Blue Cohosh and Neonatal Myocardial Toxicity

by Tieraona Low Dog, M.D., A.H.G.

Blue cohosh (*Caulophyllum thalictroides* (L.) Michx) is an attractive perennial that can be found growing throughout much of the eastern and central United States in moist, rich soil. Blue cohosh, also known as squaw root (a term no longer used because of its derogatory connotation), was said to be highly valued by indigenous women for hastening a long parturition. It was official in the United States Pharmacopoeia from 1882–1905 for labor induction. Today the herb is primarily used as a partus preparator, anti–spasmodic and emmenagogue.

Concerns over the safety of blue cohosh during the third trimester of pregnancy arose in 1996 when a report of myocardial toxicity in a newborn was published in the *New Zealand Medical Journal* (Gunn, 1996).[1] The mother had been taking a combination of herbs that included blue cohosh and black cohosh (*Cimicifuga racemosa*) prior to birth. The report suffered from failure to report dosage, full description of the herbal preparation ingested and length of usage. No clear link could be made between the birth anomaly and herb use. Then in 1998, another case report of myocardial toxicity in a newborn was reported in the *Journal of Pediatrics* (Jones, 1998).[2] The case report states a 36 year–old gravida 4, para 3 woman without significant medical history who had received appropriate prenatal care from a midwife was advised to start taking blue cohosh tablets one month prior to her due date to help induce uterine contractions. The mother took one tablet three times per day for 3 weeks during which she noticed increased uterine contractions and decreased fetal movement. (The midwife had advised her to take one tablet per day.) No drugs, alcohol, tobacco or other over–the–counter remedies were consumed. She gave birth to an 8.05 pound baby (3.66 kg) at 41 weeks following the spontaneous onset of labor. After one hour of labor the infant was delivered precipitously with apgars of 6 and 9. The infant became cyanotic and required intubation and mechanical ventilatory support within 20 minutes of delivery and was transferred to an appropriate newborn intensive care unit for evaluation and treatment.

An electrocardiogram revealed an acute anterolateral myocardial infarction. Further evaluation revealed pulmonary edema and cardiomegaly. Liver function tests were abnormal with elevated aminotransferases consistent with shock that returned to normal within ten days. After 31 days of hospitalization, the child was discharged and he remains on digoxin therapy 2 years later. The authors believe that all other causes of neonatal myocardial infarction and cardiogenic shock were excluded and that the profound congestive heart failure was due to the maternal ingestion of blue cohosh.

While this case report certainly raises concerns about the use of blue cohosh during pregnancy – there are problems with the details that make any definitive conclusion difficult. First and foremost, the product was not evaluated for appropriate identification of the botanical ingredient(s). There is no dosage provided for the herb. "One tablet taken three times per day" is relatively meaningless – how many mg were in each tablet? Was the herb taken alone or in combination with other herbs commonly found in partus preparators?

There is no question that blue cohosh contains some potentially harmful constituents. The plant is featured in standard textbooks on North American poisonous plants, and children have been poisoned by the berries[3,4]. The rhizome is known to contain the piperidine alkaloids, N–methylcytisine, baptifoline and anagyrine. N–methylcytisine has peripheral effects similar to nicotine.[5] Toxic effects include coronary vasoconstriction, tachycardia, hypotension and respiratory depression, and Rao et al reported a case of nicotinic toxicity in a woman who attempted to induce an abortion by ingesting large quantities of a tincture of blue cohosh along with slippery elm tea.[6,7] Concentrations of N–methylcytisine ranging from 5–850 ppm have been found in dietary supplements containing blue cohosh.[8] In–vitro studies have demonstrated that extracts of the whole rhizome or pure N–methylcytisine (at 20 ppm) induce major malformations in cultured rat embryos at concentrations of 20 ppm[9]; however, neither the National Institute of Environmental Health Sciences nor the Environmental Protection Agency recognize this test as an appropriate screen for human reproductive risk.

Another constituent of the plant, the quinolizidine alkaloid, anagyrine, has been associated with toxicity and teratogenicity in livestock.[10] The congenital deformity that occurs after maternal ingestion of anagyrine in lupine is called "crooked calf disease". While anagyrine is a known teratogen in livestock, it is unclear if it is teratogenic in humans.). Some researchers have postulated that the teratogenic effects only occur after metabolism by microflora in the ruminante gut. One case report in the literature describes an infant born with skeletal dysplasia and vascular anomalies after maternal consumption of anagyrine–containing goat milk.[11] Anagyrine is present in blue cohosh rhizome at a concentration of 2–390 ppm.[8] Researchers at the FDA have recommended that pregnant women avoid ingesting any amount of anagyrine until more is known about its potential teratogenicity in humans.[8] The American Herbal Products Association's *Botanical Safety Handbook* categorizes blue cohosh as a "class 2b" herb (not to be

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used during pregnancy because of its potential abortifacient activity but goes on to state that *Caulophyllum* may used (in small doses) as a parturifacient near term to induce childbirth under the supervision of a qualified practitioner.[12]

Blue cohosh also contains the glycoside, caulosaponin, which has been shown to constrict coronary vessels and exhibit oxytocic effects in vivo.[13]

What does this all mean? Studies of isolated constituents in–vitro and in vivo provide intriguing insights into understanding the pharmacology of a botanical, however there are many factors that one must account for when considering the potential benefit or toxicity when whole herb is taken orally by humans. Was the herb accurately identified? What method of extraction/administration was used? How well are the constituents absorbed across the gastrointestinal barrier? How are the constituents metabolized and excreted? What is the serum concentration of key constituents when the herb is taken in the usual and customary manner and how well do they cross the placental barrier?

Despite the shortcomings of published case reports, the chemistry and pharmacology of the plant are reasonably well known. The human case reports, flawed as they are, paint a picture that is consistent with the evidence provided by the in vitro and animal studies.

Teratogenicity can be hard to identify as hundreds of babies must be carefully examined and followed to identify even a small increased incidence of birth anomalies. Fetal alcohol syndrome (FAS) is a classic example. FAS has been present for hundreds, if not thousands, of years and yet the association of alcohol consumption during pregnancy to this syndrome was not recognized until 1972. Was blue cohosh responsible for the myocardial infarction and congestive heart failure that occurred in the infant whose mother purportedly consumed blue cohosh during her final month of pregnancy? One simply cannot say. Whole animal studies would help clarify the question of teratogenicity. While abnormal birth outcomes in animals will not exactly predict the risk in humans, the absence of birth anomalies is a very reassuring finding.

Despite the shortcomings of published case reports, the chemistry and pharmacology of the plant are reasonably well known. The human case reports, flawed as they are, paint a picture that is consistent with the evidence provided by the in vitro and animal studies. Should herbalists recommend blue cohosh as a partus preparator during the last 3–6 weeks of pregnancy? Are partus preparators even necessary? And why give an herb to increase uterine contractions 30 days before the baby is even due to arrive? Women are quite capable of bringing babies into the world without taking herbs or drugs to "prepare" for the event. Psychological/spiritual preparation seems far more important for the journey of birth than pharmacological (herbal or otherwise) interventions. One must be careful not to reduce childbirth to a pathology that must be "medically managed" by the herbalist, midwife or physician. Given the question of toxicity, it seems wise to err on the side of caution and either avoid blue cohosh during pregnancy or use only once labor has commenced when a mild oxytocic agent is deemed necessary.

References

1 Gunn TR, Wright IM. The use of black and blue cohosh in labour. *NZ Med J* 1996; 109: 410–11.

2 Jones TK, Lawson BM. Profound neonatal congestive heart failure caused by maternal consumption of blue cohosh herbal medication. *J Pediatr* 1998; 12: 550–52.

3 Hardin, JW, Arena, JM. *Human Poisoning from Native and Cultivated Plants*. Duke University Press, Kingsport, TN, USA, 1974.

4 Lampe, KF, McCann, MA. *AMA Handbook of poisonous and injurious plants*. American Medical Assoc. Chicago, Ill., USA; 1985.

5 Barlow RB, McLeod LJ. Some studies on cytosine and its methylated derivatives. *Br J Pharm* 1969; 5: 161–74.

6 Scott CC, Chen KK. The pharmacological action of N–methylcytisine. *J Pharmacol Exp Ther* 1943; 79: 334.

7 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. *J Toxicol Clin Toxicol* 1998; 36(5):455.

8 Betz JM, Andrzejewski, D., Troy, A., Casey. R.E., Obermeyer, W.R., Page, S.W., Woldemariam, T.Z. Gas chromatographic determination of toxic quinolizidine alkaloids in blue cohosh *Caulophyllum thalictroides* (L.) Michx. *Phytochem Anal* 1998; 9: 232–36.

9 Kennelly EJ, Flynn TJ, Mazzola EP, Roach, JA, McCloud, TG, Danford, DE, Betz, JM Detecting potential teratogenic alkaloids from blue cohosh rhizomes using an in vitro rat embryo culture. *J Nat Prod* 1999; 62(10):1385–9.

10 Panter KE, James LF, Gardner DR. Lupines, poison–hemlock and *Nicotiana* spp: toxicity and teratogenicity in livestock. *J Nat Toxins* 1999; 8(1):117–34

11 Ortega JA, Lezerson J. Anagyrine-induced red cell aplasia, vascular anomaly, and skeletal dysplasia. *J Pediatr* 1987; 111:87-89.

12 McGuffin M, Hobbs C, Upton R, Goldberg A, (Eds.) *Botanical Safety Handbook*. CRC Press, Boca Raton, 1997.

13 DeSmet PAGM. *Caulophyllum thalictroides*. In: De Smet PAGM, Keller, K., Hansel, R., Chandler, R.F. (Eds.) *Adverse Effects of Herbal Drugs*. Vol 2. Berlin: Springer–Verlag; 1993; 153–7.