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Original Research

A Retrospective Cohort Study of Herbal Medicines Use during Pregnancy: Prevalence, Adverse Reactions, and Newborn Outcomes

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Abstract

This study aimed to investigate the herbal medicines use prevalence and adverse drug reactions (ADRs) during pregnancy as well as the probable effects on newborn outcomes. Postpartum women with a live singleton infant were eligible if declared consent before discharge. Data was collected retrospectively by face-to-face interviews. Generally, 400 pairs of mother/infant were recruited. At least one herbal medicine was used by 325/400 (81.3%) women. Peppermint, frankincense, flixweed, olive oil, and cinnamon were the most common herbs. Overall, 26 ADRs were reported by 19/325 (5.8%) women. Gastrointestinal complaints were the most frequent herbal ADRs (18/26, 69.2%). Gestational age, Apgar scores, birthweight, complications, and malformations of newborns were similar between groups. In conclusion, herbal medicines were highly used by pregnant women, while they did not affect newborn outcomes either positively or adversely. Despite low frequency rate of herbal ADRs during pregnancy, their safety, efficacy, interactions, and potential risks need further studies.

Keywords: Adverse drug reaction; Herbal medicine; Infant; Newborn; Outcome; Pregnancy

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Introduction

Pregnant women increasingly use herbal medicines in preference to conventional medicines as they are perceived to be 'natural' and therefore 'safe' despite the little scientific-based evidences of their safety and efficacy during pregnancy and the existence of clear evidences of negative effects in some cases [1]. An analysis by Farah *et al.* [2] on the herbal adverse drug reactions (ADRs) reported to the Uppsala Monitoring Centre (UMC) of the World Health Organization (WHO), from 1968 to 1997, found substantial evidences that herbal medicines could cause serious ADRs and fatal outcomes, emphasizing on more data requirements about the type, frequency, and preventability of herbal ADRs.

Some plants have been recognized as highly poisonous, with characteristically toxic constituents. Moreover, herb-herb, herb-drug, and herb-food interactions are not fully understood. Herbal medications have been associated with harmful effects as a result of contamination or adulteration with toxic metals or even undisclosed conventional drugs [3]. The limited clinical data on the safety and efficacy of herbal medicines makes the benefit-risk assessments problematic [4].

Use of herbal drugs by pregnant women in relation to concurrent use of conventional drugs, delivery, and pregnancy outcomes has been rarely studied. This study aimed to evaluate the herbal medicines use prevalence in one month before and during pregnancy, ADRs of herbal medicines, practice of using herbal medicines, concurrent non-herbal medicines, and the probable effects on newborn outcomes.

Methods

Study design, setting, and participants

This single-centered, observational, retrospective, cohort study was approved by the ethics committee of Tehran University of Medical Sciences. The study was conducted over a period of seven consecutive months at the maternity ward of Arash hospital, which has approximately 4350 women with live births per year. Participants were enrolled two days a week from 8:00 until 16:00 o'clock. All the postpartum women with a live singleton infant within this time-frame were eligible if declared consent before discharge. Women unable to answer the questions due to limited understanding or feeling unwell were excluded. All women received oral information about the study. Then, written consent was obtained.

Variables

The questionnaire was pretested for reliability in a small sample (n = 30) of subjects. The instrument was further refined and the final version was confirmed. KR collected data of one month before pregnancy up to postnatal discharge by face-to-face interviews and filling questionnaires. Each interview lasted 18.6 ± 5.3 minutes.

Maternal socio-demographic characteristics, history of previous pregnancies and miscar-

riages, chronic diseases, complications of pregnancy, delivery, and postpartum (based on defined check lists) were assessed. Newborn characteristics (sex, gestational age at birth, 1-min and 5-min Apgar, birthweight), and complications up to discharge were noted. Relevant data of mothers and newborns were cross-checked with and/or extracted from hospital files.

Herbal and non-herbal medicines were individually explained for each participant. An open-ended question followed by indication-oriented and drug-oriented questions, based on a prepared list of common drugs, were asked to help mothers remember all their medicines. Consumption of an herbal medicine in at least half of one month before, first trimester, second trimester, third trimester, or last two weeks of pregnancy was considered as the regular use of that herb during that period.

All the herbal and non-herbal medicines (name, dosage form, administration route, dose, duration, timing, reason of use) were recorded. Incidence, causality, severity, seriousness, management, and outcome of herbal ADRs were evaluated.

Practice of using herbal drugs was evaluated regarding the place of purchase, advisers, consultation with physicians, pharmacists, and midwives (healthcare providers), and amount of use compared to non-pregnant status. Participants were also questioned about the knowledge on probable harms of herbal medicines in pregnancy and level of satisfaction with herbals effects.

Data sources

Pregnancy was defined as the time period between the first day of the last menstruation and delivery. First trimester (months 1-3), second trimester (months 4-6), and third trimester (months 7-9) were defined as 3-month periods.

Based on the WHO definition, herbal medicines included any product containing either raw or processed active ingredient(s) from one or more plant(s) whether in the form of crude plant materials, herbal preparations, or finished products for the prevention or treatment of physical and mental illnesses, improvement of symptoms, or beneficial alteration or regulation of the physical and mental status [5]. Combinations of herbal materials with synthetic compound(s), and/or isolated constituent(s) from plants, as well as flavored foods and drinks with herb(s) or spices were not defined as herbal medicines. Herbal medicines included both licensed (registered with an ATC code at the Natural Medicines Office of the Ministry of Health of Iran) [6] and unlicensed preparations (available in herbal shops).

Herbal and non-herbal medicines were categorized into different groups according to the 2019 Anatomical Therapeutic Chemical (ATC) classification system for drugs elaborated by the WHO Collaborating Centre for Drug Statistics Methodology [7]. Diseases and complications were defined and categorized based on the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) [8].

ADRs were defined according to Edwards and Aronson explanation: "a noticeably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard for future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product" [9].

All of the recorded herbal ADRs were categorized by the Medical Dictionary for Regulatory Activities (MedDRA) Terminology for System Organ Classes (SOCs), version 21.1 [10]. WHO-UMC causality scale [11], Hartwig-Siegel severity scale [12], Food and Drug Administration (FDA) seriousness criteria [13], Edwards-Aronson management scale [9], and WHO outcome criteria [14] were used for the evaluation of herbal ADRs (Table 1).

Table 1. Strategy of herbal ADRs evaluation

System organ classes	Categories	Reference scale
	• 27 SOCs	MedDRA [10]
Causality	• Certain • Probable/Likely • Possible • Unlikely • Conditional/Unclassified • Unassessable/Unclassifiable	WHO-UMC [11]
Severity	• Mild (Level 1) • Mild (Level 2) • Moderate (Level 3) • Moderate (Level 4a) • Moderate (Level 4b) • Severe (Level 5) • Severe (Level 6) • Severe (Level 7)	Hartwig and Siegel [12]
Seriousness	• Not serious • Serious - Death - Life-threatening - Hospitalization (initial or prolonged) - Disability or permanent damage - Congenital anomaly/birth defect - Required intervention to prevent permanent impairment or damage (devices) - Other serious (important medical events)	FDA [13]

Management	• No change in drug and no additional treatment • Antidote or additional specific treatment • Dose adjustment • Drug withdrawal • Change of therapy • Others	Edwards and Aronson [9]
Outcome	• Recovered/resolved • Recovering/resolving (complete recovery was expected) • Recovered with sequelae • Not recovered/not resolved • Died • Unknown	WHO [14]

Abbreviations: ADR, adverse drug reaction; SOCs, System Organ Classes; WHO, World Health Organization; UMC, Uppsala Monitoring Centre; FDA, Food and Drug Administration.

Statistical analyses

Assuming a prevalence of 28% to 36% for herbal consumption during pregnancy [15,16] (d = 0.05) and 15% non-response rate, a sample size of 400 (mother/infant pairs) was finalized. Exposed (using at least one herbal medicine one month before and during pregnancy) and unexposed women to herbal products were compared for arranged variables.

Comparisons between the groups were performed with independent samples *t*-test (mean of quantitative data) and chi-square tests or Fisher's exact test (qualitative data). Pearson correlation coefficient and multiple linear regressions were calculated to determine the relationship between variables (age, body mass index, birth place, education, occupation, and children). Statistical significance was declared at $P < 0.05$. Data was analyzed by the software of SPSS Statistics for Windows, Released 2008, Version 17.0, SPSS Inc., Chicago, IL, USA.

Demographics

Mean age of the participants was 27.3 ± 5.2 years. They were from 23/31 provinces of the country. The mean body mass index at the beginning and end of the pregnancy were 25.2 ± 5.5 and 30.7 ± 6.2 kg/m^2, respectively. Sociodemographic characteristics of exposed and unexposed women to herbal products during pregnancy are summarized in Table 2.

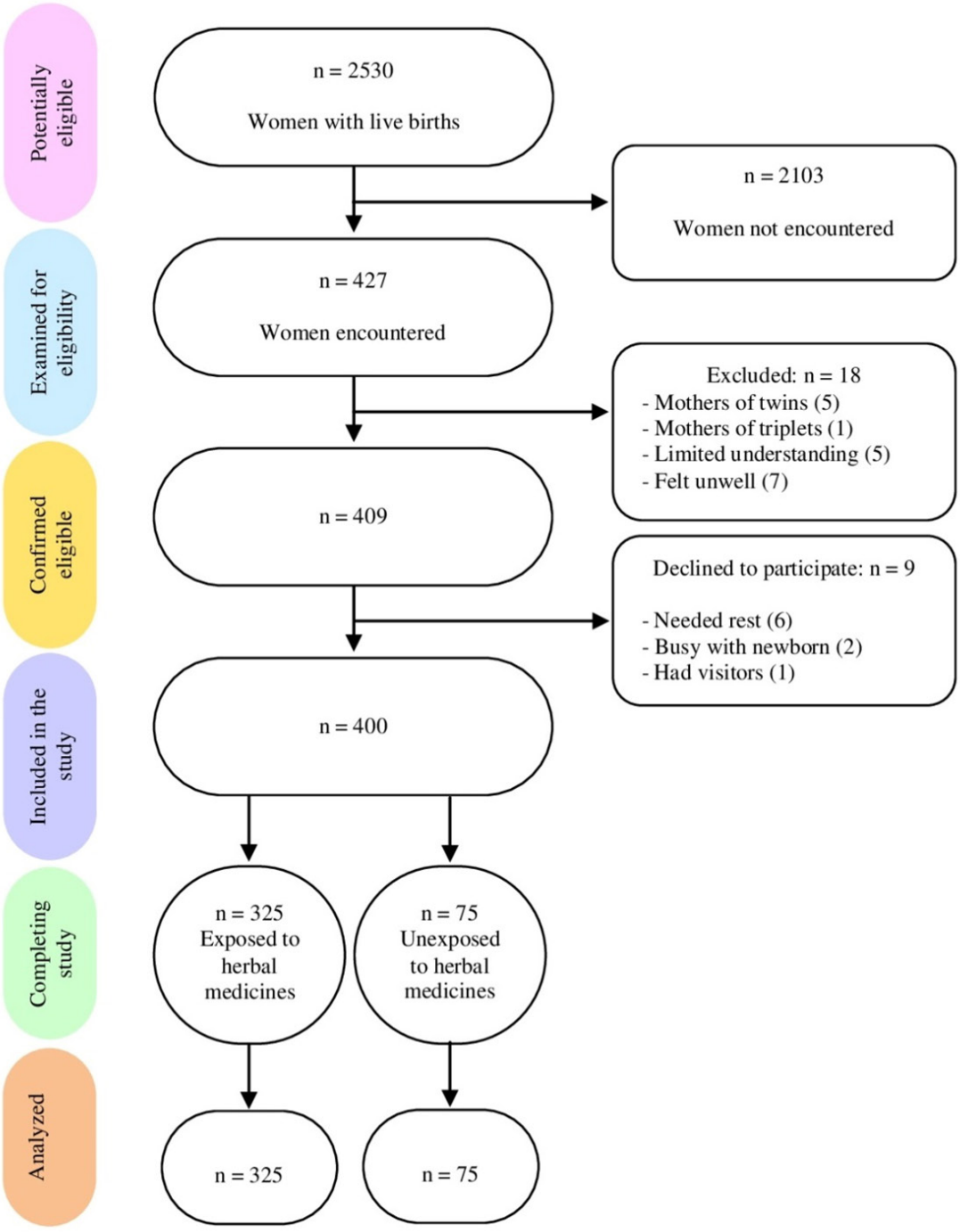

Figure 1. Flow diagram of the participants.

Table 2. Sociodemographic characteristics of exposed and unexposed women to herbal medicines during pregnancy

	Exposed n = 325 (%)	Unexposed n = 75 (%)	P value*
Age (y)			
18 – 24	108 (33.2)	22 (29.3)	0.49
25 – 34	187 (57.5)	45 (60.0)	
35 – 44	30 (9.2)	8 (10.7)	
Baseline body mass index (kg/m^2)			
< 18.5	15 (4.6)	5 (6.7)	0.57
18.5 – 24.9	160 (49.2)	34 (45.3)	
25.0 – 29.9	104 (32.0)	20 (26.7)	
30.0 – 39.9	44 (13.5)	15 (20.0)	
≥ 40	2 (0.7)	1 (1.3)	
Marital status			
Married	323 (99.4)	75 (100.0)	0.98
Divorced	2 (0.6)	0 (0.0)	
Birth place			
Urban	242 (74.5)	51 (68.0)	0.25
Rural	83 (25.5)	24 (32.0)	
Education			
Under degree	113 (34.8)	36 (48.1)	0.04
Degree	159 (48.9)	30 (40.0)	
University	53 (16.3)	9 (12.0)	
Occupation			
Unemployed	298 (91.7)	74 (98.7)	0.04
Employed	27 (8.3)	1 (1.3)	
Children (n)			
1	208 (64.0)	38 (50.7)	0.04
≥ 2	117 (36.0)	37 (49.3)	
History of miscarriage			
None	268 (82.5)	57 (76.0)	0.19
≥ 1	57 (17.5)	18 (24.0)	
History of infertility (y)			
None	288 (88.6)	69 (92.0)	0.49
0 – 1	8 (2.5)	2 (2.7)	
1 – 5	18 (5.5)	1 (1.3)	
> 5	11 (3.4)	3 (4.0)	
Fertilization method			
Natural	310 (95.4)	73 (97.3)	0.75
Other	15 (4.6)	2 (2.7)	
Type of delivery			
Cesarean	236 (72.6)	49 (65.3)	0.26
Vaginal	89 (27.4)	26 (34.7)	

Type of pregnancy†			
Planned	218 (67.1)	47 (62.7)	0.47
Unplanned	86 (26.5)	23 (30.7)	
Awareness of pregnancy† (month)			
1	227 (69.8)	52 (69.3)	
1 – 5	75 (23.1)	17 (22.7)	0.95
> 5	3 (0.9)	1 (1.3)	
Cigarette smoking	4 (1.2)	0 (0.0)	0.98
Shisha smoking	5 (1.5)	0 (0.0)	0.59

* Chi-square test

† Missing values included in percentage calculation

Higher educated (P = 0.04), employed (P = 0.04), and parity-one (P = 0.04) women were significantly more among herbal users. Additionally, multiple regression tests showed significant associations between more herbal medicines consumption and higher education (P < 0.001), employment (P = 0.02), and fewer children (P = 0.002).

Maternal complications

Mean length of hospitalization was 1.8 ± 0.9 days in both groups. Prevalence of background diseases and complications (anemias, asthma, allergies, thyroid disorders, diabetes, epilepsy, hypertension, depression) were similar between the exposed and unexposed women to herbal medicines (94/325 (28.9%) vs. 21/75 (28.0%); P = 0.87).

In one month prior to pregnancy, urogenital infections (44/325 (13.5%) vs. 12/75 (16.0%); P = 0.58) and cold/flu (14/325 (4.3%) vs. 1/75 (1.3%); P = 0.32) were the most frequent complications in both groups. During pregnancy, 394/400 (98.5%) women reported at least one pregnancy-related morbidity with a peak in the third trimester and the last two weeks of pregnancy. Herbal users reported significantly more complications during pregnancy than unexposed women (323/325 (99.4%) vs. 71/75 (94.7%); P = 0.01). Nausea/vomiting (238/325 (73.2%) vs. 48/75 (64.0%); P = 0.12), cold/flu (192/325 (59.0%) vs. 32/75 (42.7%); P = 0.01), heartburn (192/325 (59.0%) vs. 31/75 (41.3%); P = 0.01), stretch marks (174/325 (53.5%) vs. 22/75 (29.3%); P < 0.001), and edema (165/325 (50.8%) vs. 23/75 (30.7%); P = 0.002) were the most frequent records. Additionally, the incidences of constipation (54/325 (16.6%) vs. 8/75 (10.7%); P = 0.20) and threatened miscarriage (48/325 (14.8%) vs. 7/75 (9.3%); P = 0.22) were higher in users, even if not statistically significant.

Regarding delivery and postpartum complications, the two groups were not significantly different (186/325 (57.2%) vs. 44/75 (58.7%); P = 0.82). Anemias (86/325 (26.5%) vs. 26/325 (34.7%); P = 0.15) and abnormal labor (59/325 (18.1%) vs. 13/75 (17.3%); P = 0.98) were the most frequent problems.

Herbal medicines

Overall, 1322 consumption reports for 37 licensed and 96 unlicensed herbal preparations were recorded with the mean number of 4.1 ± 2.7 medicines per person during the whole pregnancy and one month earlier. Table 3 presents the most commonly used herbal drugs and the reported reasons of use. Peppermint, frankincense, flixweed, olive oil, cinnamon, borage, thyme, pennyroyal, chicory, ginger, saffron, barberry, rose, and cumin/caraway were frequently reported. Other herbs less common but still important were dill (11), fennel (7), licorice (6), castor oil (4), chamomile (4), and fenugreek (4). Herbal drugs usage in one month before, first, second, and third trimester, and the last two weeks of pregnancy were 239, 390, 394, 538, and 638 reports, respectively.

Table 3. The most commonly used herbal medicines, route of administration, and the reported reasons of use.

	n (%) in 325	Administration route	Most frequent reasons for use
Peppermint	154 (47.4)	Oral	Treatment of flatulence, abdominal pain, heartburn, nausea/vomiting, and indigestion.
Frankincense	144 (44.3)	Oral	Improving fetus brain development
Flixweed	132 (40.6)	Oral	Reducing the risk of neonatal jaundice; treatment of constipation
Olive oil	128 (39.4)	Topical, oral	Treatment of stretch marks, and constipation
Cinnamon	66 (20.3)	Oral	Treatment of hyperglycemia, heartburn, flatulence; habitual use
Borage	59 (18.2)	Oral	Treatment of palpitation, cold/flu; relaxation; delivery induction; habitual use
Thyme	55 (16.9)	Oral, inhalation	Treatment of infections; habitual use
Pennyroyal	47 (14.5)	Oral, inhalation	Treatment of infections; habitual use
Chicory	43 (13.2)	Oral	Reducing the risk of neonatal jaundice; habitual use
Ginger	40 (12.3)	Oral	Treatment of nausea/vomiting, heartburn, flatulence; habitual use
Saffron	35 (10.8)	Oral	Delivery induction; habitual use

Barberry	32 (9.8)	Oral	Treatment of anemia; habitual use
Rose	28 (8.6)	Oral	Relaxation; habitual use; treatment of constipation
Cumin/caraway	22 (6.8)	Oral	Treatment of flatulence, abdominal pain; habitual use

Regular use of herbal drugs in one month before, first, second, and third trimester, and the last two weeks of pregnancy were respectively 62, 181, 166, 260, and 339 reports, notably for flixweed (74), frankincense (54), olive oil (53), peppermint (31), chicory (20), cinnamon (18), ginger (12), borage (8), saffron (8), rose (7), pussy willow (5), dill (5), thyme (5), barberry (4), chamomile (3), fennel (3), fenugreek (3), pennyroyal (3), and licorice (1). Moreover, 84 reports of regular use during the whole pregnancy and 47 reports from one month before to the end of pregnancy were detected.

Some women reported one reason of use for >1 herb or >1 reason of use for one herb in different occasions. The majority of herbal products were used as habits to gain better health (255 reports). Other reports for reasons of use were improving fetus brain development (246), flatulence (235), reducing the risk of neonatal jaundice (227), cold/flu (204), stretch marks (170), heartburn (94), relaxation (69), abdominal pain (59), nausea/vomiting (54), hyperglycemia (32), delivery induction (31), and constipation (27).

ADRs of herbal medicines

With 16 different licensed and unlicensed herbal products, 26 ADRs were reported by 19/325 (5.8%) women. Nausea/vomiting (9/26, 34.6%) and heartburn (4/26, 15.4%) were the most prevalent ADRs (Table 4). In general, six SOCs were affected by herbal medicines: gastrointestinal system (18/26, 69.2%), cardiac system (3/26, 11.5%), skin and subcutaneous tissue (2/26, 7.7%), vascular system (1/26, 3.8%), nervous system (1/26, 3.8%), reproductive system and breast disorders (1/26, 3.8%).

Table 4. ADRs reported for herbal medicines as well as their causality, severity, and the related SOCs

n (%) in 26		Suspected medicines		SOCs
		Licensed (ATC, n)	Unlicensed (n)	
Nausea/vomiting	9 (34.6%)	Castor oil (A06AB05, 1), rose (A06AX, 1), peppermint (A03A, 1), thyme (R05CA, 1)	Frankincense (2), chicory (1), peppermint (1), mixed tisane* (1)	GIDs
Heartburn	4 (15.4%)		Chicory (2), peppermint (1), flixweed (1)	GIDs
Palpitation	3 (11.5%)	Garlic (C10AX, 1)	Peppermint (1), saffron (1)	CDs
Pruritus	2 (7.7%)	Olive oil (D02AX, 2)		SSTDs
Constipation	1 (3.8%)	Plantain + peppermint (A07BC, 1)		GIDs

Diarrhea	1 (3.8%)		Mixed tisane* (1)	GIDs
Oral irritation	1 (3.8%)	Savory (A01AD11, 1)		GIDs
Sialorrhea	1 (3.8%)		Chicory (1)	GIDs
Rectal itching	1 (3.8%)		Mixed suppository† (1)	GIDs
Cervical dilatation	1 (3.8%)		Mixed suppository† (1)	RSBDs
Hypotension	1 (3.8%)		Pennyroyal (1)	VDs
Dizziness	1 (3.8%)		Pennyroyal (1)	NSDs
Causality Probable Possible	6 (23.1%) 20 (76.9%)	3 (33.3) 6 (66.7)	3 (17.6) 14 (82.4)	
Severity Mild (Level 1) Mild (Level 2) Moderate (Level 3)	17 (65.4%) 8 (30.8%) 1 (3.8%)	7 (77.8%) 2 (22.2%) 0 (0.0%)	10 (58.8%) 6 (35.3%) 1 (5.9%)	

*The tisane contained thyme, dill, germander, cockscomb, and jujube.

†The traditional handmade suppository consisted of castor oil, pepper, licorice, cinnamon and a few other unknown plants.

Abbreviations: ADRs, adverse drug reactions; ATC, Anatomical Therapeutic Chemical classification; SOCs, system organ classes; GIDs, gastrointestinal disorders; RSBDs, reproductive system and breast disorders; VDs, vascular disorders; NSDs, nervous system disorders; SSTDs, skin and subcutaneous tissue disorders; CDs, cardiac disorders.

The most frequently reported herbal medicines for ADRs were chicory (4/43, 9.3%), pennyroyal (2/47, 4.3%), saffron (1/35, 2.9%), peppermint (3/154, 1.9%), thyme (1/55, 1.8%), olive oil (2/128, 1.6%), frankincense (2/144, 1.4%), and flixweed (1/132, 0.8%).

ADRs were 76.9% (20/26) 'possibly' and 23.1% (6/26) 'probably' related to herbal medicines. Except one 'moderate' reaction, all the others ADRs were 'mild' (Table 4). No serious ADR was detected.

To manage 8/26 (30.8%) ADRs, the medicine was discontinued; however, in 17/26 (65.4%) ADRs, the drugs were continued and required no changes. None of the patients with mild ADRs required any antidotes, additional treatments, or hospitalization for the management of reactions. Nevertheless, the management of one moderate ADR, due to a single dose of an unlicensed herbal suppository, needed symptomatic treatments. All the patients recovered completely from the ADRs.

Practice of using herbal medicines

Among 1322 reports of herbal medicines consumption, 1230 (93.0%) preparations were provided from places other than drugstores. Only 192 (14.5%) were recommended by healthcare providers. While 649 (49.1%) of uses were advised by family/friends and 391 (29.6%) were based on personal experiences.

Healthcare providers were not informed about 981 (74.2%) of herbal usage. Only 40/325

(12.3%) consulted the healthcare providers about all of their herbal medicines. Reasons for not informing healthcare providers were belief in safety of herbal medicines (151/325, 46.5%), forgetting or not knowing (47/325, 14.5%), not been asked about herbal drugs (39/325, 12.0%), low consumption (39/325, 12.0%), or possibility of their disagreement (9/325, 2.7%).

Among 400 women, 284 (71.0%) were totally unaware of herbal drugs potential harms during pregnancy. Additionally, 68/325 (20.9%) of women used herbal medicines in their pregnancy for the first time and 66/325 (20.3%) women even increased their usual consumption in this period. Self-reported evaluation showed that 183/325 (56.3%) of women were satisfied with the effects of all herbal medicines.

Non-herbal medicines

Overall, 2562 reports with the mean number of 6.7 ± 2.7 non-herbal medicines for each person were reported by 399/400 (99.8%) of women. On top of the list were 1645/2562 (64.2%) reports for supplements including vitamins (A11), minerals (A12), and omega-3 (C10AX06) followed by 286/2562 (11.2%) for anti-infectives (G01, J01, J02), 226/2562 (8.8%) for alimentary tract and metabolism (A02-07, A10), 126/2562 (5.0%) for anti-inflammatory and analgesics (M01, M02, N02), 61/2562 (2.4%) for respiratory system (R01, R03, R05, R06), and 54/2562 (2.1%) for sex hormones (G03). Non-herbal drugs were used significantly higher by herbal users than the unexposed women (6.7 ± 2.7 vs. 5.2 ± 2.4, $P < 0.001$).

Newborns

Generally, 214/400 (53.5%) boys and 186/400 (46.5%) girls were born. Regarding gestational age, Apgar scores, birthweight, hospital stay, complications, and malformations the newborns of two groups were similar (Table 5). Jaundice (61/325 (18.8%) vs. 15/75 (20.0%); P = 0.87), respiratory distresses (55/325 (16.9%) vs. 16/75 (21.3%); P = 0.40), thick meconium (16/325 (5.0%) vs. 5/75 (6.7%); P = 0.57), and hypoglycemia (3/325 (0.9%) vs. 1/75 (1.3%); P = 0.57) were the most frequent neonatal complications at birth or during hospitalization.

Table 5. Newborn characteristics of herbal exposed and unexposed women

	Exposed n = 325 (%)	Unexposed n = 75 (%)	P value*
Gestational age (wk) < 37 37 – 42 > 42	 44 (13.5) 281 (86.5) 0 (0.0)	 13 (17.3) 62 (82.7) 0 (0.0)	0.40
1-min Apgar† < 7 ≥ 7	 6 (1.8) 319 (98.1)	 3 (4.0) 72 (96.0)	0.38

5-min Apgar[†] < 7 ≥ 7	2 (0.6) 323 (99.4)	1 (1.3) 74 (98.7)	0.47
Birth weight (g) < 2500 2500 – 3999 ≥ 4000	32 (9.8) 283 (87.1) 10 (3.1)	10 (13.3) 63 (84.0) 2 (2.7)	0.67
Hospitalization (day)	2.5 ± 4.9	3.2 ± 5.4	0.24[‡]
Neonatal complications[§]	98 (30.2)	28 (37.3)	0.23
Congenital malformations[¶]	21 (6.5)	9 (12.0)	0.10

[*]Chi-square test

[†]Apgar stands for appearance, pulse, grimace, activity, and respiration, each scored on a scale of 0 to 2, with 2 being the best score.

[‡]Independent sample *t*-test

[§]At least one neonatal complication at birth or during hospitalization: jaundice, respiratory distresses, thick meconium, hypoglycemia, hypotonia, brain disorders, infections

[¶]At least one congenital malformation at birth: unstable hip, clubfoot, polydactyly, cryptorchidism, hypospadias, oral cleft, hernia, ichthyosis, glomerular disease, hydrocele, cardiac defects

Discussion

This observational cohort study on 400 postpartum women showed high use of herbal medicines during pregnancy (325/400, 81.3%), supporting the earlier studies. Reportedly, 10% to 74% of pregnant women in Africa, Australia, Europe, United Kingdom, and United States use herbal medicinal products [17]. These statistics varies from 22.3% to 82.3% in the Middle East [18].

In this study, peppermint, frankincense, flixweed, olive oil, cinnamon, borage, thyme, pennyroyal, chicory, and ginger were the most common herbs. Based on a 2015 review, the most prevalent herbal medicines among pregnant women were peppermint, ginger, thyme, chamomile, sage, aniseed, fenugreek, green tea, and garlic in the Middle East [18]. On the other hand, ginger, echinacea, cranberry, raspberry leaf, and chamomile were the most commonly used herbs by pregnant women in the Western world [19]. Diversity of popular herbal products represents the traditional and geographical variety.

Herbal ADRs detected in this study have been previously reported [20-23]. The most involved SOC in the herbal ADRs was gastrointestinal system. Similarly, in a 2019 systematic review, the most frequently reported herbal ADRs during pregnancy and postnatal period were gastrointestinal complaints [17]. None of the ADRs were ‘certainly’ related to herbal products. Multiple herbal and non-herbal medicines used as well as pregnancy-related complications weakened the

causality relationship between the ADRs and suspected herbal products. Moreover, herbal medicines are chemically rich complex mixtures, making it hard to distinguish the responsible constituent or ingredient for an observed ADR [4]. However, the incidence rate of herbal ADRs in pregnancy was low (similar to another study) [15], all non-serious and mostly mild which were managed effectively and ended in complete recovery.

Among herbal drugs used in our study, some plants with known undesirable effects on the uterus or fetus were detected: borage (mutagenic), chicory (emmenagogue, abortifacient), pennyroyal (abortifacient), cinnamon (emmenagogue), peppermint (emmenagogue), thyme (emmenagogue), saffron (emmenagogue, teratogenic, abortifacient), barberry (uterine-stimulant), ginger (abortifacient, emmenagogue, mutagenic), fennel (emmenagogue), licorice (emmenagogue), chamomile (emenagogue, abortifacient), fenugreek (uterine-stimulant), and castor oil (emmenagogue, abortifacient) [1,24]. Most of these herbs were even regularly used by some participants in at least one trimester.

For most of these herbs, evidences on the efficacy and safety in pregnancy are limited. In fact, except for ginger which has been extensively investigated and consistently found to decrease nausea and vomiting of pregnancy, there is insufficient evidences on the efficacy of other herbal medicines during pregnancy [25]. Most of the herbs are safe when used in small doses whereas excessive consumption can cause unknown effects including teratogenicity [18]. However, the fact that these unsafe herbs are among those commonly used is a matter of concern.

In a multinational study on 2673 women from 18 countries of Europe, North America, and Australia, substantial number of women used potentially harmful herbal medicines during pregnancy. This was especially worrisome since healthcare professionals more frequently recommended use of these herbal medicines than other sources [26].

Similar to previous reports [15,18,27], most women were advised by family and friends to use herbal medicines and believed they were more effective and had fewer side effects than non-herbal medicines especially during pregnancy and did not reveal this information to their physician.

Almost all women in our study used non-herbal medicines during pregnancy, although herbal users reported more non-herbal medicines, in line with the results of another study [19]. This might raise the possibility of herb-drug interactions with the potential to harm the mother and/or fetus. Moreover, there are no clear data on the adverse herb–drug interactions during anesthesia. Thus, it is recommended that patients discontinue herbal medicines two weeks before surgery and labor [25]. Nevertheless, the maximum use of herbal products was in the last two weeks of pregnancy in our study.

Herbal users reported significantly more complications during pregnancy. Pregnancy-related complications might have caused tendency for herbal drugs. On the other hand,

more medicines (herbal and non-herbal) could be a reason for more adverse reactions and complications.

The peak of pregnancy-related morbidities was in the third trimester and especially the last two weeks which was in comply with the peak time of herbal products use. However, while nausea/vomiting and cold/flu were on top of the list of pregnancy-related complications, the majority of herbal products were used habitually (to gain general better health) or targeting the fetus. In other studies, the herbs were most frequently used for gastrointestinal disorders and cold/flu symptoms and the maximum use was during the first trimester probably due to more complications in this period [18].

None of the neonatal variables were affected by herbal medicines in the present study. However, it should not be taken as an evidence of safety; and further robust studies are required. Especially as the newborns were not followed after discharge and the long-term outcomes were not assessed.

In Cuzzolin *et al*. [15] study, none of the neonatal outcomes were significantly influenced by maternal herbal use during pregnancy, with the exception of more neonates small for their gestational age among herbal users. Conversely, Nordeng *et al*. [19] found that mean birthweight was higher among the users of herbal drugs during pregnancy, mainly due to iron-rich herbs.

Interviewer-administered questionnaires provided more reliable and complete information than self-administered ones. However, collected data was mainly based on the patients' self-claim and recall bias was inevitable in our retrospective reporting. Due to the small number of users for each herbal medicine, the ADR incidence rate for each drug might not be generalizable and large clinical investigations are required.

Conclusion

Herbal medicines were highly used by pregnant women, and often concomitantly with non-herbal drugs. However, they did not affect the newborn outcomes either positively or adversely while might have increased the unnecessary risks and adverse effects. Despite low-frequent, non-serious, mild-moderate herbal ADRs during pregnancy, their safety, efficacy, drug interactions, and potential risks for fetus need further investigations in large studies. Although herbal products may offer benefits, it is important to detect even small risks that would significantly affect the benefit-risk ratio in pregnancy.

Aknowledgements

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Conflict of Interest

The authors declare no conflict of interest.

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