process, facilitating its progress, and relieving the woman of much suffering. For this purpose it is frequently administered in combination with other agents, and given in proper doses, two or three times daily. During labor, when, from fatigue, debility, or impaired uterine nervous energy, the contractions become feeble, inefficient, or very severe and of a spasmodic character, or have entirely ceased, the administration of Caulophyllum in decoction, or even in powder, will be found preferable to Ergot, as the contractions aroused by its action are less violent and spasmodic than those effected by Ergot, and more nearly resemble the natural ones. In severe after-pains, more prompt and efficient relief will follow the use of Caulophyllum, than from any other agent, in doses of from two to four grains, administered, if necessary, every one, two, or three hours. (52)

John King (1855), the renowned Eclectic physician and prolific author of botanical medicine textbooks, extolled the virtues of blue cohosh as a “preparatory parturient” in his book *American Eclectic Obstetrics*. (53) He recommended a formula called *Parturient Balsam* (Figure 7) for giving tone and activity to the uterus when its functions are “torpid or impaired.” The herbs were to be ground, mixed, and macerated in

76% alcohol for 2 days, percolated in hot water, and finally boiled down and sweetened with sugar to form an elixir. A related blue cohosh-containing formula, one more famous and currently still available on the market for gynecologic complaints and as a *Partus preparator* is called Syrupus Mitchellae Compositus—Compound Syrup of Partridgeberry (*Mitchella repens*), or more popularly, Mother’s Cordial (Figure 7). It was to be prepared similarly to Parturient Balsam.

Figure 7. Popular Eclectic Blue Cohosh Parturient Formulae

<i>Parturient Balsam</i>	<i>Mother’s Cordial</i>
Blue cohosh root (<i>Caulophyllum thalictroides</i>)	Partridge berry (<i>Mitchella repens</i>)
Spikenard root (<i>Aralia racemosa</i>)	Blue cohosh root (<i>Caulophyllum thalictroides</i>)
Black cohosh root (<i>Actaea racemosa</i> syn. <i>Cimicifuga racemosa</i>)	False unicorn root–Helonias (<i>Chamaelirium luteum</i>)
Partridge berry herb (<i>Mitchella repens</i>)	High bush cranberry (<i>Viburnum opulus</i>)
Queen-of-the-meadow root (<i>Eupatorium purpurea</i>)	
Ladies’ slipper root (<i>Cypripedium pubescens</i>)	
Comfrey root (<i>Symphytum officinale</i>)	

King echoes the Lloyds, stating that blue cohosh “will frequently be found more desirable than Ergot for expediting delivery, in all those cases where the delay is owing to fatigue, debility, or want of uterine energy; the contractions it occasions will nearly resemble the natural ones, instead of the continuous, spasmodic contractions effected by ergot.” (53) It was also reported in his textbook to be beneficial in the treatment of after-pains, for which it was to be combined with the uterine antispasmodic herb *Viburnum opulus* (cramp bark).

Scudder (1870) reported “*Caulophyllum* exerts a very decided influence upon the parturient uterus, stimulating normal contraction, both before and after delivery. Its first use, in this case, is to relieve false pains; its second, to effect co-ordination of the muscular contractions; and third, to increase the power of

these. The first and second are the most marked, yet the third is quite certain. Still if any one expects the marked influence of Ergot, in violent and continued contractions, he will be disappointed.” (54)

King's American Dispensatory by Felter and Lloyd (1898) describes blue cohosh as an oxytocic; to “relieve false pains and uterine irritability; spasmodic uterine contractions; and for uterine subinvolution.” (29) The authors of this popular textbook proclaim:

There is no doubt but that caulophyllum has a decided action upon the gravid uterus. During labor it relieves false pains and coordinates muscular contractions, at the same time increasing their power...it is a better oxytocic than ergot...it stimulates normal contraction instead of inducing spasmodic uterine action. As a partus preparator, blue cohosh has enjoyed a well-merited reputation. When used by delicate women, or those who experience prolonged and painful labors, for several weeks previous to confinement, it gives tone and vigor to all the parts engaged in the accouchement, facilitating its progress, and relieving much suffering. It is a good remedy for after-pains, especially when spasmodic in character. It is a remedy for hour-glass contraction and for spurious labor-pains. (29)

Scudder (1898) writes in *The American Eclectic Materia Medica and Therapeutics* that

We have used it often, and known of its frequently being used by others, for a few weeks prior to confinement, as a preparatory measure to the important changes which take place at that time, with greatest apparent advantage. In many instances, when the females had been invariably the subjects of tedious and difficult labors, by the use of the Leontice [blue cohosh] for two or three weeks before confinement, all that anticipated difficulty vanished, the labors were rapid and easy, and the recovery speedy when compared with previous confinements...We have known many highly intelligent ladies, who after having come to use it once, could not be prevailed to dispense with its use in subsequent pregnancies. (54)

Ellingwood (1908) deviates from the typical description of the uses of blue cohosh by suggesting its use much earlier in pregnancy--“From the end of the sixth month to the close of pregnancy is a period when many distressing symptoms are manifested, which may, in a measure, be relieved by caulophyllum”--and also as a medication to prevent premature labor, a clinical effect that would seem to be contradictory to its more common use as an emmenaogue. He purports that “The effect of caulophyllum is to prolong gestation till the fetus is fully developed, labor being a physiological process at full term, and not pathological, therefore less protracted, less painful, and less liable to accidents.” He also specifies the use of this herb to facilitate labor specifically due to its ability to contribute “to the relaxation of a rigid os, increasing the strength of the pains,” for which he states it will also “assist materially in controlling an abortion.” (55)

In addition to use by the Eclectics, numerous dispensaries, pharmacognosy texts, and materia medicas cited the use of blue cohosh as an emmenagogic or oxytocic drug, including *The National Dispensatory; A Text Book of Pharmacognosy; and Materia Medica, Toxicology, and Pharmacognosy* (41, 42, 56) It was first mentioned in the United States Dispensatory 12th edition in 1866 in which Drs. Wood and Bache wrote, “it is deemed especially emmenagogic, and is thought to promote contractions of the uterus, for which purpose, we learn, it is much employed by the ‘eclectic’ physicians...”. (57) It became an official drug in the fifth revision of the United States Pharmacopoeia and remained so through 1955, though it was removed from the list of United States Pharmacopoeia approved substances after 1880.³ The Eclectic physicians continued to use it into the early twentieth century. The American Dispensatory (1908) notes the contradictory powers attributed to blue cohosh: on the one hand it is described as “sedative, antispasmodic” yet also as oxytocic—“to have the power when uterine inertia occurs during labor to cause the contractions to become very severe, without altering their general character as does ergot.” It is simultaneously alleged to be “capable of arresting threatened abortion,” and to be “capable of originating uterine contractions and of producing abortion.” (58)

By the early-mid 20th century, quinine and eventually pituitary extract became the primary medications for labor induction. (59) With the increasing safety and controllability of the latter, a switch in the place of delivery from predominantly home to primarily hospital, and with the era of the “botanical physicians” drawing to a close, so did the use of blue cohosh as a common parturient and labor stimulant. (2)

• *Early chemical analysis*

Chemical analysis of blue cohosh can be dated to as early as 1835. In 1864, Ebert first identified saponin and glycoside fractions in the plant; soon after, an alkaloid fraction was identified. These constituents and the isolation methods used were described in detail in early American botanical-medical and

³ The spread of the use of this herb to Europe as an obstetric aid is demonstrated by its inclusion in *Lehrbuch der Biologischen Heilmittel* (1938), by physician Gerhard Madaus who discussed it for “relief of the birth,” to be taken “several weeks before the delivery,” and also “for expelling the afterbirth...”

pharmaceutical literature. (29, 52) The glycoside fraction was said to resemble quinine in appearance and was demonstrated to be soluble only in alcohol. A resinoid compound, obtained from the precipitation of a strong alcohol tincture in water, and called *Caulophyllin*, was thought to contain the “emmenagogic principle,” and was sold as the one percent solution *Lloyd’s Leontin*.(29) The National Dispensatory 5th edition (1896) cited this early pharmacology work, suggesting that no further analytical work had been done. (41) By the 1920s several compounds had been isolated: methylcytisine (a crystalline alkaloid previously called caulophylline), caulosaponin (a crystalline glucoside previously called leontin), and caulophyllosaponin (a phytosterol). (56) The plant was also known to contain a volatile oil, an enzyme, a reducing sugar, a resinous substance, and a mixture of fatty acids.

Renewed Interest: Contemporary Use

In the early 1980s there was a revival in the use of blue cohosh as a *Partus preparator* and for labor induction and augmentation, mostly by “back-to-the-landers” who were having homebirths and returning to the use of natural medicines more generally. The less than one percent of women having their babies at home in the US, most often with the assistance of lay midwives, were seeking methods to promote easier labors both to facilitate birth and to avoid going to the hospital should pregnancy extend past 40 weeks, a common “cut off point” when women report they were told by their OB-GYNs that they’d have to be induced. In the 1990s, CNMs practicing in hospitals and birthing centers also began to turn to alternative methods of labor stimulation and augmentation to help their pregnant clients meet the criteria for low-risk pregnancies that allowed them to deliver these women, rather than transferring care to an obstetrician or hospital from a birthing center.

Hygieia: A Woman’s Herbal (1978), a book by the late midwife-herbalist Jeannine Parvati Baker, re-introduced the use of blue cohosh as an emmenagogue and uterine tonic while *Wise Woman Herbal for the Childbearing Year* (1986) by herbalist Susun Weed and smaller self-published books and manuals by herbalists and midwives provided instruction on the use of blue cohosh as an emmenagogue, an abortifacient, and for labor induction and augmentation. Fledgling herbal products companies made access to blue cohosh products possible. Susun Weed, whose book is one of the highest selling herbal books in the

world, states that blue cohosh and black cohosh (*Actaea racemosa*) are “safely used as teas or tinctures only during the last 4-6 weeks of pregnancy, not before.” “Blue cohosh,” she reports, “is a reliable remedy when labor needs promoting. It does not stimulate the uterus into irregular contractions or cause any tightness or clamping down of the cervix.” She does note that “if fetal heart-tones are monitored, there may be a noticeable elevation as the blue cohosh starts to work.” (60)

More general interest in the herb began to occur in the late 1980s and early 1990s, coincidental with a generally increased public interest in natural therapies and as a reaction to increased rates of labor induction⁴ by obstetricians, for which women were seeking natural alternatives. By the late 1990s, herbal medicines hit the mainstream. Harvard physician David Eisenberg’s seminal paper in 1997 demonstrated that herbal product use was on the rise and that Americans were paying an estimated \$27 billion in out-of-pocket expenses for complementary and alternative medicines. (62) More herb books were published. Most of the entries on blue cohosh in these books carry some warning that it be used with cautions and limitations, however, these limitations might allow for, as did Susun Weed, use in the last 4-6 weeks of pregnancy. Rosemary Gladstar writes in *Herbal Healing for Women* (1993) that “It [blue cohosh] is often combined with black cohosh and used as a tea/or tincture during the last week of pregnancy to prepare the uterus for an easy birth and to stimulate uterine contraction.” She also reports on its use for prolonged labor. No precautions are provided. In Amanda McQuade Crawford’s *Herbal Remedies for Women* (1997) she states that blue cohosh is “only taken if needed,” for example, “as a uterine tonic, it is used in the early stages of pregnancy to prevent miscarriages, when it is an antispasmodic.” Even this author’s own book published in early 1997 (therefore written the same year the first case report was published)⁵ supported the use after 37 weeks as a uterine tonic. The revised edition, published in 2003, provides warnings about use

⁴ Between 1989 and 1997 the rate of labor induction in the US doubled from 9% to 18% and by 2004 it was 21.2% (61) This increase was coincidental with an increased use of botanical medicines by pregnant women and midwives in the US, including blue cohosh for induction.

⁵ The publication of the first case report went mostly unnoticed as it was a small mention in an obscure New Zealand medical journal; in fact, with the publication of the Jones and Lawson report, those authors asserted that it was the first such report, to be corrected in a letter to the editor from the authors of the initial report.

in pregnancy, discusses the case reports, and urges that it is to be used in labor, it be done so only under the guidance of a qualified obstetric health professional and with ample monitoring of mother and baby.

In the late 1990s, as herbal medicine use was becoming more commonplace amongst nurse-midwives, articles about herbs began appearing in nurse-midwifery journals. In 1995, Cindy Belew, a CNM, wrote and self-published a manual called *Herbs and the Childbearing Woman: Guidelines for Health Providers* in which she states that she only rarely uses blue cohosh in her practice, but then seemingly contradicts this when she reports personal use of blue cohosh in the last four weeks of pregnancy “to prepare women for labor *in a large number of cases* [emphasis mine].” She asserts using it as only a “very small” proportion of the dose—7-8 drops [of tincture] three times daily. She asserts that anecdotal reports by midwives of increased rates of meconium and uterine hyperstimulation have caused many to switch to using homeopathic preparations, and she also warns that “an isolated constituent of blue cohosh has hypertensive effect in animals.. Because of this, either avoid using in hypertensive clients, *or if using in hypertensive clients* [emphasis mine], use low doses for a short term and monitor the blood pressure.”

In 2005, Tieraona Low Dog, MD, also an herbalist with some experience assisting at homebirths, suggested in her book *Women's Health in Complementary and Integrative Medicine* that, while it is impossible to establish causality between the herb and case reports of adverse events in pregnancy based on the available evidence, obstetric care providers should be prudent, and avoid the use of blue cohosh during pregnancy.

(30)

During the 1980s, blue cohosh products were also becoming increasingly available in health food stores, and with a rise in Internet use as a source of health information in the 1990s, more women gained access to information about the herb and the herb itself .

The first case reports of adverse neonatal outcomes associated with maternal ingestion of blue cohosh began to appear in the medical literature in 1996. (21, 23) In spite of concerns that have arisen over its use in the past decade, blue cohosh continues to be sold in most health food stores in the US, prescribed by

obstetric care providers, and used by pregnant women. In 2004, *one* small herb company alone sold nearly 6,000 ounces of blue cohosh tincture; in 2005, 8,165 pounds of dried herb were sold commercially. (63, 64) Blue cohosh containing dietary supplements are widely available on the Internet and in health food stores. They are marketed primarily to women, with limited information on the composition of these products. (5) The products are recommended not only for use during pregnancy, but for other general gynecologic complaints. Suggested product use is as a woman's tonic, a uterine tonic, to ease menstruation, to balance uterine function, for smooth muscle relaxation to prevent miscarriage and for childbirth preparation. (5) While many sites mention some precautions with use, not all provide such warnings.

A recent study by Satchithanandam et al. analyzed fifteen blue cohosh products purchased off the Internet as dietary supplements as no commercial reference standards or methods currently exist for quantification of these products in dietary supplements. (5) The products consisted of blue cohosh roots, root powders, capsules of powdered root material, or liquid extracts. All but two of the products carried warning statements regarding use during pregnancy or lactation, for example, "Not to be used during pregnancy," "Seek expert medical advice before taking during pregnancy," "Do not use if you are pregnant or may become pregnant," "Do not use if you are pregnant or nursing."(5)

Prevalence and Patterns of Blue Cohosh Use in Pregnancy

• *Prevalence of general herb use in pregnancy*

Surveys estimate a range of approximately 7% to 45% of women using herbs during pregnancy. (11, 12, 13, 14, 66, 67) Articles and studies published in prominent nurse-midwifery and obstetric journals (i.e., *Journal of Nurse-Midwifery*, *Obstetrics and Gynecology*, and *Clinical Obstetrics and Gynecology*) indicate that a large number of CNMs use herbal medicines clinically or are interested in learning to do so. (16, 18, 19, 20)

A survey of 587 pregnant women by Glover et al. (2003) revealed that a total of 45.2% of participants in a rural obstetric population had used herbal medications. (15) In another study, approximately one-third of 463 postpartum women surveyed in the US reported having used complementary and alternative therapies

(including herbal medicines) during pregnancy. (66) In another survey, of the 734 pregnant women that responded, 46% used herbal remedies at the recommendation of their health care provider; 54% did so at the recommendation of a friend or family member. (66) A survey by Tsui et al. of patients visiting the birthing facility of the University of San Francisco or attending the University of California, San Francisco obstetrics and gynecology clinic (150 respondents over five months) found that 13% used a dietary supplement during pregnancy. (67)

A study by Hepner et. al (2000) conducted at Brigham and Women's Hospital in Boston over a 13-week period evaluated the use of botanical products by parturients. A total of 1203 questionnaires were distributed, in English and Spanish, to parturients at approximately 20 weeks' gestational age as part of a routine antepartum educational package; 734 completed surveys were collected (61% response rate). Information was gathered on the use of all prescription and non-prescription medications, including herbal remedies, the reason they were started or stopped, the types of labor analgesia being considered, and use regarding 23 commonly used herbal remedies with space provided for writing in any unnamed herbal remedy. Finally, parturients were asked whether they considered these herbal remedies to be medications. In all, 7.0% of nulliparas and 7.7% of multiparas reported the use of any herbal remedy. Forty-six percent of parturients who used herbal remedies reportedly did so at the recommendation of their health care provider. Only 14.6% of users considered herbs to be medications; 41.6% did not, with the remaining percentage unaware of whether herbal remedies were medications. (68)

In 2000, Allaire et al. conducted a survey of CNMs in North Carolina and discovered that 73.2% of 82 respondents were recommending the use of herbal medicines in clinical practice. (69) A 1999 study by McFarlin et al. demonstrated that 90% of midwives surveyed were using herbs specifically for labor stimulation. (21) A 2007 survey of Texas midwives (licensed direct entry and certified nurse midwives) by Bayles to evaluate complementary and alternative medicine, specifically herbal medicine use, found that 87% of respondents (60/69) used, recommended, or referred their clients for an herbal remedy, not including homeopathic tinctures. Licensed DEMs used, recommended, or referred their clients for a greater number of herbal therapies than did CNMs. (70)

• *Use of blue cohosh in pregnancy*

Not only is herbal medicine use prevalent amongst pregnant women, blue cohosh is among the leading herbs used. Perhaps the most important study revealing the prevalence and patterns of blue cohosh use in pregnancy was that conducted by McFarlin et al. (1999) to document the use of herbal preparations for cervical ripening, induction, and augmentation of labor by CNMs. (21) The authors conducted a national survey of 500 members of the American College of Nurse-Midwives (ACNM) by single mailing of an anonymous survey sent to every fifth name on the organization's member list. Forty-eight nurse-midwifery education programs were also surveyed to determine whether they were formally or informally educating students about the use of herbal preparations for cervical ripening, induction, or augmentation of labor. Of a 34% response rate, 90 surveys were returned from CNMs who used herbal preparations to stimulate labor and 82 were returned from CNMs who did not use herbal preparations to stimulate labor. Of the CNMs who used herbal preparations to stimulate labor, 64% used blue cohosh (castor oil was used by 93% and evening primrose oil by 60%; other herbs used included black cohosh by 45% and red raspberry by 63%). Nurse midwives working in private practice were more likely to use herbs to stimulate labor than those employed by hospitals; however, they were used in all settings. Seventy-eight percent of the CNMs directly prescribed herbal preparations to stimulate labor while 70% indirectly suggested them to clients. Only 22% had included them within their written practice protocols. Seventy-five percent of the CNMs who used herbal preparations to stimulate labor used them first or instead of pitocin. Sixty-four percent of the nurse-midwifery education programs included instruction in the use of herbal preparations to stimulate labor in their formal curricula, and 92% included informal discussions on the use of herbal preparations. (21)

In the survey of CNMs in North Carolina by Allaire et al (2000), 68.3% of respondents reporting use of botanicals in pregnancy reported using herbs for post-term pregnancy (or pregnancy approaching post-term) and/or cervical ripening; 45% reported use for labor induction; 31.7% reported using herbs for labor augmentation or treatment of dysfunctional labor. (69) Blue cohosh was reported to be commonly used for these purposes, and was the primary herb used in the treatment of dysfunctional labor.

A 2007 survey of Texas midwives by Bayles reported similar findings, with herbal therapies the most salient of the complementary and alternative therapies used for cervical ripening (83%) and labor induction (77%) by 69 respondents. Red raspberry leaf, blue cohosh, and black cohosh were the most popular herbs for cervical ripening; blue cohosh, castor oil, and black cohosh the most popular methods for labor induction. (70)

• *Reasons cited for blue cohosh use in pregnancy*

The most frequently cited reason by CNMs for using herbal preparations to stimulate labor (see Table 1) is that they are “natural”; the most common reason for not using herbal preparations was a lack of research or experience with the safety of these substances. (21) Other reasons for using herbs include: they are less interventive; they are low risk and cheaper than conventional interventions; they can be used at home or in the birth center whereas pitocin and prostaglandins cannot; they have been used traditionally by midwives; they are effective in avoiding medical induction and post-term pregnancy; and good results have been obtained when used by colleagues. (21)

These reasons for use are echoed in a 2000 survey of North Carolina CNM’s use of herbal medicines during pregnancy, with additional reasons cited as herbs being the patient’s preference, less expensive, safer than allopathic medicine, used when allopathic medicine fails, that they are more effective than traditional allopathic remedies, and more available to nurse midwives. (69) Seventy-one percent of midwives in the study by Allaire et al. reported using herbal therapies in conjunction with allopathic medicine. (69)

The most common reasons cited for *not* using herbs for labor induction, etc., were lack of research or experience, though fear of litigation and lack of acceptance by colleagues, other health professionals, and clients were also noted, as was concern about going outside of standards of care. (21)

Table 1. Reasons cited by midwives for using herbs for labor induction, cervical ripening, or labor augmentation (21, 69)	
Natural	Used traditionally
Less interventive than conventional approaches	Effective in avoiding medical intervention
Safer than conventional approaches	Good results obtained by colleagues
Less expensive than conventional approaches	Patient's preference
Can be used at home or in the birth center; more accessible	Can be used when medical interventions fail

• ***Preparations and forms of administration***

Blue cohosh was reportedly taken as a tea by Native American women; however, the preparation was more likely to be what is properly known as a decoction, a water extract similar to tea but made with a larger volume of herb material steeped for longer than tea, yielding a stronger medicinal preparation. Eclectic physicians used the crude plant in the form of powdered herb, and also prepared hydroethanolic extracts and resinoid concentrates (*Caulophyllin, Leontin*). Today the herb is taken either as a root powder in capsules or compressed tablets, or as a tincture (hydroethanolic extract). The herb is exceptionally bitter and acrid to the taste, making water based preparations such as teas, infusions, and decoctions virtually unpalatable.

• ***Dosage***

There is some variation in the doses recommended historically; however, the dose variation is not great. Generally, small amounts of the herb were recommended regardless of the form of preparation. Contemporary recommended dosage ranges and frequency of administration are also within a limited range in the herbal literature, however, they are much more variable in the midwifery literature and word-of-mouth use where the doses also tend to be higher and given more frequently for labor induction and augmentation (Table 2; Appendix 4).

The Eclectic literature gives the dose of the decoction or infusion (1 oz. root to 1 pint water) to be two to four fluid ounces every three or four hours; of the tincture (3 oz. pulverized root to 1 pint alcohol) from ten to thirty drops, three to four times a day; of the fluid extract from five to fifteen drops; and of the specific tincture, three to ten drops. (52) The 1947 Dispensatory of the United States gives the typical dose of crude herbal drug to be in the range of 0.5 to 1 grains. (45)

Table 2. Blue Cohosh Dosages*		
Crude Powder	Eclectic	Crude powder was used only prepared as an infusion or decoction+
	National Formulary (83) /US Dispensatory (45)	0.5 g 0.5 to 1 g
	Contemporary Herbal (84)	0.9-3g herb/day
Tea/Infusion/Decoction	Eclectic	Decoction or infusion (1 oz. root to 1 pint water) 2-4 fl oz. every three or four hours
	National Formulary/US Dispensatory	Decoction of 30g/pint of water given in doses of 1-2oz41
	Contemporary Herbal (87)	0.3-1.0 g as a decoction 3 times/day
	Contemporary Midwifery	Highly variable ranging from 15 drops several times daily to numerous droppers full daily (See Appendix 4).
Capsules	Eclectic+	Not specified.
	National Formulary/US Dispensatory	Not specified.

	Contemporary Herbal	Approximately 1-3 500 mg capsules/day
	Contemporary Midwifery	1-2 capsules (amount unspecified), 1-2 times/ day (mg/capsule not specified)
Tincture	Eclectic	Tincture: 5-30 drops 3-4 times/day.
	National Formulary/US Dispensatory (88)	0.5 mL/day Fluid Extract
	Contemporary Herbal (87)	• 0.5-1mL (1:1 in 70% EtOH) 3 times/day
	Contemporary Midwifery	• For labor induction either 5 drops every hour or 10 drops every 2 hours, to be taken in hot water (21). Also see Appendix 4.

*The dose and frequency of dosing may vary depending on the condition for which the herb is being administered. + The Eclectic physicians also utilized a resinoid concentration called *Caulophyllin* (taken in doses of 0.25 repeated 2-4 times/day, to 3 grains)

• ***Botanical education of obstetric professionals***

McFarlin et al. reported that 69% of CNMs who reported using herbal preparations to stimulate labor learned about them by word-of-mouth, 4% from formal research publications, and none from their formal education programs. (21) In contrast, 92% of CNM training programs reported that herbal preparations for stimulating labor were discussed informally in the program and 64% reported some formal instruction. This disparity is possibly a result of the time lapse between when these midwives graduated from their training programs and the introduction of such education into CNM training programs. (21) Lack of adequate education on the use of botanical medicines, and the desire to learn to use them was noted numerous times in the nurse-midwifery literature.

2. Hypothesis and Specific Aims of the Study

Ingestion of blue cohosh by pregnant women presents a potential risk to the embryo, fetus, and neonate due to the potential teratogenicity, fetotoxicity, and cardiotoxicity of pharmacologically active constituents in the herb and its commonly available products. Previous studies conducted on the use of herbs by midwives have demonstrated that blue cohosh is a commonly used agent for labor induction and augmentation. (16, 21) Maternal consumption of blue cohosh during late pregnancy has been implicated in profound adverse neonatal outcomes including myocardial infarction, multisystem organ ischemia, and stroke. It is this author's hypothesis that, in spite of warnings about the possible association between blue cohosh and adverse maternal and neonatal outcomes, blue cohosh continues to be used widely by midwives who either do not consider it significantly harmful, who feel they have no other reasonable options for induction when out-of-hospital birth or natural induction is preferred, or who are uncertain whether blue cohosh is, in fact, harmful. Further, it is hypothesized that, while there is a plausible relationship between the constituents in blue cohosh and purported adverse effects, the case reports of adverse neonatal outcomes in the literature do not establish causality, but that certain patterns of use may increase risk.

The specific aims of this study are to evaluate the relationship between maternal ingestion of blue cohosh in pregnancy and adverse neonatal outcomes, and use patterns of blue cohosh by obstetric care providers. In addition to presenting an exhaustive review of the historical and contemporary uses of blue cohosh in obstetrics, this study presents:

1. A systematic review of the literature on blue cohosh, and
2. A formal structured survey conducted to evaluate contemporary obstetric care provider practices.

3. Methods

A systematic review of the literature on blue cohosh was undertaken to evaluate the association between maternal blue cohosh consumption in pregnancy and adverse events and outcomes reported by midwives and in published case reports. A formal survey of midwives in the US was conducted to evaluate patterns of blue cohosh use by midwives and observed outcomes. The following methods were applied for these studies.

1. Systematic review of the literature

A comprehensive literature search was conducted using major computerized databases (MEDLINE, CAB Abstracts, CINAHL, BIOSIS, and Cochrane Library) between October and December 2008, using the subject headings ‘pregnancy AND blue cohosh;’ ‘pregnancy and *Caulophyllum thalictroides*;’ ‘blue cohosh;’ and ‘*Caulophyllum thalictroides*.’ Researchers included this author (a fourth year medical student, certified professional midwife, and professional writer), with the assistance of Holly Grossetta Nardini, a professional medical research librarian at Yale University School of Medicine.

Efforts were made to include all published and unpublished chemical, pharmacologic, in vitro, in vivo, and clinical studies involving blue cohosh in both humans and animals, as well as case reports, comments, and letters published in medical and midwifery journals. To ensure that no reports or studies were overlooked, Joseph Betz, PhD, scientific director of the United States Office of Dietary Supplements (ODS), an expert on blue cohosh chemistry, was consulted and bibliographies of the articles that were located were scanned for further relevant publications. Non-English sources were included in the scope of the search; however, none were identified. Articles involving homeopathic preparations rather than those involving crude plant products were excluded as homeopathic preparations contain no measurable active pharmacologic contents.

The use of standard scientific botanical nomenclature was important for consistency in reviewing the literature and clarifying that the intended plant (genus and species) was being investigated. Blue cohosh has been confused in several reports with black cohosh (*Actaea racemosa* syn. *Cimicifuga racemosa*), an

unrelated species that is also used for gynecologic and obstetric purposes, and which is commonly combined with blue cohosh. *Caulophyllum thalictroides* (L.) Michx. [Berberidaceae] is the official scientific name for the plant discussed in this thesis, and has been so throughout the history of recorded uses in the US botanical literature. Blue cohosh is the official, and most frequently used, common name. (2, 40) Other common names have included squawroot, papoose-root, yellow ginseng, and blueberry-root; however, common names for plants can vary geographically, culturally, and historically, and thus common names other than blue cohosh are mentioned for historical purposes only. (40-42)

A total of 10 published pharmacology papers from 1954-2008 were identified and 2 additional abstract and an unpublished senior thesis from a college biology department were obtained; 1 teratogenicity study was identified; 4 independent case reports were located and evaluated; 2 reviews of blue cohosh and 1 review of the risks of blue cohosh were reviewed: and 6 published letters were found (Table 3 and Table 4). There are no clinical trials involving blue cohosh and pregnancy. Several additional articles and letters from small herbal publications or websites were identified and reviewed, as were communications from midwife and herbal list-servs. These were not subject to peer review and were not included in the systematic review, though comments from these appear in the discussions section to illustrate several points regarding obstetric care provider practices and beliefs about blue cohosh.

Table 3. Articles Included in Systematic Review of Blue Cohosh Literature

Chemical Analytical and Pharmacology Studies

Ali Z, Khan IA. Alkaloids and saponins from blue cohosh. *Phytochemistry*. 2008;69(4):1037-42.

Berger J, DeGolier T. Pharmacological effects of the aqueous extract of *Caulophyllum thalictroides* (blue cohosh) on isolated *Mus musculus* uteri. *Bios* 2008;79(3):103-14.

Betz J, Andrzejewski D, Troy A, et al. Gas chromatographic determination of toxic quinolizidine alkaloids in blue cohosh *Caulophyllum thalictroides* (L.) Michx. *Phytochem Anal*. 1998;9:232-6.

Ferguson H, Edwards L. A pharmacological study of a crystalline glycoside of *Caulophyllum thalictroides*. *Journal of the American Pharmaceutical Association* 1954;XLIII(1):16-21.

- Flom MS, Doskotch RW, Beal JL. Isolation and characterization of alkaloids from *Caulophyllum thalictroides*. *Journal of Pharmaceutical Sciences* 1967;56(11):1515-7.
- Ganzeria M, Dharmaratne HR, Nanayakkara NP, Khan IA. Determination of saponins and alkaloids in *Caulophyllum thalictroides* (blue cohosh) by high-performance liquid chromatography and evaporative light scattering detection. *Phytochemical Analysis*. 2003;14(1):1-7.
- Jhoo J-W, Sang S, He K, et al. Characterization of the triterpene saponins of the roots and rhizomes of blue cohosh (*Caulophyllum thalictroides*). *Journal of Agricultural & Food Chemistry*. 2001;49(12):5969-74.
- Jhoo J-W, Sang S, Ho C-T. Triterpene saponins from Blue Cohosh. Abstracts of Papers American Chemical Society 2001;221(1-2):AGFD 61.
- Kennelly E, Flynn T, Mazzola E, Roach J, McCloud T, Danford D, et al. Detecting potential teratogenic alkaloids from blue cohosh rhizomes using an in vitro rat embryo culture. *J Nat Prod*. 1999;62(10):1385-9.
- Satchithanandam S, Grundel E, Roach J, et al. Alkaloids and saponins in dietary supplements of blue cohosh (*Caulophyllum thalictroides*). *Journal of AOAC International*. 2008;91(1):21-32.
- Stanley B. *Caulophyllum thalictroides* induces mild bradycardia on frog hearts in situ. St. Paul, MN: Bethel University; 2007 (unpublished).
- Woldemariam T, Betz J, Houghton P. Analysis of aporphine and quinolizidine alkaloids from *Caulophyllum thalictroides* by densitometry and HPLC *Journal of Pharmaceutical and Biomedical Analysis*. 1997;15: 839-43.

Case Reports

- Finkel RS, Zarlengo KM. Blue cohosh and perinatal stroke.[see comment]. *NEJM*. 2004;351(3):302-3.
- Gunn TR, Wright IM. The use of black and blue cohosh in labour.[see comment]. *New Zealand Medical Journal*. 1996;109(1032):410-1.
- Jones T, Lawson B. Profound neonatal congestive failure caused by maternal consumption of blue cohosh herbal medication. *J Pediatr*. 1998;132:550-2.
- Jones TK, Lawson BM. Profound neonatal congestive heart failure caused by maternal consumption of blue cohosh herbal medication.[see comment]. *J Pediatr*. 1998;132(3 Pt 1):550-2.

Rao RB, Hoffman RS, Desiderio R, Raysor D, Palmer ME, Hung OL. Nicotinic toxicity from tincture of blue cohosh (*Caulophyllum thalictroides*) used as an abortifacient. *Journal of Toxicology Clinical Toxicology*. 1998;36(5):455.

Rao RB, Hoffman RS. Nicotinic toxicity from tincture of blue cohosh (*Caulophyllum thalictroides*) used as an abortifacient. *Veterinary & Human Toxicology* 2002;44(4):221-2.

Wright I. Neonatal effects of maternal consumption of blue cohosh. *J Pediatr*. 1999;134(3):384-5.

General/Review Articles

Dugoua J, Perri D, Seely S, Mills E, Koren G. Safety and efficacy of blue cohosh (*Caulophyllum thalictroides*) during pregnancy and lactation. *Canadian Journal of Botany*. 2008;15(1).

Irikura B, Kennelley E. Blue cohosh: A word of caution. *Altern Ther Womens Health*. 1999;1:813.

Comments/Letters

Baillie N, Rasmussen P. Black and blue cohosh in labour.[comment]. *New Zealand Medical Journal*. 1997;110(1036):20-1.

Chan GM, Nelson LS. More on blue cohosh and perinatal stroke.[comment]. *NEJM*. 2004;351(21):2239-41.

Edmunds J. Blue cohosh and newborn myocardial infarction?: Response to blue cohosh abstract. *Midwifery Today*.1999(52):34-5.

Finkel R, Zarlengo K. Blue cohosh and perinatal stroke [correspondence]. *NEJM*. 2004;351(3):302-03.

Finkel R, Zarlengo K. More on blue cohosh and perinatal stroke [Correspondence]. *NEJM*. 2004;351(21):2239-41.

Jones T, Lawson B. Profound neonatal congestive heart failure caused by maternal consumption of blue cohosh herbal medication. *J Pediatr*. 2003;132 3 (Part 1).

Potterton D. More on blue cohosh and perinatal stroke.[comment]. *NEJM*. 2004;351(21):2239-41.

2. Survey on the prevalence and patterns of blue cohosh prescribing by midwives.

Working under the direction of Mark Cullen, MD, Professor of Medicine and Public Health, Yale University School of Medicine, and Director of Occupational and Environmental Medicine, Yale University School of Public Health, with the assistance of Tieraona Low Dog, MD, Director of the Fellowship in Integrative Medicine, University of New Mexico School of Medicine and Chair of the Standards Expert Committees on Dietary Supplements, United States Pharmacopoeia, a survey was designed (Appendix 2) to elicit the prevalence and patterns of use of blue cohosh amongst direct entry and certified nurse midwives. The project was reviewed and approved by the Human Investigation Committee (HIC) of the Yale University School of Medicine.

An announcement for the survey (Figure 8) and instructions for accessing it appeared in the newsletters of the *North American Registry of Midwives* and the *Midwives Alliance of North America*, national organizations whose members include direct-entry and certified nurse midwives. The survey was restricted to English-speaking midwives practicing in the United States. The survey design included questions intended to establish type of obstetric practitioner, length, volume, and setting of practice (i.e., homebirth, birthing center, hospital), indications for and rates of blue cohosh use, temporal nature of use during pregnancy (i.e., as a *Partus preparator*, to induce labor, arrest of progress, etc.), training in use of botanicals and specifically blue cohosh, knowledge of possible side-effects and contraindications, sources of information on blue cohosh use, and observed side-effects or specific outcomes in conjunction with use. (Appendix 2: Blue Cohosh Survey). Survey Monkey, the tool used for survey submissions, separated submissions from respondents' identifying data thereby allowing submissions to be made anonymously. The program was set to prevent respondents from completing more than one survey. Organization of the data was completed with the support of Errol Norwitz, MD, Professor of Obstetrics and Gynecology, Yale University School of Medicine, Co-Director, Division of Maternal-Fetal Medicine and Director, Maternal-Fetal Medicine Fellowship Program.

Survey About Blue Cohosh

by Aviva Romm, CPM

Dear Midwives,

The use of blue cohosh (*Caulophyllum thalictroides*) as a partus preparator and labor stimulant is well known among midwives. Research identifying potentially toxic compounds and published case reports of neonatal harm presumably due to maternal ingestion of blue cohosh have led to questions about the safety of this herb. As midwives and herbalists, it is for the benefit of our clients that we gain a better understanding of the relative clinical safety of this herb and the volume of actual use among pregnant women. This will ultimately help us to determine whether this herb is safe to recommend to our clients.

The accompanying url (website address) will take you to a website that will allow you to participate in a survey that will take you less than 15 minutes to complete. Simply cut and paste or type the address into your search window. This is the central part of a preliminary data collection process I am conducting to evaluate the safety of blue cohosh use in pregnancy. As a midwife, I fully recognize the need for anonymity. This survey is entirely anonymous; there will be no identifying features connecting survey respondents to their responses and no way to link your response to an e-mail address or any other contact.

To complete the survey, go to:
<www.surveymonkey.com/s.asp?u=394252322392>

If you have filled out this survey previously, please do not respond again—your responses are on record and have already been added to this electronic version. At this time the survey is focusing on the use of blue cohosh by U.S. midwives, therefore, if you practice outside of the U.S. please do not complete the survey. U.S. midwives, please pass this on to as many midwives as possible, and feel free to send it to midwife internet lists, etc. I will publish the results of this study in prominent midwifery publications by summer of 2007 so the data and findings will be easily accessible.

Please complete and return this survey by October 30, 2006.

Thank you most appreciatively!

Figure 8: Announcement for Blue cohosh survey

4. Results

1. Systematic Review of the Literature

Given the apparently common use of blue cohosh by pregnant women and the alleged possible consequences to the fetus based on pharmacologic and case reports, there is a relative paucity of research on its pharmacological activity. Concerns over the potential for teratogenicity, embryotoxicity, and severe adverse neonatal outcomes secondary to maternal ingestion of blue cohosh, its use by pregnant women to facilitate labor, and its wide availability as a dietary supplement, have led to a limited number of rigorous analytical chemistry studies in order to isolate, characterize, and quantify the constituents in the herb and in dietary supplement products. (5, 74-76) A total of 10 published pharmacology papers from 1954-2008 were identified and 2 abstracts and an unpublished senior thesis from a college biology department were obtained; 1 teratogenicity study was identified; 4 independent case reports were located and evaluated; 2 reviews of blue cohosh and 1 review of the risks of blue cohosh were reviewed; and 6 published letters or comments were found (Table 4). The abstracts were not included in the review as they reported on or reiterated similar published literature.

Most of our knowledge of the actions of blue cohosh's constituents draws upon the pharmacological action of constituents extrapolated from studies of other plants (i.e. magnoflorine from *Aristolochia bracteata*). (76) Much of the contemporary research focuses on analytical chemistry rather than pharmacodynamics. Most papers cite a 1954 pharmacology paper by Ferguson and Edwards in which the authors demonstrate the uterine smooth muscle and cardiovascular pharmacodynamics, including oxytocic and vasoconstrictive effects, of blue cohosh. (76, 77)

Table 4. Summary of Articles Included in Systematic Review of Blue Cohosh Literature

I. Chemical Analytical and Pharmacology Studies		
<i>Test</i>	<i>Findings</i>	<i>Citation</i>
High Performance Liquid Chromatography (HPLC)	In response to the presence of alkaloids in blue cohosh preparations associated with “birth defects and neonatal heart failure” and uterine stimulating saponins, the authors determined the amounts of these constituents in blue cohosh preparations, including estimates of maximum daily intake with various forms and doses of preparations.	Satchithanandam and Grundel et al. (2008)
Spectral nuclear magnetic resonance (S-NMR)	The authors discuss the oxytocic, teratogenic, and cardiotoxic effects of blue cohosh and considered it desirable to systematically investigate the roots and rhizomes of this herb. Seven triterpene saponins from the root of blue cohosh were identified; there is a discussion of the clinical relevance of these findings	Ali and Khan (2008)
Measurement of contractile forces of blue cohosh solutions on murine uterine horn	All tissues showed an increase in contractile force; strength of solution increased contractile force in a dose-dependent manner.	Berger and DeGolier (2008)
See Ferguson and Edwards, below	This biology major senior paper repeated and confirmed earlier animal tissue studies looking	Stanley (2007; unpublished)

	at cardioactivity of blue cohosh extracts by Ferguson and Edwards.	
HPLC and Evaporative Light Scattering Detection	Due to reports of adverse events associated with consumption of blue cohosh containing dietary supplements, the authors sought to develop analytical methods for standardization of dietary supplements to improve their safety and efficacy; this study found significant qualitative and quantitative variations in the saponin contents of various blue cohosh products and general uniformity in the alkaloid content.	Ganzera and Dharmaratne et al. (2003)
NMR	Given the potential for adverse effects with blue cohosh ingestion in pregnancy and limited reports in the literature on the glycosides in this herb, the authors considered it important to isolate and structurally elucidate a number of the triterpene saponins in the herb.	Jhoo and Sang et al. (2001)
Gas chromatography (GC)/ Mass spectroscopy (MS)	This study established methods for analyzing alkaloid content in blue cohosh products and confirmed their presence in over-the-counter products. Based on this the authors concluded that, until more is known about their biological activity in mammals, it is best to avoid anagryne (teratogenic compound in blue cohosh) containing products in pregnancy.	Betz and Andrzejewski et al. (1998)

HPLC and densitometry	This study was undertaken because of the need for rapid and reliable methods of determining the presence of potentially teratogenic compounds in blue cohosh containing products.		Woldemariam, Betz, and Houghton (1997)		
Column chromatography	Previously unrecognized alkaloids---baptifoline, anagyrine, and magnoflorine—were identified		Flom, Dorskotch, and Beal (1967)		
Acid and hydroethanolic isolation of crystalline glycosides from blue cohosh and subsequent in vitro and in vivo testing of action on uterine and cardiac muscle and function	Increased uterine tone and contractility, decreased cardiac perfusion and contractility were observed at various doses in a dose dependent relationship.		Ferguson and Edwards (1954)		
II. Pregnancy and Lactation					
<i>Test</i>	<i>Herbal regimen</i>	<i>Organism</i>	<i>Parameters</i>	<i>Outcome</i>	<i>Reference</i>
Teratogenicity	250 or 500 µ/mL for 45 hours	Rat embryo	In vitro rat embryo culture with blue cohosh	Both doses were lethal to the embryos	Kennelly and Flynn et al. (1999)

III. Case Reports				
<i>Adverse event</i>	<i>Herbal preparation and dose/ Duration of Treatment</i>	<i>Relevant History</i>	<i>Comments</i>	<i>Citation</i>
Perinatal Stroke	Tea; dose and duration unspecified	Female born by c-section at ~ 40 weeks' gestation after failed attempted vaginal delivery to a healthy 24-year- old G2P0. The woman took blue cohosh (amount and duration unspecified) at the recommendation of her obstetrician. Focal motor seizures of the infant's right arm at 26 hours after birth; a CT obtained at two days of age showed evolving infarct in a left MCA distribution.	Case was attributed to blue cohosh, which was thought to either be contaminated with or metabolized to benzoylecgonine; this compound is not a metabolite of blue cohosh nor found in blue cohosh products, and was most likely a cross-contaminant in assays performed or a misreading of the GC-MS performed.	Finkel and Zarlengo (2004)

Multi-organ hypoxic injury, seizure, acute tubular necrosis	Unspecified mixture of blue and black cohosh	Planned homebirth at 41 weeks 6 days gestation following a midwife attempted induction; Absent spontaneous respirations at birth; multi-organ hypoxic injury; permanent central nervous system damage	This report has been criticized for lack of obstetric history and details on the product used, dose, and duration.	Gunn and Wright (1996)
Profound neonatal heart failure	3 tablets blue cohosh (amount in tablet unspecified), 3 times daily for 3 weeks prior to due date	36 yo G4P3 with well-controlled hypothyroid took blue cohosh as a partus preparator. A 41-wk GA male infant (3.66 kg) delivered in hospital developed acute MI, profound CHF, and shock after a precipitous labor with spontaneous delivery; Poor peripheral pulses, MR, gallop rhythm, hepatomegaly, deep q-waves on ECG, extensive regional wall motion abnormalities on echocardiogram	The mother reportedly took 3 times the recommended dose; all other causes of MI and CHF were excluded and a likely causal relationship was asserted by the authors.	Jones and Lawson (1998)
Acute nicotinic poisoning	Tincture; 10-20 unspecified doses/day for 4 days	Abortion attempt: 21 year old female at 5-6 weeks gestation using blue cohosh tincture and slippery elm tea (15 cups/day for 4 days) as well as slippery elm and parsley douches as	Causality was not definitively established but is highly plausible	Rao and Hoffmann (2002)

		<p>abortifacients;</p> <p>Abdominal pain, bilious vomiting, tachycardia, hypertension, diaphoresis, abdominal fasciculations, mild low pelvic cramping</p>		
IV. General/Review Articles				
<i>Summary</i>		<i>Author qualifications</i>	<i>Citation</i>	
<p>The authors searched 7 electronic databases and compiled data according to the grade of evidence found; the authors concluded that, 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; 3) not be available to the public as an over-the-counter product. They conclude that there is an urgent need to conduct a retrospective or prospective cohort study of midwives using blue cohosh in order to determine safety.</p>		<p>PharmD, naturopath, epidemiologist</p>	<p>Dugoua and Perri et al. (2008)</p>	
<p>This article in a midwifery journal for lay midwives reviews the history of blue cohosh and concerns of its use in pregnancy; caution is urged in using the herb during pregnancy, need for further research to reach definitive conclusions is recommended, and the <i>Botanical Safety Handbook</i> (first edition) recommendations are advised.</p>		<p>Certified professional midwife</p>	<p>Perri (2002)</p>	
<p>Several adverse outcomes may be explained by fetal blue cohosh exposure and research indicates teratogenicity in a rat embryo model; the authors conclude that blue cohosh may be contraindicated in pregnancy and that women of childbearing age should consult</p>		<p>PhD candidate in plant sciences; Assistant professor of biological</p>	<p>Irikura and Kennelley (1999)</p>	

knowledgeable health professionals before using this herb.		sciences	
V. Letters			
<i>Type of publication</i>	<i>Summary</i>	<i>Citation</i>	
Letter	States that there is no published evidence that blue cohosh contains cocaine metabolites and suggests contamination as the source or suggests prenatal maternal cocaine use. The authors add, as an aside, that they consider it alarming that blue cohosh, which is unproved, is recommended considering the potential for medical and legal consequences.	Chan and Nelson (2004)	
Letter	Correcting Jones and Lawson on the assertion that their case history was the first and stating that they believe the Jones and Lawson case confirms their assertion that their own case was likely caused by cardiotoxicity secondary to maternal blue cohosh consumption.	Wright (1999)	
Letter	Addresses the implausibility of the Finkel and Zarlengo case being caused by blue cohosh stating that the known chemistry of blue cohosh does not support the presence of the cocaine metabolites reportedly associated with the adverse effect.	Potterton (2004)	
Correspondence	The authors confirm that, contrary to their case report, that blue cohosh is not known to contain benzoylecgonine or to be metabolized to this	Finkel and Zarlengo (2004)	

	cocaine metabolite and that their results likely reflect detection of a cross-reacting substance training by practitioners. case to a wide audience.	
Letter	Letter confirming the points made by Wright concerning the potential for “catastrophic fetal effects from the maternal consumption of blue cohosh during pregnancy.”	Jones (1999)
Letter	Letter challenging the assertions by Gunn and Wright, stating that no product information, dose, or duration was provided in their case report and that extrapolations between pharmacology and clinical effects cannot always be accurately made, but confirming the need for greater control and monitoring of the practice of herbal medicine quality and practitioners.	Baillie and Rasmussen (1997)

• **Modern isolation and characterization of constituents from blue cohosh**

In 1954, Ferguson and Edwards wrote a paper elegantly describing the history of the chemical investigation of *C. thalictroides* as an introduction to their investigation of the pharmacological activity of the crystalline glycosides found in the herb. (77) In addition to the work done by Ebert and Lloyd, they cite identification of the alkaloid *N*-methylecytisine (Figure 9) by Power and Salway in 1913, as well as their identification of two crystalline glycosides, and work done by Davy and Chu in 1927 to identify these glycosides. (77) Scott and Chen determined the pharmacological activity of *N*-methylecytisine. (77)

In 1967, Flom et al. (78) identified the alkaloids baptifoline and anagryne in *C. thalictroides* and were able to separate these alkaloids from *N*-methylecytisine by partition column chromatograph. They also

confirmed the presence of magnoflorine which they were able to isolate after chromatography on alumina. Studies by Woldemarian et al. and Betz et al. concentrated on isolation and determination of the alkaloids *N*-methylcytisine (Figure 9), baptifoline, anagryne (Figure 10), and magnoflorine (Figure 11). (76, 79) In the study by Betz et al., the teratogen anagryne was found in all products analyzed. (76) Kennelly et al. used activity-guided fractionation with a rat embryo culture system to detect potential teratogens and identified and characterized the alkaloids thalictroidine, taspine, magnoflorine, anagryne, baptifoline, 5,6-dehydro-*a*-isolupanine, lupanine, *N*-methylcytisine, and spartein in an extract of blue cohosh rhizomes. (74) Jhoo et al. identified seven triterpene saponins from 95% ethanol extracts of vouchered blue cohosh roots and rhizomes. (80, 81) In 2007, Ali and Khan isolated two previously unidentified alkaloids, caulophyllumines A and B, and a new saponin, cauloside H-A. (82) A 2008 paper by Satchithanandam et al. described the separation of three alkaloids and three saponins in extracts of authenticated blue cohosh, confirmation of their identifies by HPLC mass spectrometry and NMR, and used these compounds as external standards for the identification and quantification of alkaloids and saponins in commercially available blue cohosh products (Table 5). (5)

Among the three alkaloids analyzed by Satchithanandam et al., magnoflorine was present in the highest concentration in all samples. (5) All three alkaloids were found in the highest concentration in dried root material compared to liquid extracts (which ranged from 55-75% alcohol for 7 of the products and 12-15% alcohol for 2 of the products; one product was labeled as alcohol free). This is consistent with findings by Betz et al. and Ganzera et al. (75, 76) Saponins were also found in lower concentration in the liquid extracts by Satchithanandam et al. Based on these studies it can be expected that the amounts of alkaloids and saponins that might be consumed daily would be greatest from crude root/rhizome products and least from liquid extracts (Table 6).

Table 5. Alkaloids, Glycosides, and Saponins in *C. thalictroides*

Constituent class	Constituent
Quinolizidine alkaloids	<ul style="list-style-type: none"> • Baptifoline • <i>N</i>-methylcytisine

	<ul style="list-style-type: none"> • Anagyrine
Aporphine alkaloids	<ul style="list-style-type: none"> • Magnoflorine
Other alkaloids	<ul style="list-style-type: none"> • Thalictroidine • Taspine • 5,6-dehydro-α-isolupanine • Caulophyllumine A • Caulophyllumine B • Lupanine • Spartein
Saponin glycosides	<ul style="list-style-type: none"> • Caulophyllosaponin (caulophyllosapogenin + arabinose) • Caulosaponin (hederagenin) • Triterpene saponins: <ol style="list-style-type: none"> (1) hederagenin 3-O-R-L-arabinopyranoside (2) caulophyllogenin 3-O-R-L-arabinopyranoside (3) hederagenin 3-O-D-glucopyranosyl-(1f2)-R-L-arabinopyranoside (4) 3-O-R-L-arabinopyranosyl-hederagenin 28-O-R-L-rhamnopyranosyl-(1f4)-D-glucopyranosyl(1f6)-D-glucopyranoside (5) 3-O-R-L-arabinopyranosyl- caulophyllogenin 28-O-R-L-rhamnopyranosyl-(1f4)-D-glucopyranosyl(1f6)-D-glucopyranoside (6) 3-O-D-glucopyranosyl-(1f2)-R-L-arabinopyranosyl- echinocystic acid 28-O-R-L-rhamnopyranosyl-(1f4)-D-glucopyranosyl(1f6)-D-glucopyranoside (7) 3-O-D-glucopyranosyl-(1f2)-R-L-arabinopyranosyl-hederagenin 28-O-R-L-rhamnopyranosyl-(1f4)-D-glucopyranosyl(1f6)-D-glucopyranoside • Cauloside H • Leonticin D
Other	Essential oil (furfurol); phytosterols

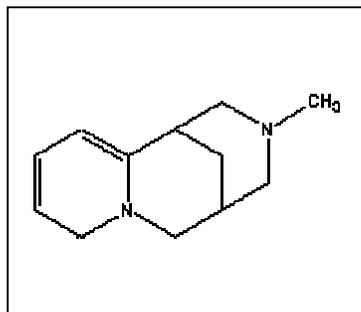
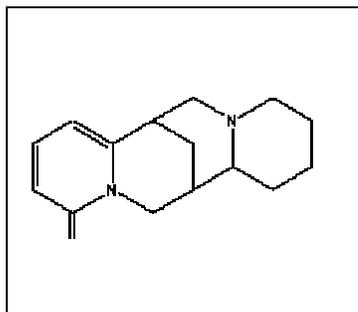
Figure 9. *N*-methylcytisine

Figure 10. Anagyrine

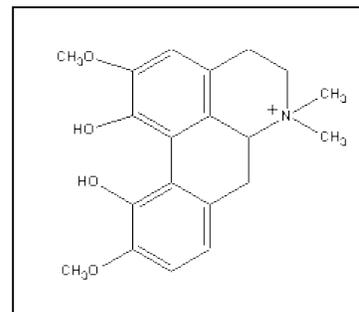


Figure 11. Magnoflorine

Table 6. Estimated Maximum Daily Intakes of Blue Cohosh Alkaloids and Saponins Based on Label Information*

<i>Product material</i>	<i>Range of alkaloids</i>	<i>Range of saponins</i>
Roots/rhizomes	20.0-75.0 mg/day	61.5-420.3 mg/day
Capsules	15.6-47.8 mg/day	76.5-190.3 mg/day
Liquid extracts	0.9-17.3 mg/day	9.1-79.1 mg/day

*Adapted from Satchithanandam et al., Alkaloids and saponins in dietary supplements of blue cohosh (*Caulophyllum thalictroides*), *Journal of AOAC International* 91(1) 21-32, 2008.

Pharmacological Actions (Pharmacodynamics)

• *Smooth muscle effects*

Uterine smooth muscle effects of blue cohosh have been reported in the scientific literature for nearly 100 years. An article in the 1916 issue of the *Journal of the American Medical Association* (45) reported on the stimulating effect of blue cohosh on uterine muscle. The author stated, however, that it was not expected that this effect would occur clinically. In 1954, Ferguson and Edwards conducted experiments using rat uterine horns (in early estrus) using doses of 0.25-0.5 mg of a crystalline glycoside from blue cohosh

extracts/70mL aerated Locke-Ringer's solution at 38C. (77) The glycoside was most likely caulosaponin. (80) The authors observed an increase in degree and rate of contraction at lower doses; at larger doses, immediately increased tone and rate of contraction, with decreased degree of contraction. A dose of 1mg/mL effected a contraction lasting approximately 90 minutes. Similar results were obtained with rabbit and guinea pig uteri. When using rat uterine strips in early pregnancy, a dose of 0.5 mg/mL as a bath produced initial stimulation followed by a period of inhibition lasting for about 1 hour. A second dose then administered (0.5mg/70 ml) led to an immediate increase in tone. In situ experimentation on rat uterus, with 5mg/kg extract administered intravenously, produced an increased degree of uterine contraction, with a slightly increased contraction rate. (77) Larger doses (8-10mg/kg) caused rapid and pronounced increase in tone and contraction rate, with a slight decrease in contraction amplitude. Increased tonus persisted for approximately 45 minutes. Eight assays conducted by Ferguson and Edwards using a United States Pharmacopoeia method for posterior pituitary injection indicated that 1mg of "glycoside G" extracted from blue cohosh possesses the activity of approximately 0.00065 units of Pituritin. (77)

In an attempt to evaluate work done by Ferguson and Edwards on the oxytocic effects of blue cohosh, Berger and DeGolier (2008) suspended murine uterine horns in a smooth muscle bath and exposed it to an aqueous extract of blue cohosh (doses ranging from 0.037–23.8 mg). All tissues showed an increase in the strength of contractile force, the frequency of the contraction, and basal tonus. Contractile forces were significantly greater with higher doses ($P=0.0027$). The stages of estrus were determined by vaginal smears and dose-dependency was consistent in all stages of estrus observed. Blocking experiments with d-tubocurarine, a nicotinic receptor antagonist, were inconclusive as decreases in contractile responses were not statistically different from the observed fatigue following controlled cumulative dosing. (89)

Magnoflorine from *Aristolochia bracteata* has demonstrated oxytocic activity,¹ while Betz et al. attribute possible oxytocic effects of this herb to the glycoside caulosaponin and caulophyllosaponin secondarily to their vasoconstrictive activity, also citing the work of Ferguson and Edwards. (76) The triterpene glycosides have been reported to have significant oxytocic activity owing to smooth muscle stimulation via an unexplained mechanism. (5) Based on the work cited above, blue cohosh has been considered an oxytocic agent.

- *Vasoactive effects*

In 1954, Ferguson and Edwards perfused turtle and frog hearts in situ with doses of 0.3-0.6 mg and 0.05-0.14 mg, respectively, of blue cohosh crystalline glycoside solutions and observed a positive inotropic effect with slight bradycardia. (77) Larger doses than these produced cardiac arrhythmias resulting in partial heart block and eventually systolic arrest. A series of small doses ultimately culminated in the toxic effects produced by a single large dose, suggesting cumulative effects. (77) Perfusion of rat hearts with 10µg/0.1 cc perfused at a temperature of 38°C produced a positive inotropic effect with slight tachycardia, and a mean reduction in blood flow of 25.6% +/-1.36 (SEM) in twelve trials. (77) Contraction of carotid spiral arteries from cattle and hogs was observed in vitro using doses of 2-10mg/70cc, with contraction proportional to the dose. (77)

Magnoflorine has been shown to induce decreased arterial blood pressure in rabbits. (76) Caulosaponin and caulophyllosaponin, derivatives of hederagenin, are reported to be cardiotoxic and hypertensive, possibly due to vasoconstrictive activity. (76) *N*-methylcytisine, pharmacologically similar to but weaker than nicotine, has demonstrated hypertensive effects. (76) The triterpene glycosides may exert a toxic effect on cardiac muscle via constriction of coronary blood vessels. (5, 74)

In an attempt to repeat research done by Ferguson and Edwards, Stanley (2007), a college senior majoring in biological sciences at Bethel University sacrificed and dissected 12 female frogs, exposing the heart tissue to connection with a force transducer. A blue cohosh extract was applied in 4 different amounts 72uL, 144uL, 360uL, and 840uL directly to the heart. Four groups of three frogs were created and each group was subject to just one of the specified doses. The force the heart exerted after application was measured by the use of a force transducer and powerlab software. The author compared the means of each of the frog's heart rates by conducting ANOVA tests to determine the significance of bradycardia. The lowest doses exhibited bradycardia effects immediately, whereas high doses initially demonstrated tachycardia followed by bradycardia. After 3 minutes of application, all heart rates returned within 10% of a control frog heart rate. Since blue cohosh is being used to promote uterine contractions, it is relevant to determine its effects elsewhere in the body. (91)

Based on the work by Ferguson and Edwards, and others, blue cohosh has been attributed with vasoconstrictive, cardiotoxic, hypotensive and hypertensive actions. It may also possess antiarrhythmic activity.

• ***Hormonal effects***

Several sources attribute estrogenic activity to blue cohosh, however, these reports seem to be erroneous, based on inaccurately repeated information. (35, 49) A 2008 review of blue cohosh safety and efficacy during pregnancy and lactation by Dugoua et al. states that “blue cohosh enhances estradiol binding to estrogen receptors and increases estradiol-induced transcription activity in estrogen-responsive cells” and “decreases luteinizing hormone (LH) levels and increases serum ceruloplasm oxidase activity, which are measures of estrogenic activity in the liver.” (35) This is attributed to Jellin et al. (2002) in Natural Medicines Comprehensive Database. The 2008 blue cohosh monograph by the Natural Medicine Comprehensive Database attributes this information to a paper by Eagon et al., (*Medicinal Herbs: Modulation of Estrogen Action*); however, this paper discusses the herb *black cohosh*, not blue cohosh. (92) In fact, a paper by Hunter et al. (93) entitled: *Influence of Exogenous Estrogen Receptor Ligands on Uterine Leiomyoma: Evidence from an in Vitro/in Vivo Animal Model for Uterine Fibroids*, on which Eagon is a co-author, explicitly states, “... some extracts contain elements that compete for ER binding...but not by extract of blue cohosh”. (93) There are no reports in the literature or other research suggesting estrogenic activity of this herb, or use for conditions where estrogenic activity might be desired.

• ***Teratogenicity and mutagenicity***

The teratogenicity of compounds, particularly anagyrine, one of the quinolizidine alkaloids in blue cohosh, has been well-established in higher mammals. (94) In bovines, it has led to the development of “crooked-calf disease”, particularly when the plant tops of anagyrine containing lupines are ingested while grazing. However, this occurs only in a very narrow window of early gestation, and is not reproducible in sheep or hamsters. (94) A case report associating human congenital “crooked” skeletal malformations in an infant (as well as a litter of puppies and goat kids) with maternal ingestion (in all the mentioned species) of milk from a family goat which had been foraging on lupin is controversial. Two studies have indicated anagyrine

teratogenicity in ruminants only, and it has been proposed that anagryrine may require metabolism by microflora in the rumen in order to have a teratogenic effect. (74, 76) The bone deformities in the infant described above were severe and samples of blue cohosh root and rhizome products in that study contained anagryrine levels similar to those implicated in that case. Betz et al. remark that it is probably advisable to avoid anagryrine during the reproductive years in any amount in dietary supplements until more is known about the biological activity of blue cohosh's constituents. (76)

In vitro rat embryo culture (REC) testing of various compounds in blue cohosh did not demonstrate teratogenicity of anagryrine in REC at tested concentrations. It should be noted, however, that evaluation of REC does not include skeletal survey. (74) Thalictridine and α -isolupanine also showed no teratogenicity, while taspine showed high embryotoxicity but no teratogenicity in REC. (74) Taspine, which is similar to other phenanthrene alkaloids such as morphine, heroin, and codeine, is found only in very low yield in blue cohosh rhizomes. (95)

N-methylcytisine, which binds to nicotine receptors in the central nervous system analogously to nicotine, has demonstrated teratogenicity in REC including major malformations—open anterior neural tube defects, poor or absent eye development, twisted tail—at medium concentrations that did not inhibit overall growth and development. (74) At higher levels, teratogenicity was exhibited, as was retardation of growth and morphogenesis. (74)

While there is variation in teratogen susceptibility among species and genotypes, precautions against using blue cohosh in the first trimester appear to be well accepted. (74, 94) However, because the herb has been used historically and continues to be used as an emmenagogue and abortifacient, obstetric care providers must remain aware of the possibility of an unsuccessful abortion attempt after use of this herb in large doses, and the risks of resultant anomalies in the surviving embryo or fetus, with close follow-up and possible discussion of the need for a clinical abortion. However, this is not the focus of this thesis. Magnoflorine is a biosynthetic precursor to taspine, a known cytotoxic agent; taspine was found by Kennelly et al. to be present only in very low concentrations in blue cohosh rhizomes. (5, 74)

• Side effects

Saponins in blue cohosh may cause gastrointestinal irritation, and contact with the crude herb itself may cause mucous membrane irritation. (77, 84, 87) Severe gastric pain has resulted from children ingesting the bright blue seeds. (76) Use of blue cohosh in large or frequent doses has been occasionally reported to cause headache, nausea, dizziness, hypotension or hypertension; however, these effects are also attributed to black cohosh (except hypertension, which is not attributed to black cohosh), and the two herbs are commonly combined, making it difficult to establish which of these herbs causes these effects. Nicotinic toxicity symptoms from ingestion secondary to *N*-methylecytisine in the herb, which binds to nicotinic receptors more weakly than nicotine, but with significant affinity, include hypotension, hyperglycemia, increased small intestine motility, tachycardia, tachypnea, diaphoresis, abdominal pain, vomiting, muscle weakness, convulsions, and fasciculations and have been reported. (5, 74, 76, 96) In mice, the LD50 of caulosaponin was 12 mg/kg and, in rats, was 20 mg/kg. An increase in activity, ataxia, and clonic seizures was observed, with death ascribed to asphyxia. (77)

Twenty-one percent of midwives in the McFarlin et al. study reported complications involving any circumstances in which herbal therapies were used. However, specific data were not elicited on when the complication occurred, whether it occurred in conjunction with cervical ripening or cervical induction, or the gestational age at which the complication occurred. (21) Use of blue cohosh and black cohosh were not reported separately, thus it is difficult to distinguish the effects of the two unrelated herbs; side effects included nausea, increased meconium stained fluid, and transient fetal tachycardia. (21)

• Lactation

Data on the safety of blue cohosh to infants of lactating mothers ingesting products containing this herb are lacking. Until further information is available, it is prudent for lactating women to avoid its use. (87, 100)

• Interactions

No case reports or clinical trials of herb-drug interactions were identified. One database mentions the theoretical possibility of additive effects if combined with hypotensive medications due to the hypotensive

effects of the herb, with nicotine due to binding of nicotine receptors, and hyperglycemic effects possibly counteracting the effects of antihyperglycemic medications. However, all of these precautions are accompanied by a very low-level of evidence or actual clinical effects. (49) *The Botanical Safety Handbook* (2008 revisions) propose an herb-drug interaction rating 'A', which is defined as "Herbs that can be safely consumed with any prescription or non-prescription drugs or other supplements; no case reports of interactions; no significant interactions in clinical trials." (101)

• ***Adulterants***

There are no expected adulterants of blue cohosh in today's commercial market. (102)

• ***Precautions and contraindications***

The herb is generally absolutely contraindicated in pregnancy or may appear with the caveat: "not for use during pregnancy except under the supervision of a qualified health professional." (35, 100) Theoretical precautions include avoidance of use by patients with hypotension, hypertension, diabetes, and cardiovascular disease; however, these precautions are not listed in the revised *Botanical Safety Handbook*, which states that based on current evidence (through November 7, 2007), there are no precautions other than during pregnancy. (49, 87, 101)

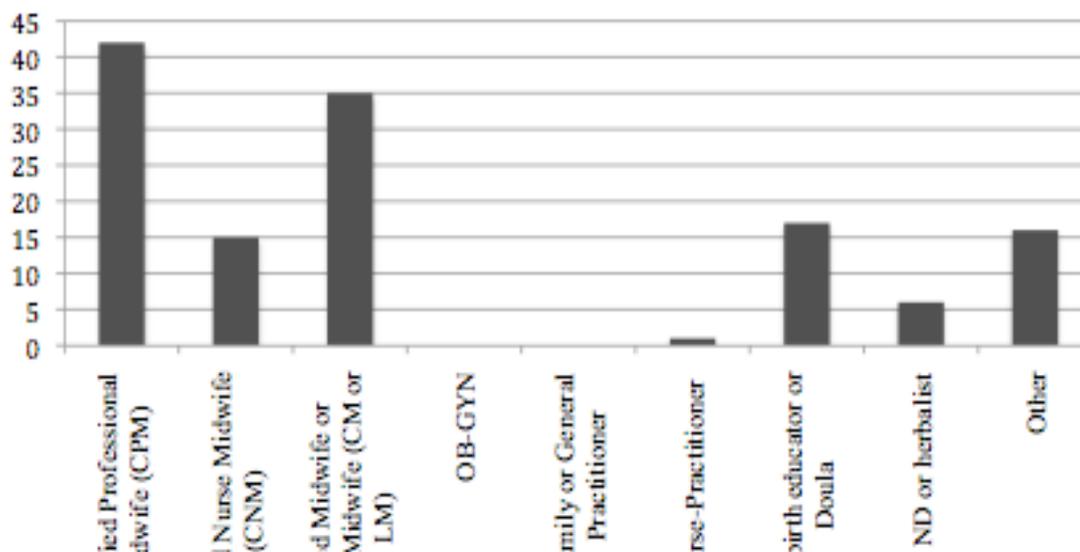
2. Midwives Alliance of North American (MANA) and North American Registry of Midwives (NARM) Blue Cohosh Survey

A total of 90 midwives responded to the survey conducted by this author, announced and published in the respective newsletters of the Midwives Alliance of North America and the North American Registry of Midwives between May and September 2005 (Figure 8). This section graphically illustrates the data that was obtained. Note that for some questions the total response number is greater than 100; this reflects the option “select all that apply.” The complete survey without data appears in Appendix 2.

• *Demographics of Midwives Using Blue Cohosh*

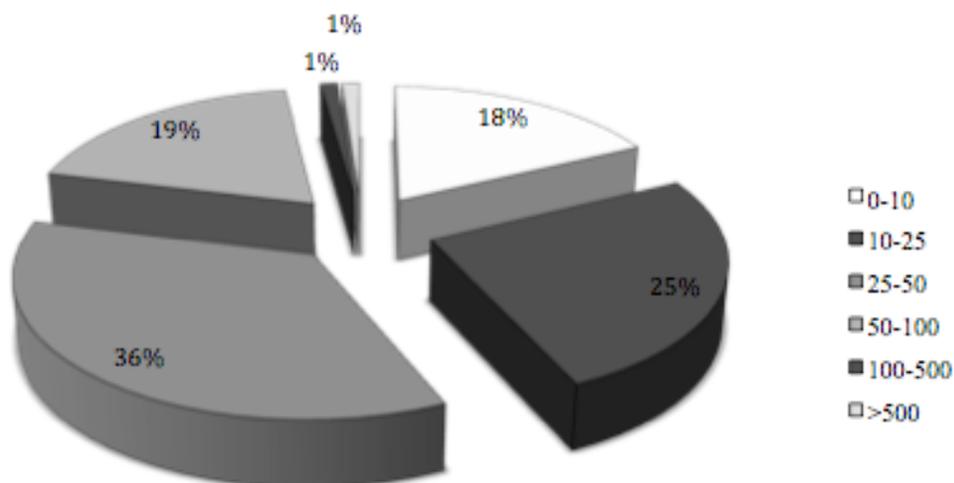
Of 89 respondents to the question “Specify your profession” there were 42 CPMs, 15 CNMs, 35 certified or licensed midwives (CM or LM), 1 nurse-practitioner (NP), and 6 naturopaths or herbalists. Three CNMs were also credentialed as CPMs. Seventeen respondents were additionally certified as childbirth educators or doulas. (Figure 12)

Figure 12. Specify your profession



The majority of respondents attend between 25 and 50 births per year (36%); 25% attend 10-25 births per year and 19% attend 50-100 births per year. Eighteen percent attend fewer than 10 births annually. (Figure 13)

Figure 13: How many births do you attend annually?



An overwhelming majority of respondents (88.9%) practiced in a homebirth setting (n=80); 28.9% were in private practice (n=26), and 27.8% practiced in hospital or birthing center (n=25). Additional practice settings included mission fields (n=1) and a community clinic (n=1). Of the CNMs responding to this question, six had practices that included homebirth, birthing center, and hospital settings. (Figure 14)

The majority of midwives' training in herbal medicine comes from self-study; professional in-service training also serves as a source of herbal medicine education. Few midwives report formal training in herbal medicine. For "other" sources 6 midwives report learning about herbal medicines in apprenticeships (herbal/midwifery) and 3 at conferences. Midwifery and herbal E-lists were also cited as a source for herbal education as was a distance-learning course. (Figure 15).

Figure 14: In what setting do you practice?

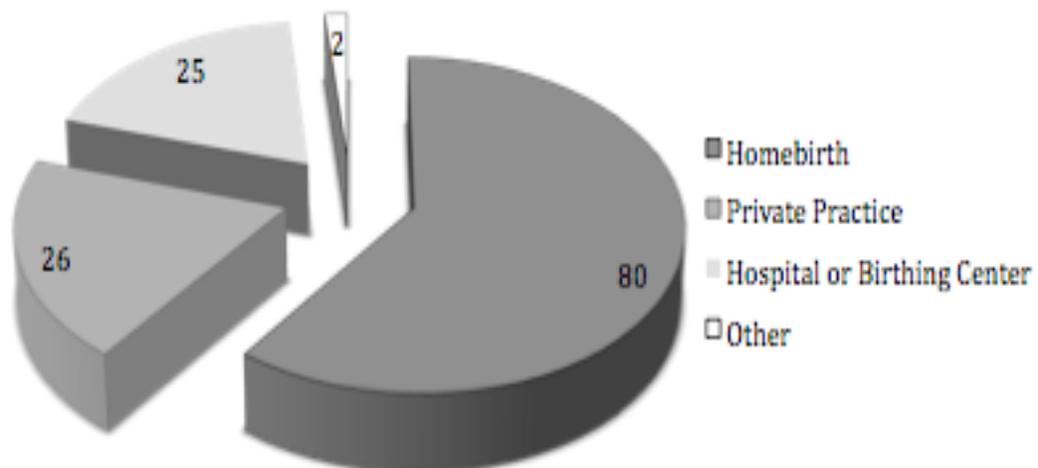
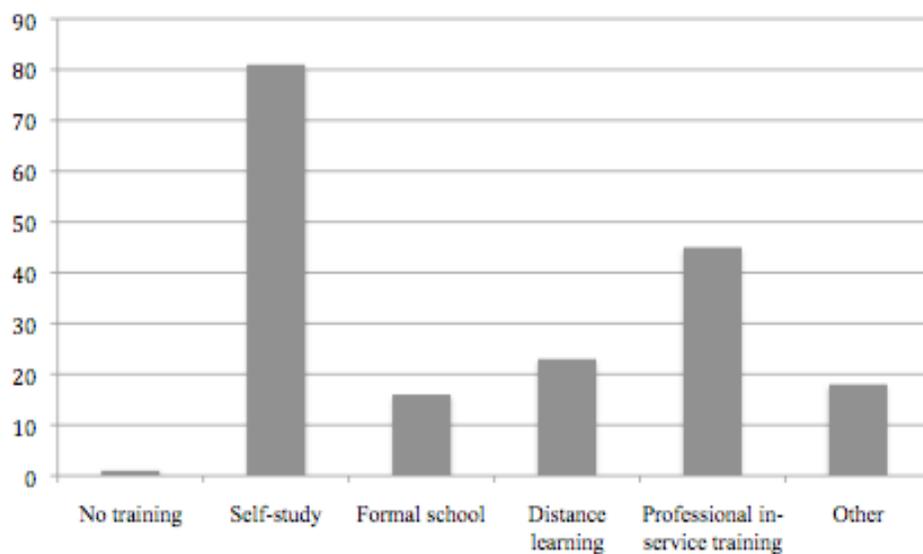


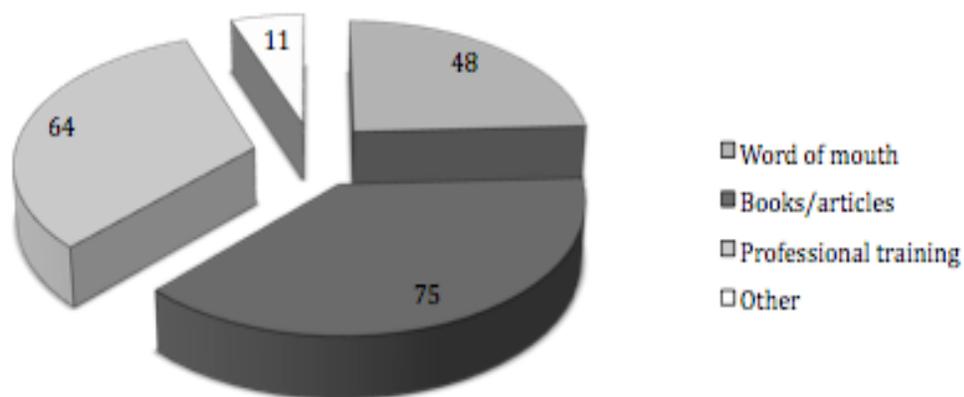
Figure 15: What is your training in the use of herbal medicines?



• *Training in and Common Reasons for Blue Cohosh Use*

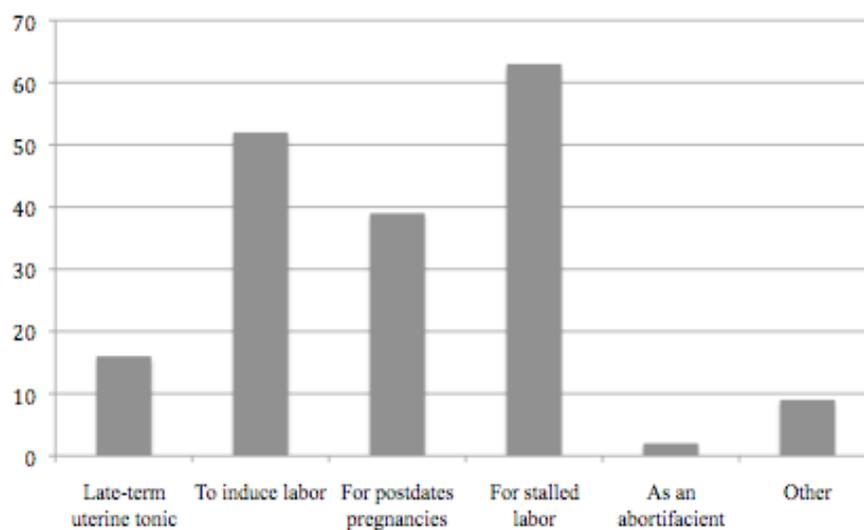
The majority of midwifery training in the use of blue cohosh comes from books, articles, and professional training; word of mouth is also a significant source of information. Other sources of information include conferences, state midwifery organization reviews of cases; personal use, other midwives (n=2), and apprenticeship. (Figure 16)

Figure 16: How did you learn to use blue cohosh?



“Stalled labor” was the most common reason reported for blue cohosh use (n=63) followed by use for labor induction (n=52), and post-term pregnancy (n=39). Additional reasons include use as a *partus preparator* (n=16), to treat postpartum bleeding/hemorrhage (n=3), as an abortifacient (n=2), and to complete a miscarriage (n=2). (Figure 17)

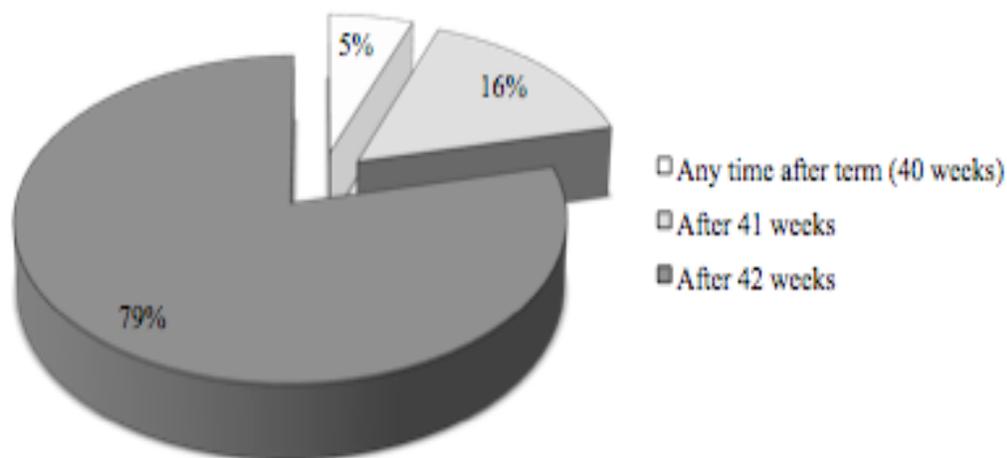
Figure 17. The most common reasons for blue cohosh reported by midwives



• *The Use of Blue cohosh for Labor Induction*

Midwives were asked at what point they consider pregnancy to be post-term. Seventy-nine percent of midwives identified “after 42 weeks’ gestation” as post-term pregnancy versus 16% considering after 41 weeks post-term, and 5% after 40 weeks. (Figure 18) ACOG defines post-term pregnancy as any pregnancy extending beyond 42 weeks (294 days) from the first day of the last normal menstrual cycle.

Figure 18: What do you consider post-term pregnancy?



Midwives historically have a lower rate of induction than OB-GYNs. This may reflect a “wait and see attitude” consistent with the midwifery philosophy of birth as a natural event, a lower risk obstetric patient population amongst midwives, or lower practice volumes. Of 86 respondents who answered this question, 81.4% (n=70) had a labor induction rate of 10% or less and 17.4% (n=15) had an induction rate of 10-20%. One respondent reported an induction rate of 20-30%. (Figure 19) The overall rate of induction of labor by OB-GYNs in the US in 2005 was 21.2% (US National Center for Health Statistics, 2006).

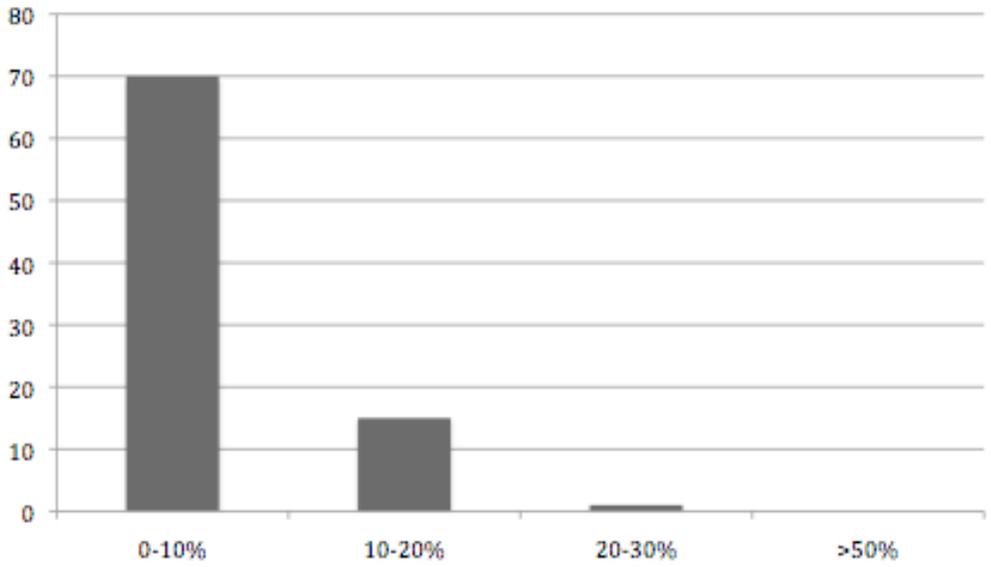
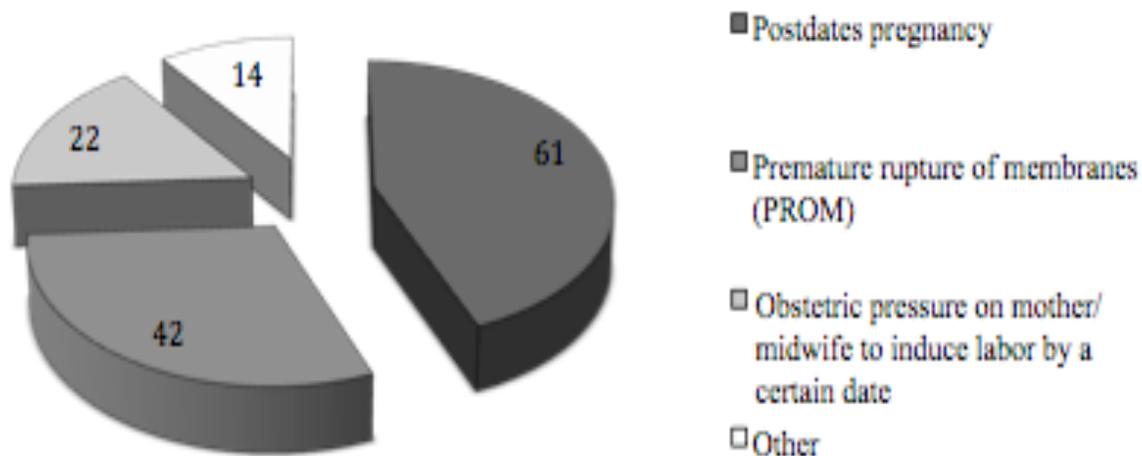


Figure 19: What is the induction rate in your practice?

Of 86 respondents to the question regarding reasons for induction, 70.9% (n=61) reported post-term pregnancy as the most common reason for induction; other primary reasons included premature rupture of membranes (PROM) 48.8% (n=42), and obstetric pressure to induce 25.6% (n=22). Additional reasons for induction included the mother wanting to induce (n=2), distress or anxiety in the parents about waiting for labor to commence on its own (n=2), PROM only if the mother is group B-strep (GBS) positive (n=1), prolonged rupture of membranes (n=1), elevating blood pressure (n=1), oligohydramnios or small for gestational age (SGA), and stalled labor more than 8 hrs (n=1). (Figure 20)

Figure 20. What are the most common reasons for induction in your practice?



Amongst 86 respondents, herbal medicine was by far the most commonly listed method for attempting to induce labor, with 70 midwives (81.4%) reporting herbal use; membrane stripping was reported by 41

respondents, while the use of conventional pharmaceuticals was low (9 and 10 midwives reporting recommending prostaglandin drugs and pitocin respectively). Other methods used included homeopathic preparations (9); nipple stimulation (with or without a breast pump) (6); sex/intercourse (5); evening primrose oil (3); castor oil (3) acupuncture/acupressure (2); repositioning the baby (1); breaking water (1); chiropractic (1); energy work (1); “Foley bulb;” (1); Kinesiology (1). (Figure 21)

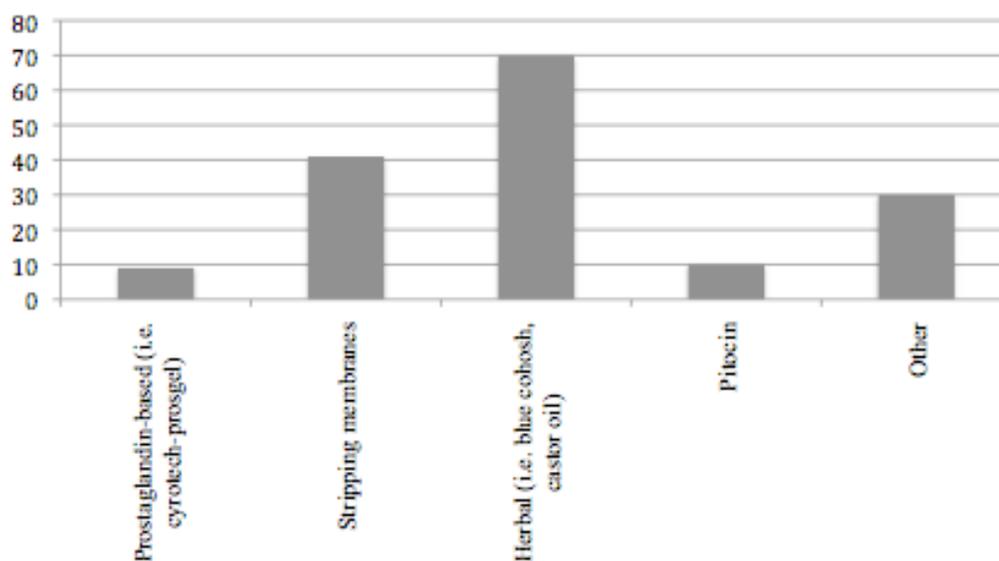


Figure 21. Most commonly cited methods of labor induction

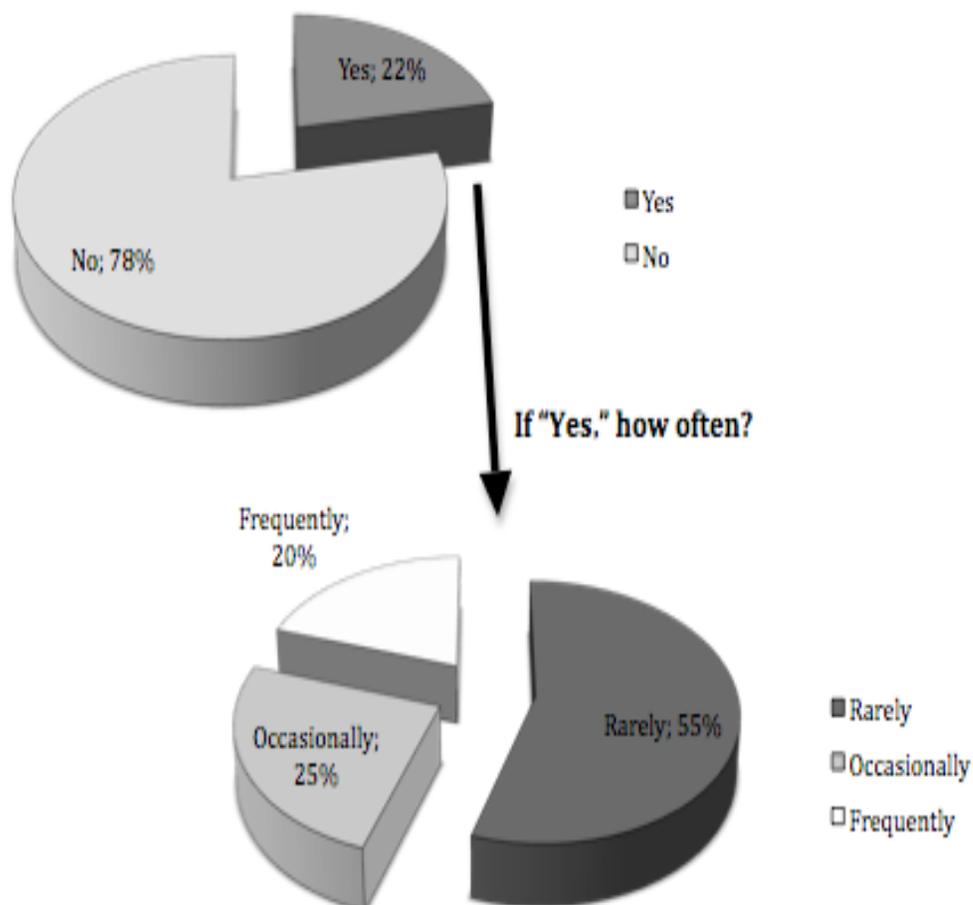
When asked about the use of blue cohosh to induce labor, 85.7 % of 84 respondents reported having used blue cohosh for labor induction at some point compared to 14.3% who reported that they had not. Of the CNM respondents, all but 2 had used blue cohosh for labor induction.

When asked about efficacy and safety, the majority of midwives (72/82 [87.8%]) considered blue cohosh an effective labor stimulant, and 84.8% of respondents (n=79) considered it safe when used this way.

• *Midwives Use of Blue Cohosh as a Partus preparator*

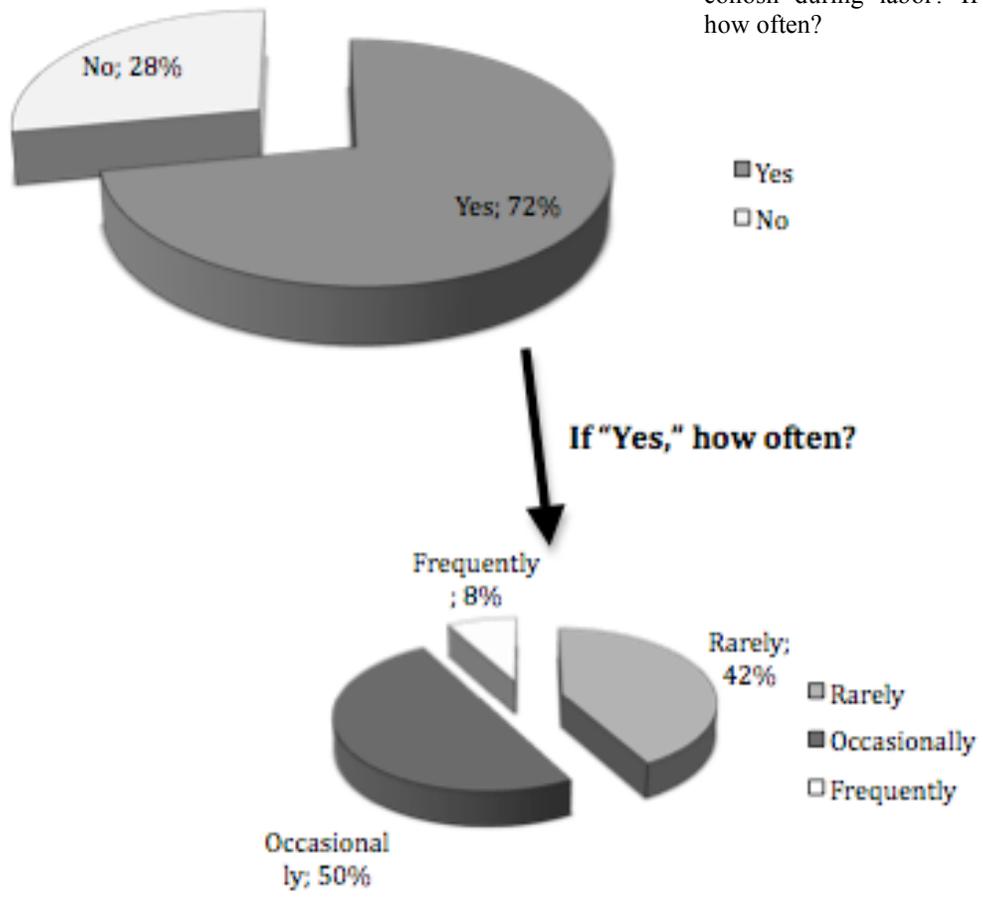
Midwives were asked whether they were using blue cohosh specifically as a *partus preparator* prior to 38 weeks' gestation rather than just for labor induction or augmentation. Of the 87 respondents to this question, 78% reported no use prior to 38 weeks' gestation whereas 22% did use it earlier than this designated time. Of those reporting early use of blue cohosh, 55% reported such use to be "rare" while 25% reported it to be occasional. Of the CNMs, one-third (n=4) had recommended use prior to 38 weeks' gestation (Figure 22). Of 83 respondents, a nearly equal distribution of midwives considered blue cohosh safe (30.1%), unsafe (36.2%), or were uncertain (33.7%) of its safety. A slight majority (36.2%) do not consider blue cohosh safe when taken as a *partus preparator*.

Figure 22. Have you recommended the use blue cohosh prior to 38 weeks' gestation?



More midwives report using blue cohosh in labor [72% (61/86)] than prior to its onset. Eight percent report frequent use, 50% report occasional use, and 42% report doing so only rarely. All but three (75%) of the CNMs have mentioned or suggested its use in labor. (Figure 23)

Figure 23. Have you ever mentioned suggested or recommended the use of blue cohosh during labor? If yes, how often?



• ***Blue Cohosh Dose, Forms of Administration, and Combination with Other Herbs***

Formulations, dose ranges, frequencies, and durations were *highly* variable (Appendix 4). Tincture is by far the most commonly used form of this herb, used by 78% of respondents; pills/capsules (11%) and tea (11%) are each used, but less frequently. Twenty percent of respondents also reports using blue cohosh in homeopathic form; several comment that they feel this is a safer option than crude herb and tincture products. (Figure 24)

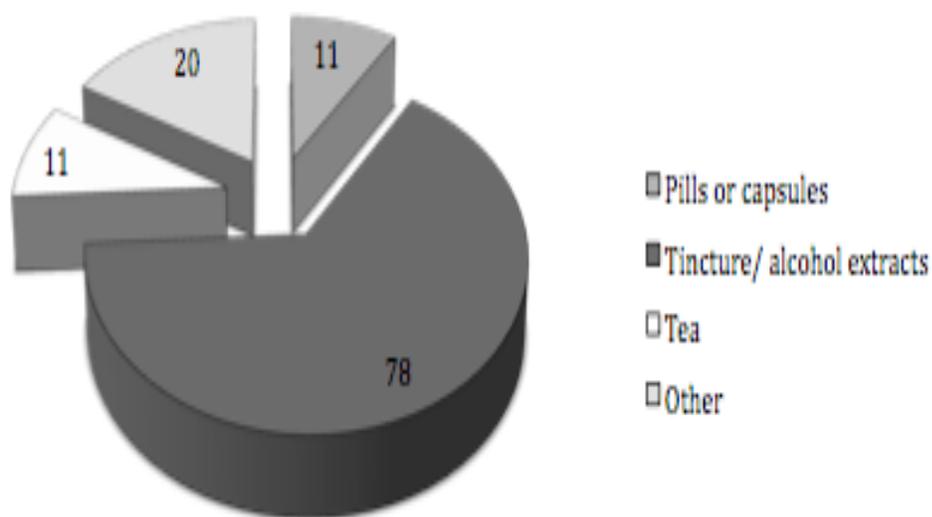


Figure 24: In what form do you typically prescribe blue cohosh?

Of 86 respondents, 87.2% use blue cohosh in combination with other herbs. These are specified in Appendix 3. Of 80 midwives reporting on product preference, 55% did not prefer a specific company. The preferred companies for the remaining of 45% are presented in Appendix 5. The reasons cited for preferences appear in Table 7.

Table 7. Reasons cited for using specific brands	
Reason	No. Respondents
High quality standards, quality control, standardized manufacturing, reputable brand	7
Made by a trusted/professional or local herbalist	5
Effective/best results	3
Friend is the manufacturer	3
Alcohol product—most effective	2
In glycerin: taste, cheap, or reliability	2
Long history of use of a product	2
Make my own	2
Organic/wild crafted/locally available	2

• ***Observed Adverse Outcomes with Blue cohosh Use***

When asked about adverse perinatal outcome with blue cohosh, the majority of midwives responding to this question (51/81 [62.9%]) reported no adverse outcomes. However, 22 adverse neonatal events were reported for an overall adverse event rate of 24.4%. These adverse vents included meconium at birth (n=10), bradycardia (n=4), tachycardia (n=5), and need for resuscitation at birth (n=3). (Figure 25)

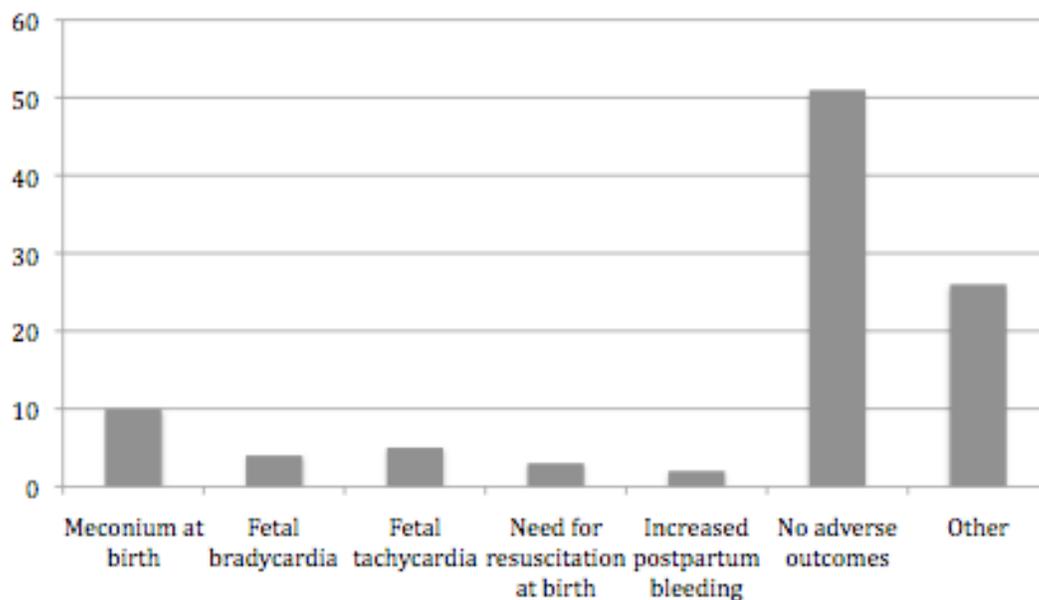


Figure 25. Observed adverse events with blue cohosh use

“Other” adverse outcomes specified by midwives included:

- “Baby who developed CP after birth; medical adviser tried to relate it to the blue & black cohosh she took 2-3 times during labor”
- “Brain damage at birth; mother had taken blue cohosh for 1 week prior to birth”
- “Slight increase of baby's heartbeat”
- Tachycardia
- “Possible bradycardia”
- Increase in maternal blood pressure
- Decrease in maternal blood pressure
- Irregular maternal pulse
- Two midwives report having seen all of the adverse effects listed, but neither was sure whether these were associated with blue cohosh use.

5. Discussion

The purpose of this study was twofold : (1) to evaluate the association between maternal ingestion of blue cohosh and adverse events as reported in prior surveys of midwife use of this herb and published case reports, and (2) to evaluate use patterns of blue cohosh by obstetric care providers. These aims were met by a systematic review of the literature and a national survey of midwives.

There is a limited amount of literature on the pharmacodynamics of blue cohosh. Studies to date clearly demonstrate potential teratogenic, fetotoxic, cardiotoxic, and oxytocic activity from this herb. However, most contemporary studies refer to a 1954 study by Ferguson and Edwards (77) for evidence of blue cohosh pharmacodynamics with no contemporary studies conducted. Given the catastrophic outcomes that have been implicated in blue cohosh use and the large volume of midwives using it, the lack of pharmacodynamic research is surprising. Most of the literature on blue cohosh consists of analytical chemistry studies done to identify, isolate, or quantify the alkaloids and saponins in blue cohosh, which are believed to be the teratogenic, fetotoxic, cardioactive, and oxytocic constituents. In spite of ubiquitous acknowledgment of the importance of clinical studies on this herb appearing in the literature since the 1990s, no in vitro or in vivo research has been conducted save two reports from college biology seniors using murine and frog tissues, respectively (89, 91); and only one of these papers is published. (89) No clinical trials, including retrospective or prospective studies, have been conducted on blue cohosh use by obstetric practitioners in spite of literature demonstrating possible adverse effects since 1996 (23) and a high volume of use by midwives demonstrated since 2000 (16). Thus, while much of the literature assumes a causal relationship between blue cohosh constituents and the reported adverse outcomes, adequate studies to establish—or even evaluate—possible causality have not been conducted.

Adverse event case reports represent potentially important sources of clinical information, alerting practitioners to adverse outcomes that might otherwise go unnoticed in the absence of formal clinical trials.

Because the literature on blue cohosh, and warnings associated with its use, refer so heavily to the published case reports on adverse events associated with maternal blue cohosh ingestion, these merit close review and attention.

A total of four case reports have appeared in the literature suggesting toxicity or adverse effects associated with blue cohosh ingestion.

(a) Gunn and Wright (1996): Blue cohosh, in combination with black cohosh, was administered by a midwife to a woman at 41.6 weeks' gestation in an attempted labor induction which resulted in the delivery of a 3840 g female with Apgars of 1, 4, and 5 at 1, 5, and 10 minutes. Resuscitation and cardiac massage were given by two independent midwives when the infant was unable to breathe spontaneously at birth. The baby gasped at 30 minutes and was transferred to the hospital where the neonate required mechanical ventilation, was reported to have seizures, and presented with acute tubular necrosis. Computerized tomography (CT) revealed basal ganglia and parasagittal hypoxic injury. At three months the infant had lower limb spasticity and required nasogastric tube feeding. The authors purported that the hypoxic-ischemic damage was secondary to myocardial toxicity possibly related to blue cohosh ingestion, though they do, in a casual mention, raise the issue of the adequacy of resuscitation training in the independent midwives as a possible factor. (23)

(b) Jones and Lawson (1998): A 3.66 kg, 41-week gestational age male was born to a 36-year-old gravida 4, para 3 after a 1-hour precipitous spontaneous delivery. Slightly meconium-stained amniotic fluid was noted with spontaneous rupture of membranes 15 minutes before delivery. Apgar scores were 6 and 9. Cyanosis and poor perfusion developed shortly after, and by 20 minutes after delivery the infant developed respiratory distress, acidosis, and shock, required intubation and mechanical ventilatory support, and was transport to the infant intensive care unit. The mother had received regular prenatal care with a CNM throughout her pregnancy, had well-controlled hypothyroidism (she was clinically euthyroid throughout the pregnancy) and no history of medical problems or substance abuse.

According to the case report, per her midwife's recommendation she began taking blue cohosh to prepare for labor. She reported taking three times the dose recommended by the midwife—3 tablets/day for 3 weeks rather than 1 tablet/day for 3 weeks. The mother reported increased uterine activity and decreased fetal movements during this time. Initial examination of the infant was remarkable for bilateral rales, poor peripheral pulses and perfusion, a gallop rhythm, mitral regurgitation murmur, and hepatomegaly. Chest radiograph revealed cardiomegaly and pulmonary edema; ECG demonstrated evidence of an acute anterolateral myocardial infarction with deep q waves in the left limb leads and in the mid and lateral precordial leads, and echocardiogram showed extensive regional wall motion abnormalities with profound hypokinesis of the left ventricular posterior wall, moderate hypokinesis of the interventricular septum, and relatively well preserved right ventricular anterior wall motion. Ventricular function was severely depressed and severe mitral valve regurgitation was present. A moderate-sized persistent patent ductus arteriosus with low-velocity bidirectional pattern of shunt flow was seen and significant pulmonary hypertension was present. Coronary artery origins were found to be entirely normal. Aminotransferases were elevated consistent with shock and shortly returned to normal values. High-frequency ventilation, high-dose vasopressor support with dopamine, and dobutamine were needed for the first 72 hours after which the infant's condition gradually stabilized and began to improve; he was extubated on day 21 but continued to receive cardiovascular support with oral digoxin, diuretics, and captopril. Follow-up echocardiographic studies confirmed the absence of a congenital coronary artery anomaly that could explain the infant's course and viral studies demonstrated no evidence of acute infection. The patient was discharged after 31 days. At 2 years of age, the child had good exercise tolerance and normal growth and development, however required continued digoxin therapy for persistent cardiomegaly and mildly reduced left ventricular function. The authors concluded that "the clinical picture of cardiogenic shock caused by myocardial ischemia is well explained by the known pharmacologic properties of blue cohosh. Other causes...were systematically excluded...The circumstantial evidence relating the cardiac injury seen in our patient to maternal ingestion of blue cohosh is very compelling." (86)

(c) **Rao and Hoffman (2002):** A 21-year-old non-smoking woman at 5-6 weeks gestation by dates who had taken 10-20 doses (unspecified amount) of blue cohosh tincture daily for four days in an abortion induction attempt presented to the emergency department complaining of two days of abdominal pain and bilious vomiting. On examination she was hypertensive to 149/62, tachycardic to 148 beats/minute, diaphoretic, weak, and had anterior abdominal wall fasciculations. Her gynecologic exam showed a non-tender uterus without cervical dilatation. Ketones were found in urinalysis and blood laboratory evaluation was normal with a serum quantitative β -hCG of 53,484 IU/L. She was diagnosed with acute nicotinic poisoning, treated with IV rehydration, and her gastrointestinal complaints resolved, with the patient reporting only mild low pelvic cramping. Voluntary termination was planned as an outpatient procedure and the patient was discharged 24-hours after hospital presentation. (96) It is believed that her nicotinic toxicity symptoms were a result of the nicotine-like activities of *N*-methylcytisine in blue cohosh. (96)

(d) **Finkel and Zarlengo (2004):** A female infant weighing 3.860 kg was born at just over 40 weeks' gestation to a healthy 24-year-old gravida 2, para 0. The *obstetrician* reportedly had advised the woman to drink a tea made from blue cohosh (product, dose, and reason unspecified). A cesarean section was performed after a failed attempt at vaginal delivery. Focal motor seizures of the infant's right arm began at 26 hours after birth, and were controlled with phenobarbital and phenytoin. A CT obtained at two days of age showed an evolving infarct in the distribution of the left middle cerebral artery (MCA). Thrombophilia studies to assess an innate tendency for excessive blood clotting in the infant were either negative or normal and the family history was negative for embolic or thrombotic disease. Urine and meconium were positive for the cocaine metabolite benzoylecgonine on screening by immunoassay, and were confirmed by gas chromatography mass spectrometry (GC-MS). Testing of the contents of the mother's bottle of blue cohosh and the contents of a sealed bottle of a different preparation of the herb gave the same results. The authors concluded either benzoylecgonine is a metabolite of both cocaine and blue cohosh or the blue cohosh was contaminated with cocaine. (22)

It is essential that case reports provide adequate information with which to evaluate causality. In the case of reports on botanical medicines, this should include, in the least, the type of product used, the duration for which the product was taken, and a comprehensive case history that allows for the exclusion of confounding variables and other possible outcome causes. The case by Gunn and Wright has been criticized for lack of adequate information on the product used (form—i.e., tea, powder, tincture, authentication of blue cohosh or other compounds in the product), dose used, and duration for which the product was taken. (97) There is no information provided on pregnancy history, maternal health status, presence of adequate prenatal care, nor the course of the labor. We do know that the baby was born without spontaneous respirations and required resuscitation by the midwives in a home setting. This is not an entirely uncommon event, even in the absence of blue cohosh use, and the advanced stage of the pregnancy may have increased the likelihood of the presence of meconium and meconium aspiration, or other factors that might have precipitated newborn hypoxia. The fact that this infant did not gasp until 30 minutes after delivery, at which time transport to the hospital was first affected is, in fact, shocking and disturbing! It is also a very plausible explanation for the baby's state of shock upon admission, seizures, and acute tubular necrosis, all of which can occur secondary to multi-organ hypoxia. While the use of blue cohosh in this case cannot be ignored, it is impossible to overlook the lengthy attempted resuscitation as an equally plausible explanation for the baby's poor neonatal status. It is impossible to determine whether the blue cohosh caused the baby to be born without respirations, however, there are numerous other possible explanations for this occurring in the context of a homebirth at a late stage of pregnancy.

Of all the case reports, the *Journal of Pediatrics* case by Jones and Lawson is the one with the greatest possibility of a plausible association between blue cohosh use and a neonatal cardiac event, though again, causality cannot be established. Other possible causes of neonatal cardiac ischemia, for example, maternal cocaine use or anomalous insertion of the fetal coronary arteries⁶, appear to have been thoroughly excluded. While the product was not analyzed nor authenticated, we at least have a general dose and an approximate duration of use—3 tablets, 3 times daily, for 2-3 weeks. This dose is reported to be three times the

⁶ Personal communication with Alan Friedman (January 2009), Director Pediatric Cardiology Yale New Haven Hospital, suggests that neonatal MI is *extremely* rare and the main two causes are maternal cocaine use and anomalous insertion of the coronary arteries.

recommended dose, but according the established doses, this might not be the case, as the mother may well have been within 3 g of crude product/day ingestion. In no dose scheme is duration specified, other than historically, when the Eclectic physicians commonly and routinely prescribed its use for three consecutive weeks in late pregnancy. While we do not know the quantity of blue cohosh in the tablets—tablets can contain anywhere from several hundred to several thousand milligrams of an herb, according to analytical chemistry studies the crude forms of this herb in powders, capsules, and tablets contains the greatest quantity of alkaloids and saponins. This does not demonstrate greater bioavailability in this form, but does raise the question of safety of tablets, etc, versus tincture which is typically the most commonly used form by midwives. During the time that the mother was taking the herb, she apparently reported increased uterine activity and decreased fetal movement.

While it is possible that this could have been a result of the purported oxytocic effects of the herb, women normally and commonly experience increased uterine activity and decreased fetal movement toward term. Did the mother seek appropriate evaluation of fetal well-being at this time to rule out fetal or placental problems? Fetal complications, including intrauterine death, begin to increase after 40 weeks gestation, independent of blue cohosh use. This is a primary impetus for induction of labor at 41 weeks by many OB-GYNs, rather than waiting until after 42 weeks as supported by ACOG and FIGO. Blue cohosh was demonstrated to decrease cardiac perfusion by as much as 25% in 1954 in vitro and in situ studies by Ferguson and Edwards, in turtle and frog models. It is impossible to rule out this effect in this case. Critics say that while this may be the case, it is the only such case report in many thousands of doses of blue cohosh used annually by pregnant women, over many decades, if not centuries of use. While this is a valid consideration, it should be recognized that even herbs such as St. John's wort and kava kava with known potential for adverse effects are associated with very few case reports, in spite of millions of annual doses consumed worldwide. The medicolegal aspects of midwifery practice may discipline midwives toward making case reports, and similarly, may deter physicians from admitting an adverse event associated with the recommendation of botanical medicine use which is generally considered outside of the standard of medical care.

The case report by Finkel and Zarlengo in the *New England Journal of Medicine* is now recognized as an erroneous association due to lack of corroboration between the agent that caused toxicity in the case report and the known chemical compounds contained in blue cohosh, but is included as it arises when searching for blue cohosh and adverse outcomes. Letters to the NEJM rebutted the possibility of benzoylecgonine as a metabolite to blue cohosh, and a response to these letters and personal communications led Finkel and Zarlengo to confirm that blue cohosh was in fact, not the source of contamination or the culprit in this adverse neonatal outcome:

We agree that blue cohosh is not known to contain benzoylecgonine or to be metabolized to this cocaine metabolite...There are several possible explanations for the apparent detection of benzoylecgonine in the neonate's urine and meconium and in a decoction of the blue cohosh that the mother used and of a second source of the herb...Rather, we believe the results reflect 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. Clearly, although the positive results of toxicologic testing for benzoylecgonine make it necessary to consider cocaine as a cause of the neonate's stroke, this is not the sole potential explanation and may be a confounding issue. Benzoylecgonine has direct vasoactive properties, presenting another plausible pathophysiologic mechanism for stroke in our case. (22, 98, 99)

The case reported by Rao et al. has a likely causal association and neatly corroborates what is known about the nicotinic effects of the herb and the events observed in a woman taking a dose that is by any standards, far above what might be recommended, though causality cannot be definitely established.

While lack of adequate information should not lead to outright dismissal of a relationship between a given product and a reported adverse event, we must be very careful to discriminate before making assertions that can wrongfully implicate a product before adequate research has been done. In the case of blue cohosh, outcomes such as cardiac or cerebral ischemic events are entirely plausible based on the limited known pharmacology and pharmacodynamics of the herb, however, lack of information in one of the cases involving neonatal outcomes prevents adequate analysis of the case, and in the other, causality cannot be established nor excluded. Thus, there is really only one legitimate case report in the literature plausibly linking blue cohosh to an adverse neonatal event and one case demonstrating nicotinic toxicity with extremely excessive doses. Survey data from anecdotal reports of midwives however, does support

midwife-observed adverse events with blue cohosh use, including tachycardia, increased meconium, and increased need for resuscitation. Unfortunately, again, product, dose, and duration are unspecified, and such events might be more common in pregnancies that are close to or at post-term, for which blue cohosh is typically prescribed.

A total of 91 midwives responded to an announcement in the newsletters of the Midwives Alliance of North America and the North American Registry of Midwives between May and September 2006 requesting the participation of midwives who use blue cohosh during pregnancy. One response was excluded as the respondent reported solely on the homeopathic use of blue cohosh.

One hundred percent of the participants whose answers were included (n=90) used blue cohosh in pregnancy. The majority of the respondents (85%) were DEMs (variably Certified Professional Midwives, certified, or licensed midwives) and approximately 17% were CNMs (one can choose to be certified as both). Respondents primarily attended births at home, birthing centers, and hospitals, with homebirth being the most common setting. This is not unexpected as both MANA and NARM were started to support, educate, and credential homebirth-oriented childbirth practitioners. Approximately 36% of survey respondents attended between 25 and 50 births annually; 25% attend 10-25 births per year and 19% attend 50-100 births per year, with induction rates ranging from 10% or less (81.4%; n=70)—far lower than the national average—to 10-20% of patients (17.4%; n=15). A sole respondent reported an induction rate of 20-30%.

Blue cohosh use is more common amongst midwives with homebirth practices (88.9%), but is not exclusive to midwives practicing in this setting, with at least 27.8% of use occurring in birthing centers and hospitals. It is important to note that the setting in which a midwife practices and her philosophies about birth, and similarly the setting in which a woman chooses to give birth and her philosophies about birth are not incidental factors in blue cohosh use; in fact, they may actually dictate blue cohosh use for labor induction and augmentation.

While the blue cohosh survey, designed specifically to evaluate the use of blue cohosh during pregnancy by midwives, attempted to “fill the gap” on knowledge of obstetric care provider clinical use of blue cohosh, there are several limitations to the survey. Most substantially, it is nearly impossible to use the results to correlate observed adverse outcomes with maternal blue cohosh ingestion. The study design did not elicit information specifically on the history and cases in which adverse events were observed by midwives, for example, weeks’ gestation at which the herb was administered, dose, or duration of use, or concurrent medical problems or pregnancy complications, in these cases. Adverse events such as increased meconium, tachycardia, or need for resuscitation may occur as a result of a post-term pregnancy, for example, leaving unanswered the question of whether the effects seen were related to the herb or confounding factors that can be attributed to a pregnancy requiring intervention. While this study is important in that it is the first to specifically look at blue cohosh use, further research to evaluate outcomes associated with use of this herb are needed, and must be designed to account for confounding variables in outcomes of post-term pregnancies or abnormal labor progress.

Normal human gestation is considered to last for 42 weeks. The standard internationally recommended definition of prolonged (or post-term) pregnancy, endorsed by the American College of Obstetricians and Gynecologists (ACOG, 1997), is 42 completed weeks (294 days) or more from the first day of the last menstrual period. (103) However, while ACOG does not make a recommendation on induction between 40 and 42 weeks, induction prior to 42 completed weeks (usually at 41 weeks), is commonly recommended by obstetricians based upon studies that have demonstrated that induction is associated with lower perinatal mortality and is more cost-effective than expectant management. In spite of 79% of respondents considering post-term pregnancy to be after 42 weeks, many midwives feel caught between their own philosophy that birth is natural and will occur on its own, at the “right” time, with a watchful waiting approach until the mother enters labor spontaneously, and external imperatives to follow the medical model of induction, commonly favored at >/- 41 weeks’ gestation, due to medical and legal pressures, or licensing requirements. The discretion of the obstetrician and the beliefs and preferences of the midwife or pregnant client may come into conflict over the point of when pregnancy has progressed “far enough.” Midwives or pregnant women may choose to induce with blue cohosh rather than undergo pharmaceutical or mechanical

induction, viewing it as a superior alternative to mechanical or medical induction because it can be done at home or in the birthing center; it can be done without recording the intervention in formal medical records. McFarlin et al. found that only 22% of midwives recorded their use of herbs in patients' charts (21). Blue cohosh is inexpensive and accessible to the mother at the health food store or on the Internet, herbs are perceived as gentler and safer, and allow the mother to remain empowered while possibly forestalling hospital admission for conventional induction. (4, 21, 104) According to Westfall (104), women who have had a pitocin induction with a prior pregnancy often describe the experience as "painful" and may be especially inclined toward using blue cohosh which is perceived as a natural, safer, and gentler alternative.

Labor induction is one of the most commonly reported reasons for use, with as many as 64% of CNMs in one study reporting its use for this purpose. (21) Only castor oil has been reported to be used more frequently.(21) Midwives report the following as their most common reasons for induction: post-term pregnancy (70.9%; n=61), PROM (48.8%; n=42), and obstetric pressure to induce (25.6%). Additional reasons for induction were elaborated as the mother wanting to induce (n=2); distress or anxiety in the parents about waiting for labor to commence on its own (n=2); PROM (n=2, with one midwife specifying only if the mother is GBS=positive): maternal blood pressure elevation (1); oligohydramnios or small for gestation SGA (n=1); and "stalled labor" for more than 8 hrs (n=1).

Significantly, 81.4% (n=86) of midwives reported herbs as their most common means of induction; other methods included "stripping the membranes;" nipple stimulation (with or without a breast pump); evening primrose oil; castor oil; acupuncture/acupressure; repositioning the baby; "breaking water;" chiropractic; energy work; "Foley bulb;" and kinesiology. Interestingly, compared to other studies where castor oil was used even more frequently than blue cohosh, the midwives in this study rarely used it (n=3) compared to blue cohosh. (21) A majority of midwives (85.7 %, n=84) reported having used blue cohosh for labor induction at some point compared to 14.3% who reported that they had not. Use was more common amongst DEMs, but prevalent in both groups.

Labor augmentation was the most commonly reported overall reason for blue cohosh use (75.9%, n=63) followed by use for labor induction (n=52), and post-term pregnancy (n=39). Sixteen midwives used blue cohosh as a *partus preparator*, while three used it to treat postpartum bleeding/hemorrhage, two as an abortifacient, and two for completion of miscarriage.⁷

When asked about use prior to 38 weeks, 78% of 87 respondents reported not using it this early; 22% did use it before 38 weeks, roughly corresponding with the number of midwives using it as a *partus preparator* (19 versus 16). Of those reporting early use of blue cohosh, 55% reported such use to be “rare” while 25% reported it to be occasional. Of the CNM respondents, one-third (n=4) had recommended use prior to 38 weeks’ gestation. Retrospectively, the question should have set the time frame queried about at prior to 40 weeks’ gestation, as it is possible that midwives are using blue cohosh as a *partus preparator* between weeks 38 and 40. Of 83 respondents to this question, there was nearly an equal distribution of midwives who considered blue cohosh safe, unsafe, or were uncertain of its safety. A slight majority (36.2%) do not consider blue cohosh safe when taken as a *partus preparator*. Many midwives are clearly aware that there is concern over the safety of prolonged use of blue cohosh in labor; many continue to use it in spite of these concerns, and many are unclear and confused about whether it can be used safely.

Use during labor is more common than prior to its onset, consistent with labor augmentation being the most common reason for use. Seventy-two percent (n=86) of midwives report having used blue cohosh in labor at some time; 50% report occasional use; 8% report frequent use, and 42% report only rarely using it in labor. Seventy-five percent of the CNM respondents have mentioned or suggested its use in labor. The majority of midwives (87.8%) responding to this question (n=82) considered blue cohosh an effective labor stimulant, and 84.8% of respondents (n=79) considered it safe when used this way.

⁷ Owing to its purported emmenagogic and oxytocic effects, midwives sometimes employ blue cohosh (often in combination with other herbs similar to protocol for labor induction), to complete an inevitable spontaneous abortion (SAB) or missed abortion (MAB). It is believed to help expel the products of conception and to control bleeding. Two midwives in the survey reported on using blue cohosh for this purpose.

Previous studies have demonstrated that most of midwife's knowledge of blue cohosh (and other herbal medicine/supplement) use comes from word-of-mouth with little-to-no formal training reported by midwives.(21) This survey confirms this finding; midwives continue to report that most of their knowledge of blue cohosh use comes from self-study (through books and articles) and word-of-mouth. Professional in-service training also serves as a source of information, and midwives seem to seek out educational experiences, for example, conferences and courses. Word-of-mouth training may actually provide a sort of built-in safety system for blue cohosh use, with midwives sharing information on uses and doses that they have found safe, and sharing adverse outcome information that they not otherwise publicly share. Few midwives report formal training in herbal medicine generally, or in the use of blue cohosh.

Tincture is the most commonly used blue cohosh herbal preparation, with 78% using it in this form; pills and tea are used much less commonly, with 11% use of each. Homeopathic use was also reported by 20% of midwives. Blue cohosh is rarely used as a single agent, rather 87.2% respondents (n=86) use blue cohosh in combination with other herbs (Appendix 3). The type of preparation influences the extractability and bioavailability of the plant's constituents; calculations based on the results of analyses of currently available dietary supplements showed that maximum daily intakes of alkaloids and saponins will vary with the form (e.g., root, liquid extract) and doses recommended in product labeling. Intakes may vary from <1 to 75 mg/day for alkaloids and 9 to 420 mg/day for saponins. (5) (Table 4) Using tincture and using the herb in combination may, speculatively, be a factor that limits the volume of possible adverse effects that may otherwise arise if this herb is truly cardiotoxic and fetotoxic in vivo, first because assays have demonstrated a higher amount of alkaloids and saponins in crude plant products (pills, capsules, tablets) than tinctures, and when used in combination, one is ingesting a smaller amount of any individual herb in a formula. Found in the list of herbs with which midwives commonly combine blue cohosh are several that have been associated with adverse effects in the general population either due to potential toxicity of the herb, use of the wrong species, or harmful substitution with a toxic herb including gelsemium, lobelia, passion flower, pennyroyal, and skullcap; or specific adverse effects in obstetric use, including pennyroyal and castor oil.

Dosing is clearly an area of enormous disparity with tremendous variability in dosing amounts and dosing protocols. Dosing categories can be divided into use for cervical ripening, use for labor induction, and use for labor augmentation. A separate dosing category is used with black cohosh, clearly a very common practice as demonstrated in this and prior surveys.

The dosing strategies and ranges reflect the predominant use of tincture described earlier in this discussion. The tincture preparations are unspecified so it is difficult to determine the amount of crude blue cohosh used to prepare these products without at least evaluating the products of each of the companies listed as preferred (beyond the scope of this paper), however, a standard ratio of herb to menstruum (water and alcohol) from a popularly used and reputable herb company (HerbPharm) is 1:5 extracted in 60-65% alcohol. This translates to roughly 1g of herb per 5 mL tincture. Midwives frequently report their doses in dropperfuls, a notoriously inaccurate means of establishing dosing as product viscosity varies as does dropper aperture and amount drawn into the dropper as the volume in the bottle decreases or variable amounts of pressure are applied when squeezing the dropper bulb. On 10 consecutive attempts I measured a dropperful of HerbPharm blue cohosh tincture from a 4oz nearly full bottle using the provided dropper, to be anywhere from 45-50 drops which I measured each time and found to be approximately 0.75-1.2 mL in a graduated Pyrex cylinder, representing an average equivalent of roughly 0.2 g of dried herb per dropperful. Using only those responses that provided an amount, frequency, and duration of use, this amounts to a daily dosage range of 1.6-3.2 g of blue cohosh from tincture, and 3 g when using the capsules. This varies from slightly up to three times higher than the classically recommended doses, and is within to only slightly higher than contemporary proposed ranges of 0.9-3.0g/day of crude material equivalent. Also, based on previously cited studies regarding variability of constituents in various product forms, one would expect to have fewer alkaloids and saponins in the tincture product than in crude dried herbs products. A lack of understanding about the potency and bioavailability of constituents of various forms of blue cohosh is illustrated by the statement from the CNM involved in the case presented by Jones and Lawson, who posted to midwives on an email list-serv, “She [the mother] took capsules (not a terribly potent form of the herb)...” (105)

Slightly fewer than half (45%) of midwives expressed a preference for specific brands, citing quality and standards as the primary reasons, followed by the products being made by a trusted, professional, or local herbalist. Several midwives conveyed precautions they observe when using blue cohosh clinically, for example, five midwives report using it only when they are present, four specifically state that they provide information and precautions to the parents either verbally or in written form, and three use it only with regular auscultation of the fetal heart rate. Additionally, when offered the opportunity to provide further information, one midwife said: “We had one baby who developed CP after birth; [the] medical adviser tried to relate it to the blue & black cohosh she took 2-3 times during labor,” and another reported: “Baby born with severe brain damage after using tonic with blue cohosh in it for a week.” A couple of midwives commented that they had seen all of the adverse events listed as possible answers, but did not know if they were related to the blue cohosh. Of course, without auditing and reviewing the records and without an appropriate control group for careful analysis and comparison, this is simply anecdote.

The results of this study demonstrate that blue cohosh continues to be widely used by midwives during pregnancy for a variety of purposes, most predominantly, labor induction and augmentation, and to a lesser extent as a preparator for parturition. Most midwives consider it safe when used for labor induction and augmentation, and are less certain of its safety when used for a longer duration as a *partus preparator*. Continued use in spite of adverse events reports and anecdotally observed side-effects appears to be based on a number of complex factors including disbelief that there is a causal association between maternal ingestion of the herb and adverse neonatal outcomes and a perceived lack of other reliable natural alternatives for induction.

Disbelief in a causal relationship between maternal blue cohosh ingestion and the adverse outcomes in the blue cohosh case reports is probably predicated on several factors: the poor quality of the case reports leading readers to believe they are meaningless, the limited number of adverse events in the literature compared to the volume of use, personal observation of safety, and a general mistrust of science and medicine common amongst herbalists and midwives engendering a mistrust of the intention behind reports. Further, a generally poor understanding of the epidemiologic aspects of toxicology and adverse events is

evident. The following statements from midwives and herbalists illustrate these points :

“I find it amusing that a single incident would be used to support such a conclusion, especially concerning how often this herb is safely used...This cardiotoxic side-effect has never been seen before. Not even with thousands of women using it for generation upon generation. This overwhelming fact makes these fears about blue cohosh tendentious.” (106)

“...one case simply does not provide sufficient information for any certain conclusion. The results would have to be reproducible in a variety of subjects before settling firmly on any explanation. Anyone can have an idiosyncratic response to an type of substance or treatment...some things, heart attacks among them, do not have a single causative factor that one can reliably point to...Possibly something happened in the ER, where staff members do not usually conduct deliveries, that contributed to the problem. Perhaps an undetected medication error or contamination occurred, or an unobserved allergic response. Conceivably, the routine newborn injection of Vitamin K could have produced a state of hypercoagulopathy in this infant, facilitating infarction...I personally know of hundreds of women who have used it in association with childbirth.” (107)

While many of her assertions are just not medically realistic, Edmunds does go on to say that she does not agree with the 3-6 week pre-labor use of the herb or the casual use of any herb, considering it inappropriate to use medicinal herbs for a prolonged period of time, preferring to reserve their use for situations where they are truly needed. (107)

The midwife involved in the Jones and Lawson report describes the association between the herb and the baby's outcomes as “bogus”. She goes on to state that “this one published case is scaring the beejeebies out of everyone, even though it's purely speculative.” (105)

Romanticization of what is natural is also prevalent amongst proponents of alternative medicine, and this idealization may be observed amongst midwives and herbalists. The effects of herbal medicines may be seen as ‘mild,’ due to the expectation that they naturally contain low concentrations of potentially harmful constituents or that the complexity of constituents versus single active ingredients in pharmaceuticals lends a buffering effect to herbs that makes them safer (the latter statement may be accurate for *some* herbs, but not necessarily for all). There may also be some amount of lack of understanding of the case reports and the very real possibility of long-term sequelae, for example, regarding the case reported by Jones and Lawson, Judy Edmunds, CPM, writes in *Midwifery Today* in “*Blue Cohosh and Newborn Myocardial Infarction: Response to Blue Cohosh Abstract*”, “I'm happy to hear of the child's fine recovery.” In fact, at two years

of age, according to the published case report, and for at least several years after according to email communications from the midwife involved, the child required continued digoxin therapy for poor ventricular function. (107)

What is clear from this study is that blue cohosh has a very long history of use as an herb to prevent and ease the difficulties of childbearing women, and for a variety of philosophical, practical, ideologic, political, and medico-legal reasons, its use remains prevalent. While the constituents in this herb are consistent with some of the observed side-effects, and even possible players in one significant adverse event report, the number of plausible reports is very low. However, as with many drugs, it can take tens of thousands of observed/documentated administrations to identify even a single causal relationship between a substance and an effect; the numbers of systematically observed uses is too low to quantify whether there are a significant number of adverse events related to use of this herb, if any. **Nonetheless, the teratogenic, embryotoxic, and cardioactive activities of blue cohosh represent potential for harm to the embryo and should never be used during the first trimester, and there is significant enough question as to whether the herb can be used safely in pregnancy at all.** Further, the most plausible adverse event occurred with long term use of several weeks as a *partus preparator*, and using capsules. The practice of use as a *partus preparator* should be fully discouraged and abandoned. While it appears that the risks associated with short term use, for example, for labor induction and augmentation may actually be quite low, and the risk may be mitigated further by using the herb only in tincture form, the preparation with the lowest quantity of the alkaloids and saponins responsible for its pharmacologic actions, at this time, until further research is done, the herb should be used only under the supervision of a qualified obstetric health professional, with proper monitoring, if at all.

• ***Recommendations for further research and blue cohosh use***

While the likelihood of a serious adverse event occurring as a result of the short-term use of blue cohosh for the induction or augmentation of labor seems unlikely based on a review of the case reports, the pharmacology of the herbs does allow for the possibility of adverse effects. There is limited information on the safe use of this herb clinically. Retrospective and or prospective studies are essential for evaluation of

blue cohosh safety and efficacy as a short term oxytocic, and should include studies comparing its safety and efficacy to medical approaches that are the current standard of obstetric care. A careful review of the currently available data suggests that:

1. Blue cohosh cannot be advised as a safe abortifacient due to the risk of teratogenicity and embryotoxicity to the embryo/fetus, and due to the risk of toxicity in the mother from the high doses that are likely required for efficacy.
2. Blue cohosh should never be used in the first trimester to prevent miscarriage or for any other reason due to the risk of teratogenicity and embryotoxicity.
3. There is not enough evidence to demonstrate efficacy of blue cohosh for the completion of a spontaneous or missed abortion, however, lack of fetal viability eliminates the fetal component of risk. Toxicity to the mother when used within the recommended dosage range appears to be minimal, however, cannot be entirely excluded.
4. Due to risk of fetotoxicity and cardiotoxicity use in the form of a *partus preparator* cannot be recommended under any circumstance.
5. Toxicity risks may be slightly mitigated by use of tinctures which have been demonstrated to contain fewer oxytocic and cardioactive alkaloids and saponins.
6. Until further research is conducted, use of this herb should be limited to short term use (i.e., less than or equal to 1 day using no more than 3 g crude herb equivalent) for labor induction or augmentation, and should occur under the guidance of a qualified obstetric health professional, with careful maternal and fetal monitoring
7. The most prudent policy is to avoid internal use of blue cohosh entirely during pregnancy until further studies evaluate safety.
8. Programs training obstetric health care providers should incorporate instruction on botanical medicine safety.

The ongoing use of blue cohosh in pregnancy by midwives and pregnant women demands that there be adequate research conducted on its safety. A number of possible models for this exist, including a fetal sheep perfusion model looking at the effects of maternal ingestion of the herb on fetal placental and cardiac

perfusion, an animal toxicology study comparing long-term and short-term ingestion (including looking for dose-dependent effects), and studies evaluating the safety of isolated constituents extracted from *Caulophyllum thalictroides* and quantifying the amounts of these constituents expected to be ingested in standardized doses of commercially and professionally available products. Longitudinal, observational clinical studies of midwife use in practice are also possible and should be explored. Efficacy studies can be done to establish whether there is indeed an oxytocic effect of this herb and, if so, at what doses of which constituents in the product. If efficacy is proven and safety established, it would be reasonable to development a standardized blue cohosh extract that will deliver a safe and effective dose thereby allowing the continued use of this traditional product.

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7. Appendices

Appendix 1: Timeline of Obstetric Uses of Blue Cohosh (*Caulophyllum thalictroides*)

Native American use	Used as an emmenaogue, uterine antispasmodic and parturient
1813	Peter Smith introduces the medical community to the uses of blue cohosh in his book <i>The Indian Doctor's Dispensatory: Being Father Smith's Advice Respecting Diseases and their Cure</i> (44)
1828	Rafinesque describes the uses of blue cohosh by Native Americans and by Indian doctors and first introduces the practice of taking the herb as a tea for 2- 3 weeks prior to labor, as done by Native American women whom, he reports, “owe the facility of their parturition to such use.” (47)
1840s-1920s	<i>Caulophyllum</i> is popularly used by the Eclectic physicians for numerous female complaints
1858	<i>Gunn's New Domestic Physician</i> describes the use of blue cohosh tea for 2-3 weeks before the expected time of labor by Native American women as a parturient, regarding which he says, ‘.the ‘confinement’ of the Indian women is a matter of but short duration and small concern. It has been abundantly proved as a valuable article in this respect by our white women.” (65)
1863-64	Saponin identified in the alcohol tincture of <i>Caulophyllum</i> and alkaloid in the acid and watery washings.
1865	After neglecting inclusion of the herb in 11 editions, The United States Dispensatory introduced it in the appendix of the twelfth edition.
1867	The Dispensatory of the United States officially lists blue cohosh as an emmenaogue and to promote uterine contractions
1880-1955	It became an official drug in the fifth revision of the United States Pharmacopoeia and remained as such through 1955, though it was removed from the list of approved substances after 1880.

1978, 1986	Reintroduction of blue cohosh as a women's herb in <i>Hygieia: A Woman's Herbal</i> (Parvati) and popularization of the herb for childbearing in <i>Herbal for the Childbearing Year</i> (Weed)
1996-1998	The first case reports of adverse effects in conjunction with blue cohosh use are published
1999-2000	Articles are published demonstrating widespread use of blue cohosh by CNMs for labor stimulation

Appendix 2: Blue Cohosh (*Caulophyllum thalictroides*) Survey

The use of blue cohosh (*Culophyllum thalictroides*)* as a *partus preparator* and labor stimulant is well known amongst midwives. Research identifying potentially toxic compounds and published case reports of neonatal harm presumably due to maternal ingestion of blue cohosh have led to new questions about the safety of this herb. As midwives and herbalists, it is for the benefit of our clients that we gain a better understanding of the relative clinical safety of this herb and the volume of actual use amongst pregnant women, and for our own benefit to determine whether this herb is safe to recommend. We hope you will take approximately 15 minutes to complete this survey, which is part of a preliminary data collection process we are undertaking to evaluate the safety of blue cohosh use in pregnancy.

As a midwife I fully recognize the need for anonymity. This survey is entirely anonymous to all but the primary researchers; there will be no identifying features connecting survey respondents to their responses.

- (Please note that this is a survey about blue cohosh (*Caulophyllum thalictroides*), not black cohosh (*Cimicifuga syn. Actaea racemosa*).
1. Specify your profession: (circle all relevant options)
 - a. Certified Professional Midwife
 - b. Certified Nurse Midwife
 - c. CM or LM
 - d. OB-GYN
 - e. Family or General Practitioner
 - f. Nurse-Practitioner
 - g. Childbirth educator or Doula
 - h. ND or herbalist
 - i. OTHER: (specify)
 2. How many births do you attend per year?
 - a. 0-10
 - b. 10-25
 - c. 25-50

- d. 50-100
 - e. 100-500
 - f. >500
3. In what setting do you practice? (Circle all relevant options)
- a. Homebirth
 - b. Private practice
 - c. Hospital or Birthing Center
 - d. Other (please specify)
4. What do you consider post-term pregnancy?
- a. Any time after term (40 weeks)
 - b. After 41 weeks
 - c. After 42 weeks
5. What is the induction rate in your practice?
- a. 0-10%
 - b. 10-20%
 - c. 20-30%
 - d. >50 %
6. What is the most common reason for induction in your practice? (Circle all relevant options)
- a. Postterm pregnancy
 - b. Premature rupture of membranes (PROM)
 - c. Obstetric pressure on mother/ midwife to induce labor by a certain date
 - d. OTHER
7. What is the most common form of induction in your practice?
- a. Prostaglandin-based (i.e., Cytotech, prosgel)
 - b. Pitocin
 - c. "Stripping membranes"
 - d. Herbal (i.e., blue cohosh, castor oil)
 - e. Other?

8. Have you ever used blue cohosh for labor induction? (circle one) YES NO
9. What is the most common reason for blue cohosh use in your practice? (Circle all relevant options)
- a. As a uterine tonic during late pregnancy
 - b. To induce labor
 - c. For post-term pregnancies
 - d. For stalled labor
 - e. As an abortifacient
 - f. Other
10. Have you ever mentioned, suggested, or recommended the use of blue cohosh prior to 38 weeks pregnancy? (circle one) YES NO
- If yes, check one:
- Rarely
- Occasionally
- Frequently
11. Have you ever mentioned, suggested, or recommended the use of blue cohosh during labor? (circle one) YES NO
- If yes, check one:
- Rarely
- Occasionally
- Frequently
12. What is your training in the use of herbal medicines? (Circle all relevant options)
- a. No training
 - b. Self-study (books, magazines, journal articles)
 - c. Formal school (specify)
 - d. Distance learning (specify)
 - e. Professional in-service training
 - f. Other

13. How did you learn about the use of blue cohosh? (Circle all relevant options)
- a. Word of mouth
 - b. Books/articles
 - c. Professional training
14. In what form do you typically use blue cohosh? (Circle all relevant options)
- a. Pills or capsules
 - b. Tincture/ alcohol extracts
 - c. Tea
 - d. Other
15. Do you generally recommend blue cohosh in combination with other herbs?
- (circle one) YES NO
- If yes, can you list some of the other herbs? _____
16. Is there any particular brand(s) of blue cohosh product you suggest?
- If yes, Why?
17. If you recommend blue cohosh, what dose information do you provide?
18. Do you consider blue cohosh safe for use when taken for several weeks during late- pregnancy?
- (circle one) YES NO
19. Have you found blue cohosh to be an effective labor stimulant? (circle one) YES NO
20. Do you consider blue cohosh safe when used as a uterine stimulant during labor?
- (circle one) YES NO
21. Have you seen any of the following adverse outcomes with the use of blue cohosh? (Circle all relevant options)
- a. Meconium at birth
 - b. Fetal bradycardia
 - c. Fetal tachycardia
 - d. Need for resuscitation at birth
 - e. Increased postpartum bleeding
 - f. OTHER

Appendix 3. Herbs Used in Formulae with Blue Cohosh

Herb	Number of Respondents (n=72)
Angelica (<i>Angelica archangelica</i>)	3
Bethroot (<i>Trilium erectum</i>)	6
Black cohosh (<i>Actaea racemosa</i>)	58
Black haw (<i>Viburnum prunifolium</i>)	1
Blue vervain (<i>Verbena officinalis</i>)	2
Castor oil (<i>Ricinus communis</i>)	5
Chamomile (<i>Matricaria recutita</i>)	2
Cotton root (<i>Gossypium herbaceum</i>)	9
Cramp bark (<i>Viburnum opulus</i>)	1
Echinacea (<i>Echinacea</i> spp.)	1
Evening primrose oil (<i>Oenothera biennis</i>)	3
Gelsemium (<i>Gelsemium sempervirens</i>)	8
Ginger (<i>Zingiber officinalis</i>)	4
Lobelia (<i>Lobelia inflata</i>)	3
Motherwort (<i>Leonorus cardiaca</i>)	6
Oregon grape (<i>Mahonia aquifolium</i>)	1
Osha (<i>Ligusticum porteri</i>)	1
Partridge berry (<i>Mitchella repens</i>)	4
Passion flower (<i>Passiflora incarnata</i>)	1
Pennyroyal (<i>Mentha pulegium</i>)	2
Red raspberry leaf (<i>Rubus idaeus</i>)	5
Shepherd's purse (<i>Capsella bursa-pastoris</i>)	2
Skullcap (<i>Scutellaria baicalensis</i>)	1
Wild yam (<i>Dioscorea villosa</i>)	1
Yarrow (<i>Achillea millefolium</i>)	1

Appendix 4: Blue Cohosh Dosing Practices from the NARM/MANA Midwife Blue Cohosh Survey

The following are the dosing comments consolidated data in the NARM/MANA Midwife Blue Cohosh Study Blue Cohosh Survey.

For cervical ripening

- 1 dropper every 3 hours for ripening (2)

For labor induction/augmentation

15 minute protocol

- Every 15 minutes (amount unspecified) for 4 doses, each night before bed until labor starts
- 2 droppers every 15 minutes for 2 hours; if labor does not start, stop taking and wait 2 days
- 1 dropperful (30-40 drops) every 15-30 minutes, depending on desired effect. Take for 4 hours, then take a break if no effect seen. Reduce dosage as contractions intensify

20 minute protocol

- 1/2 dropper every 20 minutes (2)

30 minute protocol

- Every 30 minutes alternating with 20 minutes of nipple stimulation with the breast pump (take herbs for 4 rounds, rest one hour ; repeat; works most times)
- 1 dropper in water every 1/2 hour
- 1 dropperful every 30 min for 4 hours
- 1/4 teaspoon every 30 minutes for 2 hours

Hourly protocol

- 15 drops/ hour
- 1 dropper/ hour (2)
- 1 dropper every hour for 4 hours
- 1 dropper every 1-2 hours
- 1 dropperful sublingual every 2 hours or until contractions gain strength

- 2 capsules every other hour for 6 hours only
- 1 time (amount unspecified) per every hour for up to 8-12 hours

Daily protocol

- Use a couple of droppers of the tincture 2-3 times/day. If you have plenty of contractions, don't use so much

When combined with black cohosh for labor induction

15 minute protocol

- 15 drops-1 dropperful of blue cohosh hourly alternating with black cohosh for up to 4 doses ; discontinue as soon as labor is established
- 1-2 dropper of each every 15 minutes for two hours
- 15 drops every 15 mins for 1 hour with 15 drops of black cohosh same time period -- if regular contractions begin, back off to every 1/2 hour, if not then another hour of dosing every 15 minutes
- 1 dropper every 15 mins, alternate blue & black
- 1 dropper blue cohosh, 1 dropper black cohosh and 2 droppers cotton root every 15-30 minutes

20 minute protocol

- 1 dropper every 20 min for 4 hours with black cohosh

30 minute protocol

- 20 gtts then 30 mins later 10 gtts, then 10 gtts/hour every 3 hours. So 4 hours total
- 10-20 drops every 20-30 minutes rotating between black and blue cohosh
- 1 dropper Blue under the tongue, then 30 mins later 1 dropper Black cohosh; continue alternating every 30 mins for a total of 3 doses each (6 doses combined) over a 3 hour period
- 1 dropper every half hour decreasing if adequate contraction pattern is achieved. For augmentation either 1/2 dropper every 1/2 hour to 15 minutes depending on response or 1/2 - 1 oz in an enema
- First Dose: Place 1 full dropper of each tincture together under your tongue and hold for 30 seconds, then wash them down with the juice of your choice, and wait 30 minutes. Subsequent

Doses: Place 10 drops of each tincture under your tongue and hold for 30 seconds, then wash them down with the juice of your choice. Repeat subsequent dose instructions every 30 minutes for 4 hours

- 1 dropperful of each, every 30 min for up to four hours
- 1/2 to 1 dropperful alternating with black cohosh every 1/2 hour for up to 3 hours.

Hourly protocol

- 5 drops blue and 15 drops black cohosh every hour 4 times
- Alternating dose with black cohosh every hour/2 hours for 4-6 total doses
- 20 drops every 60 minutes, alternate with Black Cohosh 20 drops every 60 minutes (on the half hour) for no more than 5 hours

Daily protocol

- For induction: 2 dropperfuls sublingual plus one dropperful Black Cohosh sublingual every four hours until contractions start
- Take 20 drops tincture or one 450 mg capsule one day in the morning (only with black cohosh), next day take then twice a day, next day take them 3 times a day, hold at that pattern for a couple of days and re-evaluate

Other

- As indicated on bottle

Precautions

General

- Apprise parents of risks associated with use (verbally or written) (4)
- Used only with the midwife present (5)
- Used only with fetal heart monitoring (3)
- Monitor fetal heart rate if used for greater than 8 hrs at 1 dropperful/hour
- Listen to heart tones or do fetal kick count between every dose

- “Assuming that it is bio-active, meaning that it actually has some effect, I feel that it is likely that the specific dose for an individual will depend heavily on individual absorption rates, a person's body weight, and other factors”
- Used only with monitoring of maternal vital signs
- Due to recent thinking that it may not be safe, I no longer use blue cohosh as a tincture, only as a homeopathic remedy
- “I do not generally recommend blue cohosh because of just this issue” [safety]
- Do not use at night because it might keep you up

Dose limits

- Not to exceed 15 ml/day
- Not to exceed 1 dropper /hour for 8 hours without checking fetal heart rate
- Use for only 1-2 days
- Do not take at night

Appendix 5: Preferred Blue Cohosh Brands

Brand	Number of Respondents (n=39)
Wish Garden Herbs	11
HerbPharm	6
<i>Self-made</i>	5
Coyote Moon Herb Company	2
Nature's Way	2
Taos Herb Company	2
Blessed Herbs	1
Boiron Homeopathy Group	1
Frontier Natural Products	1
Gaia Herbs	1
HeartSong Farm	1
Herbal Energetics	1
Nature's Sunshine	1
NF Formulas	1
Soloray by Nutraceutical	1
sWild Woman Herbs	1