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ORIGINAL ARTICLE

The Effect of Aqueous Extract of *Berberis Vulgaris* on Fetal Height and Weight during Pregnancy

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ABSTRACT

Background: Nowadays, the use of herbal medicine for the treatment of different diseases especially during pregnancy is increasing. It was shown that some herbs have irreparable effects on fetal development and on pregnancy. The aim of this study was to investigate the effect of aqueous extract of *Berberis vulgaris* on fetal height and weight during pregnancy.
Methods: In this experimental study, one-hundred and twenty adult female mice were enrolled. After confirmation of pregnancy, they were divided to four groups evaluated during first, second and third week of pregnancy. The control group mice were pregnant without any intervention. The second, third and fourth group received 2000, 3500 and 5000 mg/kg of barberry, respectively. The fetal weight and height were measured in each group and compared.
Results: In the first, second and third week of gestation, 5000 mg/kg of barberry decreased the embryo's weight and height in comparison to other groups.
Conclusion: The high dose of barberry resulted in adverse effects on fetal growth especially in the last week of pregnancy. Therefore, it should be administered with caution during gestation period.

Introduction

Herbal medicine consumption has grown over the past few years in the form of drugs or drug supplements (1, 2). It was demonstrated that most of women constantly are used to consuming herbal medicine for treatment of various diseases such as anxiety, nausea, dizziness, headache, osteoporosis menstrual disorders, dysmenorrhea, and sleep disorders (3, 4). Pregnancy is an important period during a woman's life, requiring more care and preventive measures (5, 6). Several studies have shown that a number of herbal compounds can have harmful effects on pregnancy and even affect fetal development (7-9).

Therefore, woman should consider taking herbal remedies and their effects during pregnancy which may lead to abortion and fetal teratogenicity (1, 10). Barberry with the scientific name of *Berberis vulgaris L* belongs to the *Berberidaceae* family. It is one of the herbs that has been used in conventional medicine and is from the genus of deciduous and evergreen shrubs being 1-5 m tall, and found throughout

temperate and subtropical regions of the world. Its (11, 12). Important ingredients of barberry include alkaloids, phenolic compounds and triterpenoid (13). Its therapeutic effects have been observed in liver disease (14) and amoebic diarrhea (15).

It also has antioxidant (16), anti-parasitic, and anti-inflammatory properties (17), and reduce the cholesterol level and triglycerides levels (18), and decreases hypertension (16). Some of the barberry ingredients pose negative effects on pregnant women and the fetus. Among them, dihydropalimitinum hydroxide (DPH), due to its anti-estrogenic property, causes endometrial atrophy and also deprive the cells from oxygen (19). Barberry can pass through the placenta and induce a teratogenic influence and can affect the growth and differentiation of various embryonic tissues (12).

Berberine is one of the main alkaloids and another ingredient of barberry that can cause contraction in uterine smooth muscle and lead to abortion. Additionally, it has toxic and teratogenic effects on the fetus at high doses (20). These factors result in the lack of complete feeding of the fetus, impaired growth and development, lack of adequate blood supply to the fetus and the placenta, and fetal abnormalities and abortions (19). Berberine also increases the level of bilirubin and cause neonatal jaundice in newborn babies (20). So this study was undertaken to investigate the effect of aqueous extract of *Berberis vulgaris* on fetal height and weight during pregnancy.

Materials and Methods

In this experimental study, after harvesting the *Berberis vulgaris* (barberry fruit), they were washed and exposed to free air to be dried in shadow condition. They were later kept in refrigerator in glass containers for further use. To prepare the aqueous extract of barberry, 30 g of the dried powder was weighed by a digital scale, and then 100 ml of sterile distilled water was added, while the glass container was heated to 80°C and placed in the water bath at 60°C. After 24 hours, the mixture was passed through a funnel and filter paper. To determine the lethal dose, the LD50 method was used. So three different doses were selected based on previous studies and injected intra-peritoneally. The lethal dose in half of the mice was considered as LD50. In the present study, it was found that the lethal dose was 5000 mg/kg of animal body weight.

A standard two milliliters syringe equipped with a feeding needle as a gavage needle was used. In order to open the mouth of the animal, the neck skin was stretched to easily enter the mouth and the esophagus and to inject the solution into the esophagus. In each cage, 5 female and 2 male mice were caged for 24 hours to mate. Vaginal plaque confirmed the pregnancy. After ensuring of the mating, they were assessed in different weeks of pregnancy. Totally 40 female mice were included and divided into four equal groups. The control group compromised 10 pregnant mice that were kept without any treatment intervention. The experimental group 1 to 3 received a daily dose of 2,000 mg/kg, 3500 mg/kg of barberry extract as gavage. In experimental group 2, there were 10 adult female mice, which received 3500 mg/kg and 5000 mg/kg of barberry aqueous extract per day by gavage. The animals were sectioned after 1, 2 and 3 weeks.

The mice were purchased from Laboratory Animal Center of Shiraz University of Medical Sciences, Shiraz, Iran. The animals were kept at controlled temperature (22.0±2.0°C) and lighting (12 h light/dark cycles) and had free access to food and water. All experiments were undertaken based on Iran Veterinary Organization rules and regulations for working with laboratory animals. This study was financially supported and ethically approved by Shiraz Branch, Islamic Azad University, Shiraz, Iran. SPSS software (Version 20, Chicago, Il, USA) was used for statistical analysis. Kolmogorov-Smirnov, One-way ANOVA, Kruskal-Wallis, Paired T and Wilcoxon signed rank test were used to compare the groups. The level of significance was considered less than 0.05.

Results

The information on fetal height and weight from first to the third week of pregnancy in the control and experimental groups was shown in Table 1. Regarding fetal weight in the first week of pregnancy, there was a significant decrease in fetal weight in experimental groups 2 and 3 compared to the control and the experimental group 1 (P<0.05). The height of the fetus in the first week of the gestation in the experimental groups 2 and 3 was considerably lower than the experimental group 1 and the control group (P<0.05). The fetal weight in the second week in experimental group 3 significantly decreased when compared to the control group and the experimental group 1. The fetal weight in experimental group 2 showed a significant decline compared to the control group (P<0.05).

Regarding fetal height in the second week, the experimental group 3 demonstrated a significant decrease compared to the control and experimental group 1. This decline was significant between experimental group 2 and the control group (P<0.05). For fetal weight in the third week, it significant

Table 1: The fetal height and weight from first to the third week of pregnancy in different groups

Variable	Control	Experimental 1	Experimental 2	Experimental 3
Fetal height (First week)	1.716±0.452b	1.462±0.381b	0.429±0.091a	0.194±0.049a
Fetal weight (First week)	0.778±0.203b	0.742±0.191b	0.122±0.100a	0.085±0.030a
Fetal height (Second week)	1.140±0.099a	1.058±0.173b	0.866±0.533bc	0.384±0.074c
Fetal weight (Second week)	0.277±0.018c	0.230±0.181bc	0.184±0.042ab	0.121±0.033a
Fetal height (Third week)	2.250±0.353c	1.223±0.183b	1.193±0.141b	0.146±0.042a
Fetal weight (Third week)	1.150±1.010b	0.397±0.065a	0.083±0.015a	0.030±0.010a

reduced in experimental groups 1, 2 and 3 when compared to the control group (P<0.05). Considering fetal height in the third week, the experimental groups 1, 2 and 3 displayed a significant decline compared to the control group. The experimental group 3 revealed a significant decrease in comparison to the experimental groups 1 and 2 (P<0.05). Comparing fetal weights in the first, second and third weeks of pregnancy, when the maximum dose was applied, the fetal weight decreased more in experimental groups and the reduction was significant when compared to the control group (P<0.05). Comparison of fetal height in the first, second and third weeks of pregnancy when the maximum dose was administered, fetal height reduced more in experimental groups from the first to third week of pregnancy.

Discussion

Most pregnant women believe that traditional medicine are not harmful and have no negative effects on mother and their fetus. so they use herbal medicines to treat gastrointestinal and sleep disorders, stress, headaches and nausea (4, 21). Congenital defects can be due to inherited and environmental factors. One of the most important environmental factors is some medications that were used during pregnancy (22). Many teratogenic agents are known to affect the specific tissues and the development of the fetus. Losing weight and height are also fetal defects that can be caused by various causes like herbal medicines (23).

In this study, the effect of barberry on height and weight of embryo of pregnant mice during the first, second and third week of pregnancy was investigated showing that increase in the administered dose led to a decrease in fetal weight. During the first and third week, weight loss was more prominent. The height of the embryo also showed a decrease when high doses of the barberry extract was used. In the first and third week of pregnancy, the decrease was

higher than the second week of pregnancy. It has been shown that barberry has ingredients that can reduce the blood pressure, maternal lipids and fetal weight (24).

Ingredients similar to those of the flavonoids in barberry fruit can alter the pathway of the hypothalamus-pituitary axis and significantly reduce the estrogen and progesterone levels, that may lead to abortion (25). In fact, changes in the level of sex hormones can cause an imbalance in the embryo implantation (26). In Macaca monkeys, hormonal fluctuations resulted in reduction of fetal weight and death after implantation (26). The impact of barberry extract on mice fetal development was investigated showing that the antro-caudal length of the embryos that received the aqueous extract of barberry reduced compared to the control group. It was probably due to the presence of berberine, one of the most important alkaloids in barberry (27).

Berberine is an organic cation that easily passes through the cell membrane and causes DNA changes. In addition, fetal cells are severely divided, and the creation of the protoberberine complex with DNA can reduce the growth of the fetus (27). Berberine also inhibits tyrosine hydroxylase, which leads to a reduced dopamine in cells (28). Also similar to our study, it was demonstrated that dopamine injection increased prolactin level and improved sexual function, so berberine in caused a reduction in dopamine and prolactin levels and impaired sexual function together with a decrease in fetal growth (29).

Conclusion

The results of this study showed that the effect of barberry extract had adverse effects on fetal height and weight during pregnancy which was dose-dependent.

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