Case Report

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# Anhydramnios, Intrauterine Growth Restriction and Echinacea angustifolia Intake: A Case Report

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## Abstract

A preterm newborn developed anhydramnios and intrauterine growth restriction after maternal *Echinacea angustifolia* intake during pregnancy. A 34-year-old primigravida woman was admitted to the hospital for an emergency caesarean delivery at 35 weeks' gestation due to anhydramnios and intrauterine growth restriction. Maternal laboratory parameters were all within normal limits, while the histological examination revealed several placental infarctions. Before and during her pregnancy, she was not affected by a chronic disease and had no complication or problem requiring a drug treatment. At her booking visit at 27 week gestation, clinical examination was unremarkable. Thereafter, she suffered for a fastidious common cold that she successfully treated with a product containing *Echinacea angustifolia* (one tablet every day for 7 weeks). The newborn (birth weight 1,330 g) did not show serious complications. In this report the development of anhydramnios and intrauterine growth restriction in a preterm newborn after the 27th week of gestation could be well correlated with impaired maternal and foetal blood flows. On the light of a physiological pregnancy where diseases, drug treatments or other risk factors were absent, the only event that could have presumably influenced placental blood flow is a regular maternal consumption (every day for about two months) of an herbal product containing *Echinacea angustifolia*, given its potential effects on foetal angiogenesis. Even if it is difficult to demonstrate a clear relationship between *Echinacea* intake and intrauterine growth restriction observed in our preterm infant, a prolonged use of this herb during pregnancy should be avoided also on the light of the paucity of available data in this area.

**Keywords:** *Echinacea*; Anhydramnios; Intrauterine growth restriction

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## Introduction

Between 4 to 7% of all pregnancies are complicated by intrauterine growth restriction (IUGR), primarily due to placental insufficiency or other causes indirectly leading to it. Defects of the placental membranes or of the umbilical cord, as well as some maternal habits or pathologies and drug treatments have to be considered risk factors for sub-optimal growth and oligohydramnios [1].

In recent years an increased interest has been observed toward herbal products as alternative treatments to conventional drugs during pregnancy, because of natural origin and then considered free of risks [2]. Despite very few trials have been performed during pregnancy to document the potential benefits of herbal products and data on their safety are limited [3], many pregnant women use these products for a variety of conditions, often on a self-treatment basis [2].

Echinacea extracts, among the most popular herbals available in the marketplace, exert immunomodulatory, antioxidative and anti-inflammatory activity and are currently used for the prevention and treatment of common cold, flu and upper respiratory tract infections [4]. Echinacea ingestion during pregnancy is usually considered to be safe, even if there is insufficient knowledge concerning this use [3].

In this work, we report a case of anhydramnios and IUGR observed after maternal intake for 7 weeks of an herbal product containing *Echinacea angustifolia*.

## Case Report

A 34-years-old primigravida woman (70 kg, 160 cm) was admitted to the hospital for an emergency caesarean delivery at 35 weeks' gestation due to anhydramnios and IUGR. The diagnosis was insufficient fetal development, antepartum complications, fetal weight at 5th percentile compared to gestational age.

At admission, laboratory investigations revealed normal haemoglobin and haematocrit values (10.4 g/dL and 32.9 mg/dL respectively). Platelet count, white blood cell count, plasma glucose, serum creatinine and liver enzymes

**Table 1.** Causality Assessment Through the Naranjo Scale

| Naranjo probability scale | Yes | No | Don't know | Score |
|---|---|---|---|---|
| 1. Are there previous conclusive reports of this reaction? | +1 | 0 | 0 | 0 |
| 2. Did the adverse event appear after the suspect drug was administered? | +2 | - 1 | 0 | +2 |
| 3. Did the adverse reaction improve when the drug was discontinued? | +1 | 0 | 0 | 0 |
| 4. Did the adverse reaction reappear when the drug was re-administered? | +2 | - 1 | 0 | 0 |
| 5. Are there alternate causes that on their own could have caused the reaction? | - 1 | +2 | 0 | +2 |
| 6. Did the reaction appear when a placebo was given? | - 1 | +1 | 0 | 0 |
| 7. Was the drug detected in the blood (or other fluids) in concentrations known to be toxic? | +1 | 0 | 0 | 0 |
| 8. Was the reaction more severe when the dose was increased or less severe when decreased? | +1 | 0 | 0 | 0 |
| 9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure? | +1 | 0 | 0 | 0 |
| 10. Was the adverse event confirmed by any objective evidence? | +1 | 0 | 0 | 0 |
| Total score | | | | +4 |

Interpretation: ≤ 0, doubtful; 1 - 4, possible; 5 - 8, probable; > 9, highly probable.

were also all within normal limits. She was Rh compatible with the baby's blood and she had no TORCH infection or chromosome abnormalities (amniocentesis revealed normal karyotype). Before the delivery, an artery Doppler study was performed: the blood-flow velocity measurement of umbilical artery and middle cerebral artery revealed respectively a pulsatility umbilical artery index of 1.08 (60° percentile for gestational age) and a pulsatility middle cerebral artery index of 0.91 (< 5° percentile for gestational age).

The placental histological examination revealed a weight of 270 g, a diameter of 14 × 13 cm, a thickness of 2 cm; an umbilical cord of 38 cm with a diameter of 1.5 cm with two arteries and one umbilical vein inside and covered by Warthon's jelly. There was no evidence of acute or chronic amnionitis and villitis, but several placental infarctions (about 50%).

During her pregnancy, the diet was equilibrated (protein, lipids, glucides, vitamins) and maternal weight gain was 8 kg.

No risk factor potentially influencing pregnancy emerged from family history. On her maternal side, her father suffered from hypertension.

Before and during her pregnancy, she was a non-smoker and no alcohol drinker. She had no previous spontaneous abortions, she was not affected by a chronic disease (diabetes, hypertension, kidney disease, allergies, neurological problems etc.) and throughout pregnancy she had no complication or problem, therefore no drug treatment was necessary. Only an iron supplement was taken.

At her booking visit at 27 weeks' gestation, clinical examination was unremarkable (ultrasound fetal biometric measurements did not reveal any problem) and her body mass index was normal.

After this visit, she suffered from a chronic cold, therefore she decided to use a phytotherapic product, considering this less toxic than a traditional drug. She bought in a herbalist's shop a commercial product called "Ekinflu e-82" (Forza Vitale Srl, Naple, Italy) containing hydro-alcoholic extracts of *Echinacea angustifolia* 0.96 g, devil's claw 0.85 g and myrrh 0.16 g in association to other herbs in very small amounts (thyme 0.027 g, oregano 0.027 g and garden savory 0.027 g). She took one tablet of the herbal product (2.4 g) every day for 7 weeks, despite indications recommended one tablet three times daily for 1 - 2 weeks. She considered this treatment satisfactory and she did not observe adverse manifestations during the consumption. She did not develop any respiratory compromise with chronic cold and she did not undergo any serologic testing for viral infections such as EBV or adenovirus.

The newborn (birth weight 1,330 g) did not show serious complications at birth (respiratory distress syndrome, bronchopulmonary dysplasia, necrotizing enterocolitis). Suspected neonatal sepsis, hypoglycaemia (relatively common in an IUGR infant) and hyperbilirubinaemia were pres-

ent and were the cause of hospitalization and prolonged stay in the nursery (for one month).

## Discussion

The development of the embryo occurs in close association with and in proximity to capillary ingrowth [1]. The vast majority of cases of fetal growth restriction are the result of ischaemic placental disease, where normal angiogenesis (critically important to ensure adequate blood flow) is altered [5].

In this report, the development of anhydramnios and IUGR in a preterm newborn after the 27th week of gestation could be correlated with the assumption that an IUGR occurring in third-trimester pregnancy is characterized by impaired blood flows [6]. IUGR occurs as a result of a failure of elongation, branching and dilatation of the capillary loops as well as a failure of terminal villi formation. Consequently, feto-placental blood flow is severely impaired and transplacental gas exchange is poor [1]. However, it is difficult to explain this on the light of a "physiological" pregnancy where diseases, drug treatments or other risk factors such as smoking and alcohol habits were absent, but overall routine ultrasound made at 27 weeks' gestation did not reveal any problem. The only event that occurred during pregnancy was a chronic cold treated with regular consumption (for 7 weeks), longer than that recommended, of a herbal product containing *Echinacea angustifolia*, devil's claw, myrrh and other herbal extracts in very small amounts. It is reasonable to exclude that the maternal common cold, probably due to an adenovirus, could be involved in the development of this serious IUGR. So, a possible role of these herbs in fetal growth needs to be elucidated.

Given the lack of data on the effects of devil's claw and myrrh during pregnancy, the use of these herbs is not recommended during this period [7]. In particular, there are no data on the effect of devil's claw and myrrh on fetal angiogenesis in humans or pregnant animals. This is also true for the other herbs present in small amounts in the herbal product.

Instead, the role of echinacea could be more substantial. The score obtained using the Naranjo probability scale for the assessment of causality was 4 (Table I), showing a possible relationship between IUGR and anhydramnios development and echinacea intake for 7 weeks.

Short-term use of echinacea is associated with a relatively good safety profile, with a slight risk of transient, reversible, adverse events [3, 7]. However, the use of echinacea products during pregnancy should be cautious on the light of the paucity of available data in this area.

Some data seem to indicate that fetal malformations do not occur in relation to the consumption of this herb during pregnancy, while conflicting is its implication on spontaneous abortion. Chow et al [8] found, in a murine model, a reduction in the number of viable fetuses after a daily consumption of *Echinacea purpurea* during early pregnancy. One prospective study on the use of different echinacea products at standard doses (from 0.25 to 1 g three times daily as tablets or tinctures for 5 to 7 days) during human pregnancy showed no statistically significant difference in spontaneous abortions or malformations between users and non-users, but a virtual doubling in the number of spontaneous abortions was observed [9]. So, this study is not sufficient to document the safety of echinacea in pregnancy, since the herb was taken at a standard dosage (usually 1 g daily of dried herb is indicated) but overall for a too short period (5 - 7 days of treatment) to affect pregnancy outcome.

More interestingly in relation to our case, some experimental murine models suggest that echinacea products may influence fetal angiogenesis and then promote fetal growth restriction. Some authors [10] suggested that the most important mechanism influencing fetal development in case of *Echinacea sp*. intake by pregnant mice might be its influence on angiogenic activity and pro-angiogenic cytokines content in developing tissues: in pregnant mice a highly statistically significant decrease in VEGF and bFGF (the most potential angiogenesis promoters) concentrations was observed in fetal tissues, suggesting that this may lead to a decrease in the angiogenic activity and therefore to developmental abnormalities such as fetal growth restriction.

Even if the amount of echinacea contained in the herbal product is considered standard for humans (0.96 g), our woman took the product for a long period with a possible cumulative effect on fetal development (in total 47 g of *Echinacea angustifolia* in 7 weeks, 0.67 g/kg) and in every case at higher doses compared to those used in experimental murine models [8, 10]. So, if the experimental dose given to mice reduced VEGF and bFGF concentrations significantly, this could have also happened in our woman.

In conclusion, even if it is difficult to demonstrate a clear relationship between echinacea intake and IUGR, it is reasonable to hypothesize an influence of this herb taken for a long period on fetal angiogenesis since our pregnant woman did not show any other factor influencing fetal growth. The ultrasound examination was normal at 27 weeks' gestation and a temporal correlation undoubtedly exists between prolonged echinacea intake from the 28 weeks' gestation and the delivery at 35 weeks' gestation of a preterm newborn with IUGR.

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## Declaration of Interest

The authors report no conflicts of interest. The authors alone

 

are responsible for the content and writing of the paper.

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