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Berberine-Containing Herbs and Pregnancy

by Kerry Bone

Berberine-containing herbs such as golden seal (*Hydrastis canadensis*) and barberry (*Berberis vulgaris*) are traditionally said to be contraindicated in pregnancy. The *British Herbal Pharmacopoeia* 1983 is one such source of this information.[1] In most earlier texts or articles it is not always clear as to why this contraindication might exist. Certainly in the case of golden seal the concern was that its reputed oxytocic effect might induce premature labor. But since this activity was largely attributed to hydrastine,[2] which is not found in barberry, it is difficult to understand why the contraindication also existed for barberry. The Chinese herb Huang Lian (*Coptis chinensis*) is rich in berberine, but is commonly used during pregnancy (see below).

Berberine has caused uterine contraction in both non-pregnant and pregnant experimental models.[3] In another study that investigated 10 berberine-containing plant extracts, stimulation or relaxation of isolated uterus occurred depending upon the extract tested. Results did not correlate with berberine content. This suggests that a berberine-containing herb will not necessarily produce uterine contractions merely because of the presence of berberine.[4]

A different concern over berberine has arisen in the recent literature. The incidence of kernicterus in premature Chinese infants with neonatal jaundice has been reported to be in some cases associated with exposure to Huang Lian either by direct administration, transplacental absorption or via breast milk.[5] It is thought that the berberine is displacing bilirubin from its protein carrier, leading to a substantial increase in unbound bilirubin and associated adverse consequences. Such a finding would argue against the use of berberine-containing herbs in late pregnancy.

Recent concerns also exist over potential teratogenic or maternal toxic effects from berberine. The maternal LOAEL (lowest observed adverse effect level) for mated rats fed berberine chloride dihydrate from gestational day 6 to day 20 was measured at 531 mg/kg/day. The maternal NOAEL (no observed adverse effect level) was 282 mg/kg/day. In contrast, the developmental LOAEL was 1313 mg/kg/day and the NOAEL was at 531 mg/kg/day.[6] A follow-up study using the same protocol found similar results, but there was an absence of a significant effect for berberine on developmental toxicity, meaning the developmental toxicity NOAEL could be raised to approximately 1100 mg/kg/day berberine.[7] This indicates that doses less than 1 g/kg of berberine chloride dihydrate to the mother had no observable effect on offspring.

Golden seal also appears to lack teratogenic activity at normal doses. Reduction in average fetal body weight per litter was observed in the offspring of mated mice fed golden seal root powder (7.7 g/kg/day) from days 6–17. However, no significant developmental toxicity was observed below this dosage. Maternal liver weights were increased at doses greater than 2 g/kg/day, but histopathological lesions were absent.[8]

At a high oral dosage of 1.86 g/kg, golden seal did not have an adverse effect on reproductive outcome in rats. Fetal weights were slightly increased when the herb was administered from days 1–8 and days 8–15 of gestation. There was no difference in placental weight, the number of resorptions or litter size and there were no externally visible malformations. The herb was administered as an ethanol extract and the dose administered was the highest possible for which ethanol remained below the teratogenic threshold.[9]

However, the same research team published a subsequent study that compared these *in vivo* results with an *in vitro* whole embryo culture study.[10] In this model treated embryos were exposed to 0.5 to 6.0 mcL/mL of golden sea extract for 26 hours in the culture medium, which represents high levels of exposure. Toxic effects were clearly evident for the golden seal from this *in vitro* model. Higher levels of exposure also caused developmental abnormalities, whereas there were no adverse effects from the golden seal for the lowest level (0.5 mcL/mL), either toxic or developmental. The authors attributed these marked differences between the *in vivo* and *in vitro* models to the poor absorption of golden seal (especially the alkaloids) from the digestive tract. They concluded that, at the normal human oral dose, golden seal is unlikely to be absorbed to an extent to be unsafe to use in pregnancy, despite the apparent toxic effects *in vitro*.

However, an analysis of a total of 14,551 live births in Taiwan from 1984 to 1987 (but only recently published) has raised a concern for Huang Lian and hence possibly for other berberine-containing herbs.[11] After adjustment for confounding factors, taking Huang Lian during the first trimester of pregnancy was found to be associated with an increased risk of congenital malformations of the nervous system (adjusted odds ratio 8.62, 95% confidence interval 2.54 to 29.24). The exact nature of these malformations was not specified, but it excluded neural tube defects. The absolute incidence of these defects in the whole population assessed was 0.2%.

Commentary

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

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