

Herbal medicinal product use during pregnancy and the postnatal period: a systematic review.

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Herbal Medicinal Product Use During Pregnancy and the Postnatal Period

A Systematic Review

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OBJECTIVE: To report the incidence and nature of herbal medicinal products' adverse events and herb–drug interactions used by some pregnant and postnatal women.

DATA SOURCES: The Allied and Complementary Medicine Database, the Cumulative Index to Nursing and Allied Health Literature, EMBASE, the Cochrane Library, MEDLINE, Scopus, Web of Science, and ClinicalTrials.gov were searched from inception until August 2018.

METHODS OF STUDY SELECTION: Any studies reporting adverse events, herb–drug interactions or absence thereof associated with herbal medicinal products used during pregnancy or the postnatal period were included. Conference abstracts, pilot studies, and nonhuman studies were excluded. All included studies were critically appraised by two independent reviewers.

TABULATION, INTEGRATION AND RESULTS: Database searches retrieved 3,487 citations. After duplicate removal and review of titles, abstracts, and full-text, 115 articles were critically appraised. After excluding irrelevant and low-quality articles, 74 articles were

included for data extraction and synthesis. Adverse drug reactions, congenital malformations, fetal growth retardation or herb–drug interactions were the primary study objective reported by 19 of the 74 included studies, 16 cohort studies, one cross-sectional survey, and two randomized controlled trials. A total of 47 herbal medicinal products and 1,067,071 women were included in this review. Use of almond oil was associated with preterm birth (odds ratio 2.09, 95% CI 1.07–4.08), oral raspberry leaf was associated with cesarean delivery (adjusted odds ratio [AOR] 3.47, 95% CI 1.45–8.28); heavy licorice use was associated with early preterm birth by 3.07-fold (95% CI 1.17–8.05). African herbal medicine mwanaphepo was associated with maternal morbidity (AOR 1.28; 95% CI 1.09–1.50), and neonatal death or morbidity. Fourteen studies reported absence of adverse events. Four studies reported herb–drug interactions, but none studied adverse events arising from them.

CONCLUSION: The use of herbal medicinal products during pregnancy and the postnatal period should be discouraged until robust evidence of safety is available.

SYSTEMATIC REVIEW REGISTRATION: PROSPERO, CRD42017081058.

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Herbal medicinal products are any plant-derived product (ie, leaves, roots, flowers), in any form, taken as a preventive or curative treatment.¹ Although herbal medicinal products have been used for centuries in Asia, Africa, and Latin America, it is only over the past decades that use has attracted attention in the Western world.² Despite the lack of robust efficacy and safety data, the use of herbal medicinal products is widespread and increasing throughout North America and Europe.^{3–7}

Women have been identified as the major users of herbal medicinal products, both for maintenance of

health and treatment of disease.^{8–12} This widespread use extends into pregnancy, where reportedly between 10 and 74% of pregnant women in Africa, Australia, Europe, the United Kingdom, and the United States use herbal medicinal products.^{13–23} In the United Kingdom, approximately 40% of pregnant women use herbal medicinal products to treat pregnancy related problems or as nutritional supplements to better pregnancy outcomes.^{16,17} This use of herbal medicinal products appears to extend into the postnatal period with 31% of breastfeeding women reporting the use of complementary and alternative medicines, including herbal medicinal products, to treat a variety of ailments²⁴ or to improve milk flow.²⁵

A further potential issue is that of herb–drug interactions. Data from Australia, Europe and North and South America suggest that 12–81% of pregnant women use prescription medicines.^{26–30} It is estimated that between 2.5% and 20.3% of these pregnant women also use herbal medicinal products.^{31–34} This concurrent use of herbal medicinal products and prescribed medicines gives rise to the possibility of herb–drug interactions with the potential to harm the mother–fetus dyad.^{35,36}

Owing to a variety of reasons, including a lack of appropriately designed and powered studies, low reporting rates to inadequate regulatory supervision, and the widely held belief that herbal medicinal products are natural and hence safe, the prevalence of adverse events and herb–drug interactions associated with herbal medicinal product use is unclear. Because there are reports of severe adverse events such as perinatal stroke,³⁷ severe hyponatremia,³⁸ and lead poisoning,^{39–41} it is important to explore the prevalence of these and other adverse outcomes.

Previous published systematic reviews on the safety of herbal medicinal products have focused on randomized controlled trials, and excluded cohort studies or case reports.^{42–49} Furthermore, these systematic reviews have been assessed as being of low quality.^{50,51} Currently there are no published systematic reviews on adverse events and herb–drug interactions associated with herbal medicinal product use during pregnancy and the postnatal period. The aim of this systematic review was to retrieve primary literature reporting the incidence and nature of adverse events and herb–drug interactions, to determine whether herbal medicinal product use during pregnancy and the postnatal period is associated with adverse maternal or child outcomes.

SOURCES

The Allied and Complementary Medicine Database, the Cumulative Index to Nursing and Allied Health Literature, EMBASE, the Cochrane Library, MEDLINE,

Scopus, Web of Science, and ClinicalTrials.gov were searched from inception until August 2018. Only publications in English were included.

A three-step search strategy was applied. An initial limited search of MEDLINE was done, followed by analysis of the text words contained in the title and abstract, and of the index terms used to describe the article. A second search using all identified keywords and index terms was done across all included databases. Thirdly, the reference list of all identified articles and reports was searched for additional studies. The following search string was used:

(antenatal* OR prenatal* OR pregnan* OR postnatal* OR “postpartum*” OR “puerperium*” OR “breastfeeding*” OR “breast feeding*” OR lactati* OR maternal) AND (“herbal medicine*” OR “medicinal herb*” OR “herbal therap*” OR phytotherap* OR “traditional medicine*” OR “herb*” OR “galactagogue herb*” OR “herb* galactagogue*” OR “medicinal plant*” OR “botanical*” OR food supplement* OR liquorice* OR licorice* OR stevia OR senna) AND (“safe*” OR “adverse effect*” OR “adverse event*” OR “adverse reaction*” OR “side effect*” OR “adverse drug* reaction*” OR “drug* interaction*” OR “herb drug interaction*” OR “herb-drug interaction*” OR “drug herb interaction*” OR “drug-herb interaction*” OR “drug* hypersensitivity*” OR hypersensitivity* OR “unwanted effect*” OR “undesired effect*” OR “unwanted reaction*” OR “undesired reaction*”) NOT (vitamin* OR animal product* OR rat* OR mouse OR rabbit* OR mice OR sheep OR chick* OR pig* OR dog* OR sow* OR cow* OR monkey* OR agricultural* OR “veterinary*” OR “animal* model*” OR “in vitro” OR “cell model*”).

STUDY SELECTION

We included human studies that focused on pregnant or postnatal women. Randomized controlled trials, nonrandomized comparative studies, meta-analysis, observational studies, mixed-methodology studies, case reports and case series were considered for inclusion. Only studies that reported adverse events (including side effects, adverse drug reactions, malformations, or adverse birth outcomes), or absence thereof, or herb–drug interactions were included.

We excluded the following types of articles: conference or symposium abstracts; preliminary reports; pilot studies; correspondence articles; studies focusing on homeopathic treatments; or other alternative treatments (eg, aromatherapy, acupuncture, relaxation therapy); and low-quality case reports (see Article Quality Assessment [Appendix 1, available online at <http://links.lww.com/AOG/B334>]). The shape, active components, and molecular mechanisms

of the herbal medicinal products were not a review objective and will not be discussed in this article.

Only studies reporting any safety issue arising from herbal medicinal products used during pregnancy or the postnatal period in any country, adverse events or herb–drug interactions were assessed. Studies comparing herbal medicines with a placebo, positive controls, or no comparator were also included.

Quality assessments were conducted by two independent reviewers (Y.M.B. and D.S.) using modified versions of the Critical Appraisal Skills Programme quality assessment tool for randomized controlled trials⁵² and cohort studies⁵³ and the Joanna Briggs Institute Checklist for case reports.⁵⁴ High quality was stated as at least 14 out of 17 points for interventional studies, at least 11 out of 14 points for observational studies, and at least 7 out of 8 points for case reports. These cut-points were established by the review team considering the most relevant items of the checklists. All interventional and observational studies were included irrespective of quality score. Only high-quality case reports were included.

A tailored spreadsheet was prepared for data extraction and data synthesis. All studies identified during the database search were assessed for relevance to the review protocol and quality assessed based on information from the title, abstract and full text review by two independent reviewers (Y.M.B. and D.S.). A third reviewer was consulted if consensus could not be reached (J.S.M.). Where information was missing from the studies, contact with authors was attempted, where practical, via email; however, no responses were received.

The following key data were extracted from selected literature: details of the authors; country of publication; year of publication; herbal medicinal product; study population; setting; recruitment; incidence; nature of adverse events; and herb–drug interactions (classification, severity, patient outcomes). Data extracted for trials were the generation of allocation sequence, concealment of allocation, outcome measures, and other risks of bias. For cohort studies, the data extracted were appropriateness of exposed and control recruitment, inclusion and exclusion criteria clearly stated, appropriate validation of exposure, appropriate analyses, and enough follow-up information.

Owing to lack of study homogeneity, a meta-analysis was not appropriate; therefore, a narrative synthesis of the results was conducted. Where available, odds ratios (ORs) were reported and presented in a forest plot for descriptive purposes only, no meta-analysis was conducted.

A systematic review protocol was registered by PROSPERO.⁵⁵ The PRISMA checklist was used to guide the reporting of the systematic review.

RESULTS

Database searches retrieved a total of 3,487 citations. After removal of duplicates, title and abstract screening, and full-text screening, 115 articles were critically appraised. Only 74 articles were included for data extraction, synthesis and narrative analysis (Fig. 1). Included studies were performed in 24 different countries. Twenty-nine interventional studies, 26 observational studies, and 19 case reports were reviewed.

Fourteen interventional^{56–69} and 11 observational studies^{34,70–79} were graded as high quality; 10 interventional^{80–89} and 13 observational studies^{14,31,90–100} were graded average quality, and five interventional^{101–105} and two observational studies^{24,106} were graded poor quality. These poor-quality studies were still included in the review, only low-quality case reports were excluded (Fig. 2).

Excluding case reports, specific safety concerns, such as adverse drug reactions, congenital malformations, fetal growth restriction and herb–drug interactions, were the primary study objective reported by 19 studies, 16 cohort studies,^{31,34,70–75,77–79,92,95,96,98,100} one cross-sectional survey,⁷⁶ and two randomized controlled trials.^{64,68}

A total of 47 herbal medicinal products and 1,067,071 women were included in this review. Sample size ranged from 27 to 500 women in interventional studies, 187 to 860,215 women in observational studies, and one to five women in case reports. Seven studies collected data during the first trimester of pregnancy;^{71,82,85,88,96,105,107} 10 during the second trimester;^{41,58,67,81,83,84,87,89,101,108} 12 during the third trimester;^{38,62,64,80,91,92,100,102,103,106,109,110} five throughout pregnancy;^{69,70,75,90,95} five around the time of labor (a few hours before or after delivery);^{37,59–61,77} nine throughout pregnancy and the postnatal period;^{14,31,39,72–74,78,79,111} three during the third trimester and the postnatal period;^{40,112,113} 20 during the postnatal period only;^{24,34,56,63,65,66,68,76,86,94,97–99,104,114–119} and two did not specify the precise point during pregnancy of data collection.^{57,93}

The methods used to identify adverse events and herb–drug interactions were clinical examination;^{37–41,56,57,59,60,63,70,81,82,105,107–112,114–119} patient interviews;^{61,65,78,86,93,100,106} patient questionnaires;^{24,31,34,72–74,76,85,90,94,95,97–99} diary cards;^{62,66,68} laboratory or imaging studies (ie, hematologic and biochemical results, ultrasonography);^{71,79,102,120} and review of medical records.^{14,64,65,75,77,88,91,92,96,100,113} Eleven studies did not mention how adverse events or herb–drug interactions were identified.^{58,67,69,80,83,84,87,89,101,103,104}

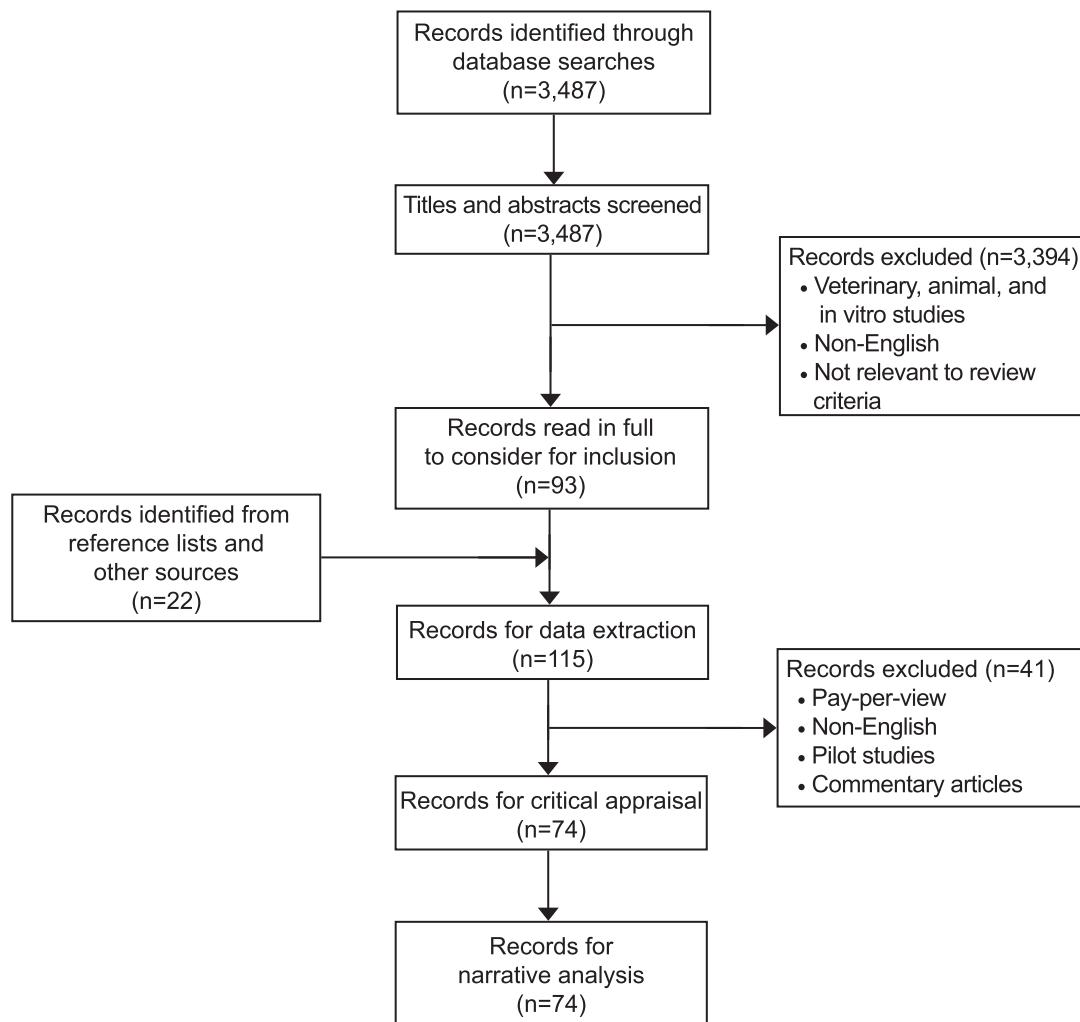


Fig. 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart.

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Thirty-one studies identified and reported the incidence of adverse events.^{14,24,56,61,64–70,72–75,81–84,86–89,93–96,99,100,105,106}

Fourteen studies reported that no adverse events were observed^{57,58,60,62,63,68,71,80,85,101–104,118} (see Appendixes 1–4, available online at <http://links.lww.com/AOG/B334>, for details). Table 1 reports the most commonly used herbal medicinal products and their reported safety issues.

The most frequently reported adverse drug reaction, for all assessed herbal medicinal products, was gastrointestinal complaints. One study comparing the use of capsaicin-containing chili to placebo for the treatment of gestational diabetes mellitus demonstrated a higher rate (60%) of loose stools, gastrointestinal irritation, and diarrhea in women using the study drug compared with none in the placebo group.⁶⁹ Otherwise, the rates of adverse drug reac-

tions were the same in all interventional studies in the study drug compared with comparator.

Topical use of almond oil during the third trimester to avoid stretch marks was associated with preterm birth (birth before week 37 of pregnancy) (OR 2.09, 95% CI 1.07–4.08).⁹⁴ When chamomile was used as a substitute for caffeinated tea in the second and third trimester, it was associated with fetal ductus arteriosus constriction, determined by fetal echocardiography in a case report,¹²⁰ and breast engorgement and a significant (50%) increase in milk production, when used during the postnatal period in another case report.¹¹⁶ Chamomile use during the third trimester was reported in one study to be associated with a higher incidence of preterm birth ($P<.002$), shorter newborns ($P<.05$), and low birth weight ($P<.002$)⁹⁹ compared with nonusers, whereas

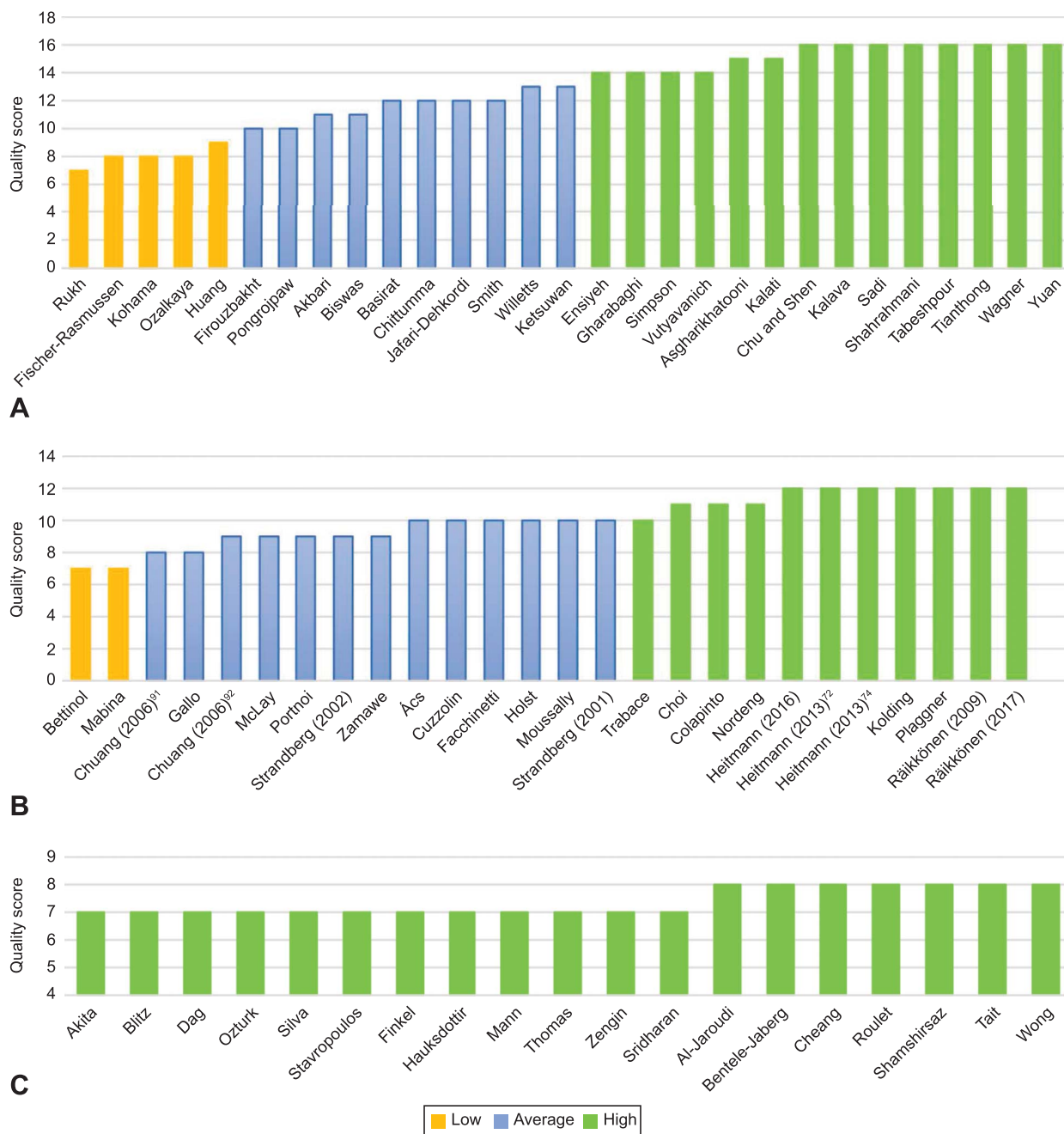


Fig. 2. Quality scores. Interventional studies (n=29) (A), observational studies (n=26) (B), and case reports (n=19) (C). Muñoz Balbontín. *Safety of Herbal Medicines During and After Pregnancy*. *Obstet Gynecol* 2019.

a similar study reported no significant increased odds of low birth weight (OR 2.1; 95% CI: 0.99–4.60).⁹⁴

Ginger is used to treat nausea. The most frequently reported adverse drug reactions were esophageal reflux,⁸⁹ heartburn,^{61,66,67,81,83,84,87,89} abdominal discomfort^{67,84} and increased nausea.⁸⁴ Heartburn and reflux (n=4), an allergic reaction (n=1), and dehydration (n=1) were reported to be severe enough for study

withdrawal in one average-quality, randomized controlled trial that included 48 women who were up to 20 weeks pregnant and were taking ginger.⁸⁹ The use of ginger throughout pregnancy was associated with a nonsignificant increase in the incidence of stillbirths (OR 7.8, 95% CI 0.9–70.3)⁷⁰ and a significant decrease in gestational age at delivery and neonatal head circumference ($P<.05$ and $P<.002$, respectively)⁹⁹

Table 1. Reported Safety Issues of the Most Commonly Used Herbal Medicinal Products During Pregnancy and the Postnatal Period

Herbal Medicinal Product (No. of Reports)	Indication	Adverse Events	Herb–Drug Interactions	Reference(s)
Aloe (3)	Skin conditions	Itching and rash	Insulin—additive hypoglycemic effects	76,93,94
Almond oil (2)	Skin conditions	Itching and rash, preterm birth	No reports	93,94
Chamomile (5)	Various	Fetal ductus arteriosus constriction, fetal tachycardia; preterm delivery, low birth weight, smaller newborns; breast engorgement and tenderness	Diazepam—additive sedative effects; propranolol—inhibition of CYP1A2 and CYP2D6; diclofenac—inhibition of CYP2C9; ondansetron—inhibition of CYP1A2; chlorpromazine—inhibition of CYP2D6; dihydrocodeine—additive sedative effects; co-codamol—additive sedative effects; NSAIDs; benzodiazepines	31,76,94,99,113,116
Cranberry (2)	Urinary tract infections	Spotting in the 2nd and 3rd trimesters	Diazepam—inhibition of CYP2C9; diclofenac—inhibition of CYP2C9	72,76
Echinacea (2)	Upper respiratory tract infections	Hypospadias, cleft lip, hypoplastic left heart syndrome, inguinal hernia, hydronephrosis, syndactyly, duplicate renal pelvis, laryngotracheomalacia, trisomy 18	No reports	73,95
Evening primrose oil (1)	Labor induction	No adverse events were diagnosed in case or placebo groups	No reports	60
Fenugreek (1)	Increase milk production	Toxic epidermal necrolysis: fever, headache, bullous exanthema, skin erosions	No reports	114
Ginger (17)	Nausea and vomiting	Reflux, heartburn, mouth irritation, headache, dry mouth, bloating, sweating, body ache, loose stools, diarrhea, drowsiness, sedation, arrhythmia, stomach-ache, increased nausea, allergy, dehydration. Spotting in the 2nd and 3rd trimesters. Ventricular septal defect, right lung abnormality, pelviectasis in newborns. Shorter gestational age and smaller head circumference of newborns.	Metformin—additive hypoglycemic effects, might increase insulin levels; insulin—additive hypoglycemic effects; aspirin—inhibit thromboxane synthetase and decrease platelet aggregation, increased odds of bleeding; nifedipine—significantly inhibits platelet aggregation, synergic effects	58,61,66,67,70,74,81–84,87–89,96,99,101,105
Licorice (4)	Not specified	Increased odds of early preterm birth, rule-breaking and aggressive behavior, and ADHD in children aged 8.1 y. Early puberty in girls, ADHD problems in adolescents, very early-onset severe preeclampsia	No reports	78,79,97,98
Raspberry leaf (3)	Labor induction	Hypoglycemia, higher percentage of cesarean deliveries vs nonusers. Diarrhea, constipation, nausea, vomiting, headache, heartburn, uterine tightening, dizziness, bloating	Insulin—possible additive hypoglycemic effect (not reported as such, not registered in NMCD)	34,64,110

ADHD, attention-deficit/hyperactivity disorder; NMCD, Natural Medicines Comprehensive Database.

compared with nonusers. The use of ginger (7.8% vs 5.8% nonusers [$P=.007$])⁷⁴ and cranberry (9.7% vs 5.8% nonusers [$P<.001$])⁷² after week 17 of pregnancy was associated with vaginal bleeding (spotting) during 2nd and 3rd trimesters.

Licorice candy consumption in the second trimester (18 weeks of gestation) was associated with severe, very early-onset preeclampsia in a case report.¹⁰⁸ Heavy licorice candy consumption (greater than 500 mg/wk) throughout pregnancy was associated with preterm birth and early preterm birth (birth before week 34 of pregnancy) (adjusted odds ratio [AOR] 2.5, 95% CI 1.1–5.1⁹⁷; AOR 3.07, 95% CI 1.17–8.05,⁹⁸ respectively) compared with nonusers. Moreover, heavy licorice candy consumption in pregnancy was associated with a variety of psychosocial issues during childhood⁷⁸ and markers of early puberty for girls 12 years of age⁷⁹ in the offspring (Fig. 3).

Mwanaphepo, an African herbal medicine used for labor induction, was associated with maternal morbidity (ie, emergency cesarean delivery, assisted vaginal delivery, premature rupture of membranes, any postnatal morbidity and any delivery problem) (AOR 1.28; 95% CI 1.09–1.50) and neonatal death or

morbidity (ie, neonatal death, meconium-stained liquor, low birth weight, preterm birth and any neonatal morbidity) (AOR 1.22; 95% CI 1.06–1.40).¹⁰⁰

Raspberry leaf, when used to induce and shorten labor, was associated with cesarean delivery (AOR 3.47, 95% CI 1.45–8.28).³⁴ Maternal hypoglycemia was reported in one case report.¹¹⁰ Gastrointestinal complaints (28%), headache (1%), uterine tightening (2%), and dizziness (1%) were reported in one randomized controlled trial.⁶⁴ Senna use during pregnancy was associated with polyhydramnios (OR 3.8, 95% CI 1.6–8.9), weakly associated with influenza or common cold (OR 1.9, 95% CI 1.5–2.4), and acute digestive maternal diseases (OR 1.8, 95% CI 1.2–2.89).⁹⁰

Hepatotoxicity was reported in six case reports associated with: three different lead-contaminated Ayurvedic medications used to maintain pregnancy,^{39–41} a herbal tea contaminated with senecionine,¹¹⁹ a lead-contaminated mountain germander infusion,¹¹⁵ and a lead-contaminated fennel and cumin infusion¹¹⁷ each used to increase milk production in the postnatal period.

No significant difference in the incidence of congenital malformations between case and comparator groups has been reported for ginger,^{70,74,96}

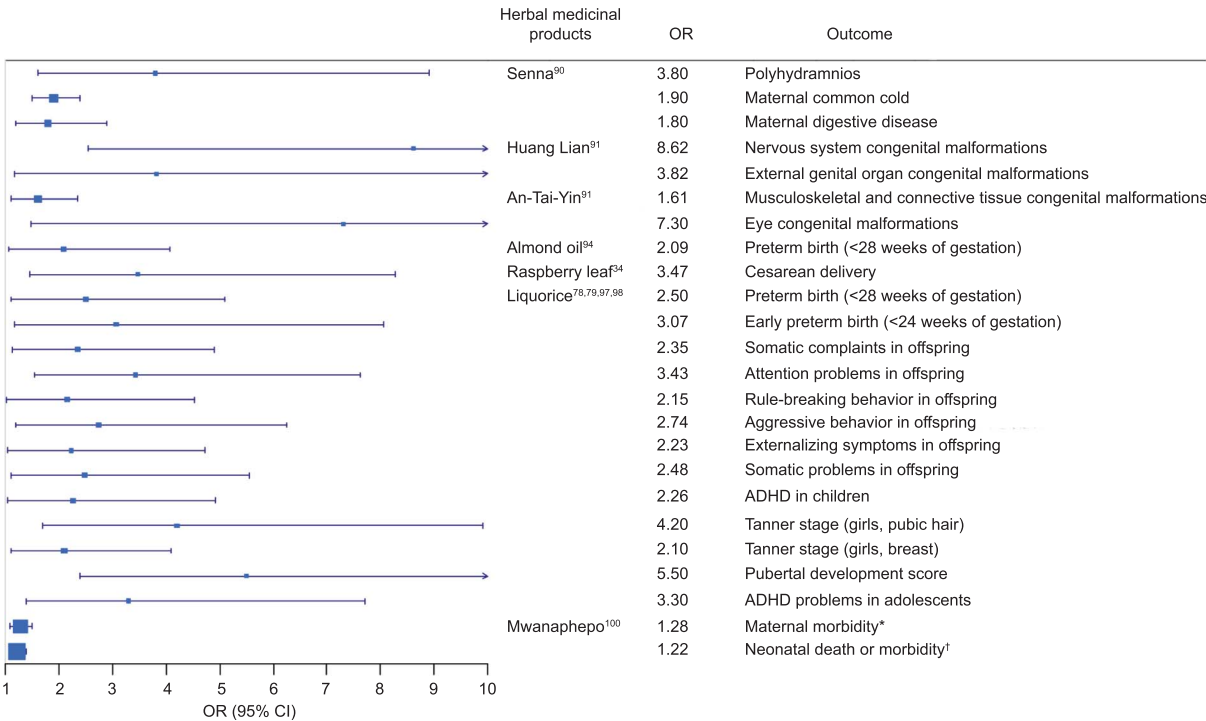


Fig. 3. Forest plot for adverse events of herbal medicinal products. *Maternal morbidity includes cesarean delivery, assisted vaginal delivery, premature rupture of membranes, any postnatal morbidity, and any delivery problem. †Neonatal death or morbidity includes neonatal death, meconium-stained liquor, low birth weight, preterm birth, and any neonatal morbidity. OR, odds ratio; ADHD, attention deficit hyperactivity disorder.

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echinacea,^{73,95} cranberry,⁷² senna,⁹⁰ and St. John's wort.⁷⁵ However, Chuang and colleagues reported an association between Huang Lian (*Rhizoma coptidis* for skin conditions) use during the first trimester and nervous system congenital malformations AOR 8.62, 95% CI 2.54–29.24) and external genital organ congenital malformations (AOR 3.82, 95% CI 1.18–12.40) in the offspring.⁹¹ Moreover, use of An-Tai-Yin (*Angelica sinensis*) and parsley (for prevention of miscarriages) during the first trimester was associated with musculoskeletal and connective tissue congenital malformations (AOR 1.61, 95% CI 1.10–2.36), and eye congenital malformations (AOR 7.30, 95% CI 1.47–36.18) in the offspring.⁹¹ Considering the wide CIs reported in these studies, these effect sizes should be considered weak.

Four studies reported herb–drug interactions, but none studied adverse events arising from them. Herb–drug interactions were reported in two cross-sectional surveys^{34,76} and two prospective cohort studies.^{14,31} Of these, only three reported their incidence,^{31,34,76} two reported how they were assessed,^{31,76} and none reported the incidence of adverse events arising from the identified herb–drug interactions.

Reported herb–drug interactions involved aloe, chamomile, cranberry, ginger, ginseng, common sage, iron-rich herbs and dandelion (see Appendixes 1–4, <http://links.lww.com/AOG/B334>, for details). Chamomile used alongside prescribed medicines such as diazepam, propranolol, diclofenac, ondansetron, chlorpromazine, dihydrocodeine, and co-codamol was associated with potentially severe herb–drug interactions owing to possible additive sedative effects.^{34,76} One randomized controlled trial reported 1.6% (1/61) of their participants took other medications alongside ginger,⁸³ and a cross-sectional survey reported ginger was taken with metformin, insulin, aspirin, and nifedipine and could be associated with herb–drug interactions.⁷⁶ One prospective cohort study reported no increased odds of adverse pregnancy outcomes when cranberry was used together with antibiotics to treat urinary tract infections.⁷² One case report¹¹⁰ mentioned additive glucose lowering effects when insulin (Lispro) and raspberry leaf were taken simultaneously but did not address this as a potential herb–drug interaction.

The role of herb–drug interactions in the causation of adverse events in pregnant woman has not been assessed. A full list of herbal medicinal products and associated adverse events and herb–drug interactions are available in Appendixes 1–4 (<http://links.lww.com/AOG/B334>).

DISCUSSION

Robust studies that aim to identify and study the causality of adverse events or herb–drug interactions and associated adverse events arising during pregnancy and the postnatal period as a primary objective are not currently available. Current data suggest that herbal medicinal products such as almond oil, chamomile, licorice, and raspberry leaf used during pregnancy may be associated with adverse maternal and perinatal outcomes or toxicity from contaminants.

Studies focusing on herb–drug interactions are few, although of average to high quality, and did not assess or report adverse events arising from identified herb–drug interactions. Moreover, available evidence demonstrates that widely used herbal medicinal products such as topical almond oil,⁹⁴ chamomile,¹²⁰ ginger,^{58,61,66,67,70,74,81–84,87–89,96,99,101,105} licorice,^{78,79,97,98} and raspberry leaf³⁴ may be associated with adverse perinatal outcomes. Although the majority of available studies were graded as average and many underpowered, potentially harmful adverse events arising from use of specific herbal medicinal products have been reported (Fig. 3).

The daily use of topical almond oil for stretch marks during the third trimester has been reported to increase the odds of preterm birth.⁹⁴ The authors hypothesized that continuous rubbing of the belly might stimulate premature myometrial contractions and that components of almond oil might act as prostaglandin precursors. However, only 168 women were exposed to almond oil and the data were collected retrospectively, therefore providing underpowered assumptions and introducing recall bias. Moreover, dosage, surface area of application and almond formulation used were not provided and therefore causality cannot be objectively demonstrated.

The evidence for chamomile during pregnancy reports increased odds of preterm delivery,⁹⁹ reduced length of newborns, and low birth weight.⁹⁴ However, both studies were underpowered and of average quality. Chamomile has also been identified as a common source of potentially severe herb–drug interactions when used concurrently with prescribed medicines.^{34,76} Considering the scarce evidence available, chamomile should be used with caution during pregnancy.

The use of ginger during early pregnancy has been associated with a variety of mild to severe, non-dose-dependent adverse drug reactions, ranging from dry mouth to worsening of nausea and dehydration⁸⁹; use during late pregnancy has been associated with bleeding or spotting during the second and third

trimesters,⁷⁴ prematurity, and reduced head circumference at birth.⁹⁹ It has to be noted that formulation, dose, and exposure period were not standardized in these studies. Ginger has also been identified as a source of potentially significant herb–drug interactions with insulin, metformin, and nifedipine, medicines commonly used during pregnancy.⁷⁶

The use of raspberry leaf has been associated with cesarean delivery by 3.5-fold³⁴; however, this study involved only 34 exposed women. Raspberry leaf has also been associated with hypoglycemia when used with insulin.¹¹⁰ Until there are more safety data, it could be suggested that raspberry leaf should not be used for labor induction because its adverse effects may outweigh its perceived benefit.

Heavy licorice consumption (500 mg glycyrrhizin/wk) throughout pregnancy was reported to increase the odds of preterm birth (AOR 2.5, 95% CI 1.1–5.1)⁹⁷ and early preterm birth (AOR 3.07, 95% CI 1.17–8.05).⁹⁸ However, these studies were of average quality, used retrospective data and did not validate exposure. Nonetheless, they had adequate sample sizes and considered validated outcomes. Moreover, glycyrrhizin, the active component in licorice, is recognized to cause developmental issues.^{78,79,121}

The traditional use of mwanaphepo to induce labor in Malawi was associated with maternal morbidity (ie, emergency cesarean delivery on, assisted vaginal delivery, PROM, among others) (AOR 1.28; 95% CI 1.09–1.50) and neonatal death or morbidity (including neonatal death, meconium-stained amniotic fluid, LBW, PTB, among others) (AOR 1.22, 95% CI 1.06–1.40).¹⁰⁰ This average quality cross-sectional analysis used grouped retrospective data, which may introduce bias and error,¹²² and did not validate exposure to the herbal medicinal products. Neither the dosage nor specific preparation of mwanaphepo were reported. Considering the latter, the reported effect sizes in this study should be considered weak.

The absence of adverse events were reported in 11 interventional studies assessing evening primrose oil capsules,⁶⁰ dill infusion for labor induction,⁸⁰ red sage for oligohydramnios,⁵⁷ ginger for nausea and vomiting during pregnancy,^{58,101} Chinese herbal medicine for intra-uterine growth restriction,¹⁰² quince for nausea and vomiting in pregnancy,⁸⁵ pine bark¹⁰³ and 1% green tea ointment⁶³ for episiotomy wound healing, saffron for labor induction,⁶² and a polyherbal infusion to increase milk production.¹⁰⁴ One prospective cohort study assessing tea (black green, and herbal) consumption during pregnancy

and adverse birth outcomes also reported absence of adverse events.⁷¹ More than half of these studies were of poor^{101–104} or average quality.^{80,85} Moreover, those studies deemed to be of high quality suffered from a variety of methodologic issues, including small sample sizes,^{58,62} absence of a power calculation,⁶⁰ short exposure period,⁵⁸ and failure to validate exposure.⁷¹ Therefore, these studies should not be taken as evidence of safety based on absence of harm, and further robust studies are required.

This review includes all types of studies (interventional, observational and case reports) that report adverse events or herb–drug interactions arising from herbal medicines (including polyherbals) taken during pregnancy and the postnatal period. All interventional and observational studies were included, regardless of quality. However, only high-quality case reports were included because they are considered low scientific evidence per se. Non-English language articles were excluded, possibly leaving out important information from nontranslated articles. Owing to the large number of herbal medicinal products available worldwide and the lack of standardization in reporting the names of herbal medicinal products, it is possible that relevant literature was omitted and that not all herbal medicinal products were reported.

Collective evidence confirms that adverse events and herb–drug interactions arising from herbal medicinal products used during pregnancy and the postnatal period are under-studied and under-reported. Herb–drug interactions are not reported or investigated in the majority of studies. This is of concern given the high prevalence of use of herbal and conventional medicines during and after pregnancy.

The evidence-based use of herbal medicines needs to be backed by robust scientific studies. Currently, there is not enough information to recommend the safe use of herbal medicinal products during pregnancy and the postnatal period. Most herbal medicinal products are recommended and used on the grounds of tradition, historic or anecdotal evidence. Adverse events are generally under-reported to clinical staff, also the use of herbal medicinal products. The U.S. Food and Drug Administration, the European Medicines Agency (European Union), and the Medicines and Healthcare Products Regulatory Agency (United Kingdom) do not subject herbal medicinal products to the same quality standards as medicines. Stricter pharmacovigilance measures should be taken to avoid possible harm arising from current herbal medicinal product use during pregnancy and the postnatal period. Considering the 30 years of evidence of possible harm presented, we

conclude herbal medicinal products should not be recommended during pregnancy until robust evidence of safety is available.

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PEER REVIEW HISTORY

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