Reproductive Toxicology 72 (2017) 153–158

Reproductive Toxicology

journal homepage: www.elsevier.com/locate/reprotox

Herbal laxatives and antiemetics in pregnancy

Reza Samavati, Eszter Ducza, Judit Hajagos-Tóth, Robert Gaspar*

Department of Pharmacodynamics and Biopharmacy, University of Szeged, Hungary

ARTICLE INFO

Article history:
Received 1 February 2017
Received in revised form 24 May 2017
Accepted 5 June 2017
Available online 10 June 2017

Keywords:
Pregnancy
Laxatives
Antiemetic
Herbal
Safety

ABSTRACT

Constipation appears in the 2nd and 3rd trimester of pregnancy, while nausea is the strongest in the 1st trimester. This review summarizes the applicability of herbal laxatives and antiemetics in pregnancy.

A human study has shown that flax oil as laxative is safe from 2nd trimester. Human data is not available about the rhubarb, but animal studies reveal that its emodin content induces fetal abnormalities. Fenugreek induces teratogenic malformation both in human and animals. Senna seed is proved as a safe laxative in pregnancy. The antiemetic ginger is safe during 1st trimester, but it reduces the gestational period when applied from the 2nd trimester. Cannabis induces fetal neurological disorders while fennel can shorten the gestational age.

There is herbal alternative for laxative therapy (senna) for the whole length of pregnancy, but nausea and vomiting might be reduced by herbal medicine (ginger) safely in the 1st trimester, only.

1. Introduction

Several maternal symptoms may cause difficulties during pregnancy. Even milder disorders may challenge the therapy because of the risk of teratogenic or embryotoxic consequences. A Dutch population-based cohort study found that 5% of pregnant women receive potentially teratogenic drugs during pregnancy [1]. The majority of pregnant women try to avoid pharmacotherapy, and have better confidence towards alternative therapies, especially in the last trimester of pregnancy. According to a survey, the most common alternative remedies are the oral herbal products among women in the third trimester [2], although their safety is not always proved. Additionally, there are the different kinds of oriental herbal shops among the major sources of herbal products, where the advertisements and the provided information do not always comply with the regulations [3].

Constipation, nausea and vomiting are among the most frequent complaints in pregnancy.

Constipation mainly appears in the second and third trimester, its prevalence is around 40% during pregnancy [4]. The most common consequences of long term constipation are hemorrhoids and anal fissures [5]. Several factors can be mentioned as potential reasons for the symptom: slower gastrointestinal (GI) transit time, higher plasma level of progesterone and mechanical obstruction [6].

The global prevalence of nausea is about 70%, while vomiting occurs in half of pregnancies [7]. The high plasma level of human chorionic gonadotropin and the increased placental mass are among the main factors that increase the severity of vomiting and may lead to hyperemesis gravidarum. This condition is one of the most frequent reasons for the hospitalization and the electrolyte therapy of pregnant women [8]. The major problem is that nausea and vomiting appear in the first trimester, when any type of pharmacological or herbal treatment might have a teratogenic risk and may cause fear in mothers [9].

The aim of this review is to summarize the risks of well-known herbal laxatives and antiemetics in pregnancy by presenting preclinical and clinical evidence.

2. Search strategy

A systematic literature search for toxicity of herbal laxatives and antiemetics during pregnancy in PubMed, Google Scholar and Web of Knowledge was performed (1980–2016). Search words were " herbal laxatives", "herbal antiemetics", followed by the "toxic", "adverse effects", and "gestation", or "herbal medicines" combined with "prenatal", "postnatal", "during pregnancy", "teratogenic effect", "safety", and " harm" respectively. Search was limited to the English language. Cohort studies, reviews, Meta-analyses and randomized-controlled trials were selected. Human studies have been included in the review when the number of participants was higher than 600 and the study interval was at least 4 years. Animal studies have been included when human data were

* Corresponding author at: Eotvos Street 6, Szeged H-6720, Hungary.
E-mail address: gaspar@pharm.u-szeged.hu (R. Gaspar).

http://dx.doi.org/10.1016/j.reprotox.2017.06.041
0890-6238/

not available or few. The total number of identified papers is not recorded, but 76 articles were reviewed in this publication.

3. Herbal laxatives in pregnancy

3.1. *Rhubarb* (Rheum emodi)

Rhubarb contains emodin, a purgative resin (6-methyl-1,3,8-trihydroxyanthraquinone). The cytotoxic effects of emodin were investigated on mouse embryos at the blastocyst stage, followed by embryonic attachment and outgrowth *in vitro* and *in vivo* implantation by embryo transfer [10]. After the treatment of blastocysts with 25–75 μM emodin, they observed significantly increased apoptosis and a corresponding decrease in total cell number. In comparison with the control group, blastocysts pretreated with emodin showed a significantly lower implantation success rate. Furthermore, *in vitro* treatment with 25–75 μM emodin was associated with decreased fetal weight and increased resorption of post-implantation embryos. Through an *in vivo* mouse model, they showed that consumption of drinking water contaminated with emodin can lead to apoptosis and reduced cell proliferation, and inhibited early embryonic development in the blastocyst stage.

In another investigation, the developmental toxicity of emodin was evaluated in mice and rats [11]. They selected low dose of 425 ppm/day emodin for rats according to (National Toxicology Program, 2002a), because it was not likely to cause maternal or fetal toxicity. In this study the middle dose was 850 ppm/day and high dose of 1700 ppm/day was expected to cause significant maternal toxicity when it was administrated during the embryo/fetal development, and possibly reduced fetal body weight. Doses were applied through NIH-07 ground rodent diet from the gestational day 6 until the day 20. Mice were treated with low dose 600 ppm/day of emodin due to same reason as described for rats. Chosen dose was based on a significant decrease in maternal weight gain from pregnancy days 15–17 during a screening study (National Toxicology Program, 2000) at the low dose of 750 ppm (115 mg emodin/kg/kday). In this case the middle dose was 2500 ppm/day. The selected high dose 6000 ppm/day was applied during embryo/fetal development. Administration route was similar to rats and started from the pregnancy day 6 until day 17. The treatments outcome did not show any maternal death, but maternal body weight, weight gain during treatment, and corrected weight gain were observed in a decreasing pattern in the rats. Moreover, these symptoms appeared more significantly during treatment at the high dose. In mice, maternal body weight and weight gain were decreased at the high dose as well. Other evaluated parameters such as fetal sex ratio, prenatal mortality, live litter size and morphological development were unaffected in both rats and mice. On the other hand, they observed at the high dose that rat average fetal body weight per litter was unaffected, while it was significantly reduced in mice.

Controlled human data is not available about the emodin effects during pregnancy. In males, however, it inhibits the human sperm function [12].

3.2. *Fenugreek* (Trigonella foenum graecum)

Fenugreek is cultivated worldwide and it is one of the oldest traditional medicinal plants. Traditionally, it is known as a cooking herb but the seeds are also known to settle the stomach and relieve constipation. Toxicological animal studies evaluated the acute toxicity of the fenugreek leaves and seeds and have shown that the teratogenic dose of fenugreek can differ between species and sexes [13].

In rat treated by fenugreek seed powder during the first ten days of pregnancy (175 mg/kg/day), anomalies were reported [14] including inverted/averted claw (18% and 21%), shoulder joint defect, tail kinking, non-ossified skull bones and neural pore (18%), clubbing of hind limb (9%), and enlarged neural canal (6%). In an acute treatment study during the organogenesis period (day 10 of gestation), a single intraperitoneal dose of fenugreek aqueous extract (0.8, 1.6 and 3.2 g/kg) increased the mortality rate in embryos in a dose dependent manner [13]. Another separate study also reported that fenugreek decoction (0.8, 1.6, and 3.2 g/kg), administrated intraperitoneally to rats, decreased the fetal ear to ear diameter and increased the fetal mortality rate [15]. Additionally, single intraperitoneal injection of fenugreek leaf aqueous extract (3.2 g/kg) in the day 10 of the pregnancy (the time of organogenesis initiation and development of limb bud) can cause severe adverse alterations in the fetus, such as disorder in developing the long bone of the hind limb [16].

Studies on mice showed that lyophilized fenugreek seeds aqueous extract supplementation (500 and 1000 mg/ kg/day) during the whole gestation period decreases the litter size, increases pup mortality, reduces body weights (body weight was measured at postnatal days 1, 7, 14, 21 and 28), and induces malformations (cleft palate formation and a bump on head in newborns), growth retardation, altered neurobehavioral in the post weaning period [17]. Body weight at birth time has shown 27% reduction in the case of 1000 mg/kg treated mothers and 32% in the 500 mg/kg treated group compared with control puppies. Brain weight reduced 10% in both treated groups. Similar consequences have been proved in rabbits: the diets containing 30% fenugreek seeds caused a significant reduction in fetal development due to the reductions of both fetal and placental weights and litter size at gestation day 20 [18].

Prenatal exposure to the aqueous extract of fenugreek seeds (500 or 1000 mg/kg/day) can also induce a significant decrease in the locomotor activity in both male and female mice, suggesting that aqueous extract of fenugreek seeds induces a depressive effect in the offspring [17].

In humans, congenital malformation cases such as hydrocephalus, anencephaly, cleft palate and spina bifida were reported among women who consumed fenugreek seeds during gestation [13]. Interestingly, there are case reports of neonates being born with a peculiar odor following maternal consumption of fenugreek just before delivery, which supports the transplacental passage of fenugreek compounds to the fetus [13,19].

It emerges from this evidence that fetal malformations, growth disturbance and disordered function might be the consequences of fenugreek seeds containing an estrogenic feature agent that perturbs the endometrial lining system and interferes with fetal growth. Therefore more investigation is required to clarify the fenugreek teratogenic compound(s).

3.3. *Flaxseed* (Linum usitatissimum)

Flax is also known as common flax or linseed. It contains various dietary components such as a high content of n-3 fatty acids, fibers and other compounds [20]. Flax is the main herbal source of secoisolariresinol diglucoside which is precursor of enterolacton and entrodiol [21]. These lignans have similar structure to 17β-estradiol that could express estrogen agonist or antiestrogen like effects depending on dose, stage of development and duration of treatment [22–24]. Moreover, it also contains a detectable amount of cadmium, which can activate the estrogen receptor (ER). It is revealed that estrogenic exposures at the early life stages can modify susceptibility to developing breast cancer. The maternal dietary intake of 5% or 10% flaxseed during pregnancy or lactation (between postpartum days 5 and 25) might affect 7,12 dimethylbenz[*a*]anthracene (DMBA)-induced mammary tumorigenesis in the rat offspring. It is

proclaimed that both in utero and postnatal 5% and 10% flaxseed exposures can shorten mammary tumor latency, and 10% flaxseed exposure increased tumor multiplicity, compared to the controls [25].

Additionally, in 8-week-old rats, flaxseed exposure (10% in utero) increased lobular ER-α protein levels, and both in utero and postnatal flaxseed exposures dose-dependently decreased ER-β protein levels in the terminal end buds (TEBs) lobules and ducts. Exposures to flaxseed cannot alter the number of TEBs or affect cell proliferation within the epithelial structures. In the other group of immature rats that were fed 5% defatted flaxseed diet for a week (7 days), exposure to cadmium through the diet was six-fold higher than allowed for humans by the World Health Organization, and cadmium significantly accumulated in the liver and kidneys of the rats. It remains to be determined whether the increased mammary cancer in rats exposed to flaxseed through a maternal diet in utero or lactation was caused by cadmium present in flaxseed, and whether the reduced mammary ER-β content was causally connected to the increased risk of mammary cancer among the offspring. The preclinical study of Collins et al. shown that high flaxseed (up to 40%) and defatted flaxseed (up to 26%) content of the meal had not any apparent action on pregnancy in rats [26]. Only one human study is available about the effect of flaxseed in pregnancy. Flax oil capsule were given between gestational weeks 12 and 27 for almost 400 pregnant women, but no difference was found in timing of spontaneous delivery. This study suggests that flaxseed oil is not harmful in the 2nd and 3rd trimester of pregnancy, although further investigations are necessary to get more evidence for the safety of flax oil consumption during pregnancy [48].

3.4. *Senna seed* (Cassia occidentalis)

Senna occidentalis, also known as septicweed, coffee senna and coffeeweed is a pantropical traditional medical plant. The seeds are roasted, brewed and served as tea to treat hemorrhoids, gout, rheumatism, diabetes, and it has diuretic and laxative effects as well. It was used as an antidote for several types of poison and as a potent abortifacient [27].

In an animal model, the possible toxicity effect of oral sub-acute administration of senna during pregnancy has been investigated in female Wistar rats [27]. They were treated in the period of organogenesis during pregnancy (pregnancy days 1–14), at doses 250 and 500 mg/kg. After euthanasia of the animals, the reproductive parameters were evaluated on the 20th day of pregnancy. No statistically significant differences were found between the control and the treated groups in fetal, placental and ovarian weights; in the number of implantation and resorption sites; in the number of corpus luteum and in pre- and post-implantation loss rates. However, the numbers of dead fetuses were increased after doses of 250 and 500 mg/kg of senna.

In goat, it is reported that perinatal exposure (from pregnancy detection on day 27 after mating until delivery) to senna in different concentrations (1, 2 and 4% senna seed in the food) can cause fetal death and resorption of fetuses at higher concentration. Besides that, one dam from the higher dose treated group had tissue lesions as vacuolations in hepatocytes and kidneys; also, cardiac muscle and skeletal necrosis was detected. It can cause lesions in sciatic nerve cells as well. Therefore it is suggested that 4% of senna seed in the food of goats is toxic during pregnancy, but lower concentrations (1 or 2%) have less toxicity in natal and post-natal body development [28].

A human retrospective study (data from 1980 until 1996) in Hungary showed that, out of 22,843 cases with congenital abnormalities (CA), in 506 (2.2%) cases the mothers were treated with senna, while among 38,151 control newborn infants without CA, 937 (2.5%) were born from mothers who had senna treatment, and out of 834 malformed controls with Down syndrome, 26 (3.1%) cases had mothers with the use of senna. These women used senna in doses between 10 mg and 30 mg, but most of them used 20 mg daily [29]. They did not find a higher risk for 23 different CA groups after the senna treatment during the second and/or third month of pregnancy among 260 mothers (i.e. in the critical period of most major CAs, compared with their 500 matched controls). They also reported that pregnancy duration was a bit longer (0.2 week) and the rate of preterm birth was lower (6.6% vs. 9.2%) as compared with mothers who were not exposed to senna.

In a separate evaluation they revealed, if severe constipation in pregnant women requires laxative drug treatment, senna can be administered safely because they did not find a high rate of CA among the offspring of pregnant women whose severe constipation had been treated with senna [30].

4. Herbal antiemetics in pregnancy

4.1. *Marijuana* (Cannabis sativa)

Cannabis is the most widely used illicit drug amongst pregnant women with a prevalence of use ranging from 3 to 30% in various population. It has a strong antiemetic effect; theoretically it might be used for the treatment of nausea or morning sickness during pregnancy. However, its safety is more than doubtful. Animal and human studies were carried out to clarify the toxicity of cannabis in pregnancy.

In a study, pregnant mice were exposed (nasal) for 5 min daily to cannabis (0.2 g) smoke from gestational day 5.5–17.5 or filtered air (control). It was found that 5 min of daily cannabis exposure can decrease the birthweight, but the litter size was not reduced; interestingly, even the number of male pups per litter was higher. Additionally, the weight of wet placenta was increased but fetal to placental weight ratio was decreased in male fetuses, which showed a sex-related effect. Exposed females presented reduced maternal net body weight gain at the end of gestation, despite a slight increase in their daily food intake compared to the control group [31].

Another study applying behavioral assays, extracellular field potential recordings and whole-cell patch clamp recordings investigated the maternal exposure to the CB1 cannabinoid receptor agonist WIN 55–212–2 (WIN) in rats [32]. Treated pregnant rats showed a significant decrease in the rearing frequency, total distance moved and mobility of the offspring, but they showed a significant increase in the righting reflex time, the grooming frequency and immobility. They also reported a significant impair in neuromotor function. However, the amplitude of population spikes (PS) recorded from the cerebellar Purkinje cell layer of offspring increased following synaptic blockage. Maternal exposure also deeply affected the intrinsic properties of Purkinje neurons of offspring. This treatment increased the firing regularity, firing frequency, amplitude of after hyperpolarization, the peak amplitude of action potential and the first spike latency, but on the other hand it decreased significantly the time to peak and duration of action potentials, the instantaneous firing frequency, the rate of rebound action potential and the voltage “sag” ratio. Besides these animal studies, there are several other investigations which revealed the teratogenic and toxic effect of cannabis exposure during the prenatal period in animals [33].

On the other hand, there is some evidence that shows cannabis use during pregnancy and lactation in humans can cause various damages to the fetus and newborn babies during breastfeeding.

In a cohort study, 5588 nulliparous women at 15 ± 1 and 20 ± 1 weeks of pregnancy were investigated [34]. Cases were

included: 278 preeclampsia, 470 gestational hypertension, 633 small-for-gestational-age, 236 spontaneous preterm births, and 143 gestational diabetes cases, which were compared separately with 4114 non-cases. Continued maternal marijuana use at 20 weeks of pregnancy was associated with spontaneous preterm births that were independent of cigarette smoking status and socioeconomic index. By another evaluation, among 8138 women in the cohort, 680 (8.4%) of them used marijuana during pregnancy. Women who used marijuana were younger; had inadequate prenatal care; and used tobacco, alcohol, and other drugs as well. Medical comorbidities did not differ between groups. It was concluded that marijuana use in pregnancy may not be an independent risk factor for poor neonatal outcomes in term pregnancies [35].

There is a review focused on the cannabis-mediated maternal effects on the central nervous system and sensitization to late-onset chronic and neuropsychiatric disorders [36]. They did compare clinical and preclinical experimental studies on the effects of fetal cannabis exposure until early adulthood as well. Preclinical experimental models confirmed clinical studies and revealed that cannabis exposure can evoke significant molecular modifications to neurodevelopmental programs, which lead to neurophysiological and behavioral abnormalities. There are more documents that confirm cannabis can cause significant neurobiological and neuropsychiatric consequences on the human fetus [37]. Analyzing of the birth outcomes data from 24874 women with cannabis use in a cohort study during 7 years (2000–2006) at the Mater Mothers' Hospital in Brisbane/Australia, shown low birth weight (odds ratio (OR) = 1.7; 95% confidence interval (CI): 1.3–2.2), preterm labor (OR = 1.5; 95% CI: 1.1–1.9), small for gestational age (OR = 2.2; 95% CI: 1.8–2.7), and more frequent admission to the neonatal intensive care unit (OR = 2.0; 95% CI: 1.7–2.4) [38]. Similar adverse birth outcomes (low birth weight) were reported after the maternal cannabis use during pregnancy [39].

4.2. *Fennel* (Foeniculum vulgare)

The effects of fennel essential oil (FEO) on the uterine contraction and evaluation of lethal dose 50% (LD_{50}) in rat were studied [40]. It was found that after the administration of different doses of FEO (10, 20, 25, 40 and 50 μg/ml), the oxytocin (0.1, 1 and 10 mU/ml) – and prostaglandin E2 (5×10^{-5} M) – induced contractions were reduced significantly. The estimated LD_{50} was 1326 mg/kg for FEO. Any damage in the vital organs of the dead animals did not report.

The teratogenicity of FEO was investigated on the rat embryo limb buds [41]. The results showed that FEO at a low concentration (0.93 mg/ml) caused a significant reduction in the number of stained differentiated foci. On the other hand, FEO significantly diminished differentiation at higher doses, however paradoxically high dose of 3.72 mg/ml could not cause a significant effect. They did not observe statistical difference in the number of foci between the control group and the exposed group to the 50 μl of ethanol (as the highest concentration of vehicle) in 1 ml of culture medium. They suggest that the FEO at the applied concentrations may have a toxic effect on fetal cells, but they did not report any evidence of teratogenicity.

In a cohort study involving 630 pregnant women, collected data from mothers revealed that regular consumption of fennel during pregnancy can lead to shorter gestational age in women compared to non-users [42].

4.3. *Ginger* (Zingiber officinale)

Ginger has been used world-widely against pregnancy-induced nausea and vomiting during the centuries. However, its safety in pregnancy is still doubtful and there is a continuous debate on its application, especially in the first trimester.

The effect of ginger, a common morning sickness remedy, on fetal development in rat was investigated. Ginger produces 6- gingerol, which gives the spicy taste to ginger. 6- gingerol is thought to be a potential teratogenic due to its effect on some essential embryonic developmental processes (i.e. disruption of angiogenesis). It is confirmed by its capacity to inhibit the proliferation and tube formation of primary cultured human endothelial cells through down regulation of cyclidin D and also inhibition of tumor growth in mice by its anti-angiogenic activity [43]. Moreover, it can induce apoptosis, DNA mutation, decrease cell migration and motility in a dose dependent manner, arresting the cell cycle and stop cancer cells proliferation. Therefore, it can be embryotoxic in the first trimester when ginger might be taken to relieve morning sickness.

In a preclinical study, 20 or 50 g/L ginger tea were administered to rats from pregnancy day 6–15, through their drinking water. After the sacrifice on day 20, no toxic signs were observed in the mothers. However, the embryonic loss in the treated groups was double compared to controls. The fetuses that were exposed to ginger tea were significantly heavier than controls; this effect was more expressed in female fetuses and was not linked with increased placental size. Treated fetuses also showed advanced skeletal development [44]. The results suggest that in utero exposure to ginger tea results in increased early embryo loss with increased growth in surviving fetuses. 630 pregnant women with ginger intake were participated in a study for 4 years in an Italian public hospital. Shorter gestational age and smaller circumference of the newborn's skull were observed [42].

Although according to data from 1966 until September 2004, ginger has been proposed as a safe and efficacious alternative to conventional antiemetic drugs [45], some opinions suggest that it would be prudent to avoid using either ginger or its extracted compounds [46]. On the other hand, the greatest review about the application of ginger in pregnancy claims that ginger is safe for nausea and vomiting in the first trimester. Even the American College of Obstetrician and Gynecologists and the U.K. National Health Service have accepted ginger as an applicable antiemetic in early pregnancy [47].

Table 1
Classification of herbal laxative and antiemetic according to their safety.

	Safety				
Therapeutic use	*Safe to use*	*Use with precaution*	*More evidence is required, not recommended*	*Forbidden*	*No human data are available*
Laxative	- Senna	Flaxseed (2nd and 3rd trimester)	Fenugreek	–	- Rhubarb -Flaxseed (1st trimester)
Antiemetic	Ginger (1st trimester)	Fennel, Ginger (2nd and 3rd trimester)	–	-Cannabis	–

5. Conclusion

From ancient times until today herbal medicines had a long journey from being a medicine at that time to becoming a healthy remedy source in the 21st century. Regarding all the mentioned studies and investigations, contrary to popular belief, herbal medicines cannot be safe all the time, especially during pregnancy.

A conclusion of gestational safety of herbal laxatives and antiemetics is shown in Table 1. During pregnancy the majority of the herbal drugs for constipation can be harmful, especially if they have been taken in the first trimester. Available clinical evidence proves that the only harmless gestational herbal laxative is senna using even through the whole gestational period. The most harmful herbal drug which is commonly used by pregnant women (cannabis) can be teratogenic and embryotoxic even at low doses and therefore its use as an antiemetic is not recommended. However, ginger seems to be safe as a gestational antiemetic, but only in early pregnancy.

References

[1] I.M. Zomerdijk, R. Ruiter, L.M.A. Houweling, R.M.C. Herings, S.M.J.M. Straus, B.H. Stricker, Dispensing of potentially teratogenic drugs before conception and during pregnancy: a population-based study, BJOG: Int. J. Obstet. Gynaecol. 122 (2015) 1119–1129, http://dx.doi.org/10.1111/1471-0528.13128.

[2] A.R. Pallivalapila, D. Stewart, A. Shetty, B. Pande, R. Singh, J.S. McLay, Use of complementary and alternative medicines during the third trimester, Obstet. Gynecol. 125 (2015) 204–211, http://dx.doi.org/10.1097/AOG.0000000000000596.

[3] L. Teng, D. Shaw, J. Barnes, Characteristics and practices of traditional Chinese medicine retail shops in London, UK: a cross-sectional study using an observational approach, J. Ethnopharmacol. 173 (2015) 318–329, http://dx.doi.org/10.1016/j.jep.2015.07.027.

[4] G.H. Shin, E.L. Toto, R. Schey, Pregnancy and postpartum bowel changes: constipation and fecal incontinence, Am. J. Gastroenterol. 110 (2015) 521–529, http://dx.doi.org/10.1038/ajg.2015.76.

[5] T. Poskus, D. Buzinskiene, G. Drasutiene, N.E. Samalavicius, A. Barkus, A. Barisauskiene, J. Tutkuviene, I. Sakalauskaite, J. Drasutis, A. Jasulaitis, A. Jakaitiene, Haemorrhoids and anal fissures during pregnancy and after childbirth: a prospective cohort study, BJOG: Int. J. Obstet. Gynaecol. 121 (2014) 1666–1671, http://dx.doi.org/10.1111/1471-0528.12838.

[6] P. Rungsiprakarn, M. Laopaiboon, U.S. Sangkomkamhang, P. Lumbiganon, J.J. Pratt, Interventions for treating constipation in pregnancy, Cochrane Database Syst. Rev. 9 (2015) CD011448, http://dx.doi.org/10.1002/14651858, CD011448.pub2.

[7] T.R. Einarson, C. Piwko, G. Koren, Prevalence of nausea and vomiting of pregnancy in the USA: a meta-analysis, J. Popul. Ther. Clin. Pharmacol. 20 (2013).

[8] M.J. Castillo, J.C. Phillippi, Hyperemesis gravidarum a holistic overview and approach to clinical assessment and management, J. Perinat. Neonatal Nurs. 29 (2015) 12–22, http://dx.doi.org/10.1097/JPN.0000000000000075.

[9] L.A. Magee, K. Chandra, P. Mazzotta, D. Stewart, G. Koren, G.H. Guyatt, Development of a health-related quality of life instrument for nausea and vomiting of pregnancy, Am. J. Obstet. Gynecol. 186 (2002) S232–S238, http://dx.doi.org/10.1067/mob.2002.122604.

[10] M.H. Chang, F.J. Huang, W.H. Chan, Emodin induces embryonic toxicity in mouse blastocysts through apoptosis, Toxicology 299 (2012) 25–32, http://dx.doi.org/10.1016/j.tox.2012.05.006.

[11] G.D. Jahnke, C.J. Price, M.C. Marr, C.B. Myers, J.D. George, Developmental toxicity evaluation of emodin in rats and mice, Birth Defects Res. B: Dev. Reprod. Toxicol. 101 (2004) 89–101, http://dx.doi.org/10.1002/bdrb.20002.

[12] T. Luo, N. Li, Y. qiao He, S. qi Weng, T. Wang, Q. xing Zou, X. hui Zeng, Emodin inhibits human sperm functions by reducing sperm [Ca2+]i and tyrosine phosphorylation, Reprod. Toxicol. 51 (2015) 14–21, http://dx.doi.org/10.1016/j.reprotox.2014.11.007.

[13] M. Ouzir, K. El Bairi, S. Amzazi, Toxicological properties of fenugreek (Trigonella foenum graecum), Food Chem. Toxicol. 96 (2016) 145–154, http://dx.doi.org/10.1016/j.fct.2016.08.003.

[14] N. Sethi, D. Nath, R.K. Singh, R.K. Srivastava, Antifertility and teratogenic activity of some indigenous medicinal plants in rats, Fitoterapia 61 (1990).

[15] M. Araee, M. Norouzi, G. Habibi, M. Sheikhvatan, Toxicity of Trigonella foenum graecum (Fenugreek) in bone marrow cell proliferation in rat, Pak. J. Pharm. Sci. 22 (2009) 126–130.

[16] Z. Mozaffari, M. Azarnia, S. a Angaji, Evaluation of toxic effects of Trigonella foenum-graecum leaf aqueous extract on development of long bone tissue in rat fetus, J. Med. Plants Res. 4 (2010) 1148–1155, http://dx.doi.org/10.5897/JMPR09.437.

[17] L. Khalki, M. Bennis, Z. Sokar, S. Ba-m, The developmental neurobehavioral effects of fenugreek seeds on prenatally exposed mice, J. Ethnopharmacol. 139 (2012) 672–677, http://dx.doi.org/10.1016/j.jep.2011.12.011.

[18] A. Kassem, A. Al-Aghbari, M. Al-Habori, M. Al-Mamary, Evaluation of the potential antifertility effect of fenugreek seeds in male and female rabbits, Contraception 73 (2006) 301–306, http://dx.doi.org/10.1016/j.contraception.2005.08.020.

[19] S.H. Korman, E. Cohen, A. Preminger, Pseudo-maple syrup urine disease due to maternal prenatal ingestion of fenugreek, J. Paediatr. Child Health 37 (2001) 403–404, http://dx.doi.org/10.1046/j.1440-1754.2001.00617.x.

[20] A. Goyal, V. Sharma, N. Upadhyay, S. Gill, M. Sihag, Flax and flaxseed oil: an ancient medicine & modern functional food, J. Food Sci. Technol. 51 (2014) 1633–1653, http://dx.doi.org/10.1007/s13197-013-1247-9.

[21] L.U. Thompson, P. Robb, M. Serraino, F. Cheung, Mammalian lignan production from various foods, Nutr. Cancer 16 (1991) 43–52, http://dx.doi.org/10.1080/01635589109514139.

[22] W.E. Ward, J. Chen, L.U. Thompson, Exposure to flaxseed or its purified lignan during suckling only or continuously does not alter reproductive indices in male and female offspring, J. Toxicol. Environ. Health A 64 (2001) 567–577, http://dx.doi.org/10.1080/15287390152627246.

[23] W.E. Ward, Y.V. Yuan, a M. Cheung, L.U. Thompson, Exposure to purified lignan from flaxseed (Linum usitatissimum) alters bone development in female rats, Br. J. Nutr. 86 (2001) 499–505, http://dx.doi.org/10.1079/BJN2001429.

[24] J.C.L. Tou, L.U. Thompson, Exposure to flaxseed or its lignan component during different developmental stages influences rat mammary gland structures, Carcinogenesis 20 (1999) 1831–1835, http://dx.doi.org/10.1093/carcin/20.9.1831.

[25] G. Khan, P. Penttinen, A. Cabanes, A. Foxworth, A. Chezek, K. Mastropole, B. Yu, A. Smeds, T. Halttunen, C. Good, M. Sari, Maternal flaxseed diet during pregnancy or lactation increases female rat offspring's susceptibility to carcinogen-induced mammary tumorigenesis, Reprod. Toxicol. 23 (2007) 397–406, http://dx.doi.org/10.1016/j.reprotox.2007.02.002.

[26] T.F. Collins, R.L. Sprando, T.N. Black, N. Olejnik, P.W. Wiesenfeld, U.S. Babu, M. Bryant, T.J. Flynn, D.I. Ruggles, Effects of flaxseed and defatted flaxseed meal on reproduction and development in rats, Food Chem. Toxicol. 41 (2003) 819–834, http://dx.doi.org/10.1016/S0278-6915(03)00033-4.

[27] T.P. Aragão, M.M.A. Lyra, M.G.B. Silva, B.A. Andrade, P.A. Ferreira, L.F. Ortega, S.D. da Silva, J.C.P. da Silva, M.C.C.A. Fraga, A.G. Wanderley, S.S.L. Lafayette, Toxicological reproductive study of Cassia occidentalis L. in female Wistar rats, J. Ethnopharmacol. 123 (2009) 163–166, http://dx.doi.org/10.1016/j.jep.2008.11.030.

[28] M. Barbosa-Ferreira, J.A. Pfister, A.T. Gotardo, P.C. Maiorka, S.L. Górniak, Intoxication by Senna occidentalis seeds in pregnant goats: prenatal and postnatal evaluation, Exp. Toxicol. Pathol. 63 (2011) 263–268, http://dx.doi.org/10.1016/j.etp.2010.01.004.

[29] N. Ács, F. Bánhidy, E.H. Puhó, A.E. Czeizel, Senna treatment in pregnant women and congenital abnormalities in their offspring-a population-based case-control study, Reprod. Toxicol. 28 (2009) 100–104, http://dx.doi.org/10.1016/j.reprotox.2009.02.005.

[30] N. Ács, F. Bánhidy, E.H. Puhó, A.E. Czeizel, No association between severe constipation with related drug treatment in pregnant women and congenital abnormalities in their offspring: a population-based case-control study, Congenit. Anom. (Kyoto) 50 (2010) 15–20, http://dx.doi.org/10.1111/j.1741-4520.2009.00252.x.

[31] S.G. Benevenuto, M.D. Domenico, M.A.G. Martins, N.S. Costa, A.R.L. de Souza, J.L. Costa, M.F.M. Tavares, M. Dolhnikoff, M.M. Veras, Recreational use of marijuana during pregnancy and negative gestational and fetal outcomes: an experimental study in mice, Toxicology 376 (2015) 94–101, http://dx.doi.org/10.1016/j.tox.2016.05.020.

[32] M. Shabani, N. Hosseinmardi, M. Haghani, V. Shaibani, M. Janahmadi, Maternal exposure to the CB1 cannabinoid agonist WIN 55212-2 produces robust changes in motor function and intrinsic electrophysiological properties of cerebellar Purkinje neurons in rat offspring, Neuroscience 172 (2011) 139–152, http://dx.doi.org/10.1016/j.neuroscience.2010.10.031.

[33] M. Schneider, Cannabis use in pregnancy and early life and its consequences: animal models, Eur. Arch. Psychiatry Clin. Neurosci. 259 (2009) 383–393, http://dx.doi.org/10.1007/s00406-009-0026-0.

[34] S.Y. Leemaqz, G.A. Dekker, L.M. McCowan, L.C. Kenny, J.E. Myers, N.A.B. Simpson, L. Poston, C.T. Roberts, Maternal marijuana use has independent effects on risk for spontaneous preterm birth but not other common late pregnancy complications, Reprod. Toxicol. 62 (2016) 77–86, http://dx.doi.org/10.1016/j.reprotox.2016.04.021.

[35] S.N. Conner, E.B. Carter, M.G. Tuuli, G.A. MacOnes, A.G. Cahill, Maternal marijuana use and neonatal morbidity presented as a poster at the 35th annual meeting of the society for maternal-fetal medicine, San Diego, CA, Feb. 2–7, 2015, Am. J. Obstet. Gynecol. 213 (2015) 422e1–422e4, http://dx.doi.org/10.1016/j.ajog.2015.05.050.

[36] D. Calvigioni, Y.L. Hurd, T. Harkany, E. Keimpema, Neuronal substrates and functional consequences of prenatal cannabis exposure, Eur. Child Adolesc. Psychiatry 23 (2014) 931–941, http://dx.doi.org/10.1007/s00787-014-0550-y.

[37] D. Jutras-Aswad, J.A. DiNieri, T. Harkany, Y.L. Hurd, Neurobiological consequences of maternal cannabis on human fetal development and its neuropsychiatric outcome, Eur. Arch. Psychiatry Clin. Neurosci. 259 (2009) 395–412, http://dx.doi.org/10.1007/s00406-009-0027-z.

[38] M.R. Hayatbakhsh, V.J. Flenady, K.S. Gibbons, A.M. Kingsbury, E. Hurrion, A.A. Mamun, J.M. Najman, Birth outcomes associated with Cannabis use before and during pregnancy, Pediatr. Res. 71 (2012) 215–219, http://dx.doi.org/10.1038/pr.2011.25.
[39] T.D. Metz, E.H. Stickrath, Marijuana use in pregnancy and lactation: a review of the evidence, Am. J. Obstet. Gynecol. 213 (2015) 761–778, http://dx.doi.org/10.1016/j.ajog.2015.05.025.
[40] S.N. Ostad, M. Soodi, M. Shariffzadeh, N. Khorshidi, H. Marzban, The effect of fennel essential oil on uterine contraction as a model for dysmenorrhea, pharmacology and toxicology study, J. Ethnopharmacol. 76 (2001) 299–304, http://dx.doi.org/10.1016/S0378-8741(01)00249-5.
[41] S.N. Ostad, B. Khakinegad, O. Sabzevari, Evaluation of the teratogenicity of fennel essential oil (FEO) on the rat embryo limb buds culture, Toxicol. Vitro 18 (2004) 623–627, http://dx.doi.org/10.1016/j.tiv.2004.02.008.
[42] L. Trabace, P. Tucci, L. Ciuffreda, M. Matteo, F. Fortunato, P. Campolongo, V. Trezza, V. Cuomo, Natural relief of pregnancy-related symptoms and neonatal outcomes: above all do no harm, J. Ethnopharmacol. 174 (2015) 396–402, http://dx.doi.org/10.1016/j.jep.2015.08.046.
[43] O.J. Mohammed, M.L. Latif, M.K. Pratten, Evaluation of embryotoxicity for major components of herbal extracts using the chick embryonic heart micromass and mouse D3 embryonic stem cell systems, Reprod. Toxicol. 59 (2016) 117–127, http://dx.doi.org/10.1016/j.reprotox.2015.12.003.
[44] J.M. Wilkinson, Effect of ginger tea on the fetal development of Sprague-Dawley rats, Reprod. Toxicol. 14 (2000) 507–512, http://dx.doi.org/10.1016/S0890-6238(00)00106-4.
[45] S.A. Boone, K.M. Shields, Treating pregnancy-related nausea and vomiting with ginger, Ann. Pharmacother. 39 (2005) 1710–1713, http://dx.doi.org/10.1345/aph.1G086.
[46] D.M. Marcus, W.R. Snodgrass, Do no harm: avoidance of herbal medicines during pregnancy, Obstet. Gynecol. 105 (2005) 1119–1122, http://dx.doi.org/10.1097/01.AOG.0000173415.38704.0e.
[47] M. Ding, M. Leach, H. Bradley, The effectiveness and safety of ginger for pregnancy-induced nausea and vomiting: a systematic review, Women Birth 26 (2013), http://dx.doi.org/10.1016/j.wombi.2012.08.001.
[48] V.K. Knudsen, H.S. Hansen, M.L. Osterdal, T.B. Mikkelsen, H. Mu, S.F. Olsen, Fish oil in various doses or flax oil in pregnancy and timing of spontaneous delivery: a randomised controlled trial, BJOG 113 (5) (2006) 536–543.