Medicinal plants, herbal medicines, and pregnancy: effects on fetal morphology

Fernanda Sardinha de Abreu Tacon[1],, Carolina Leão de Moraes[1],, Vergílio Pereira Carvalho[1],, Lélia Luanne Gonçalves Ramos[1],, Natália Cruz e Melo[2],, Waldemar Naves do Amaral[1],
[1]Universidade Federal de Goiás, R. 235, s/n - Setor Leste Universitário, 74605-050, Goiânia, Brazil
[2]Universidade Federal de São Paulo, Rua Loefgren, 1984 - Vila Clementino, 04040-003, São Paulo, Brazil
**Corresponding author: fernandabreu2010@yahoo.com.br*

ABSTRACT: To develop strategies of alternative public policies, it is necessary to know which plants and phytotherapics are most used, mainly by pregnant women, guaranteeing adequate use. The objective of the study is to identify the socio-demographic profile, to detect which medicinal plants and / or phytotherapics are most used and the possible risks for fetal morphology. A case-control study, conducted between July 2017 and October 2018. For the evaluation of clinical and epidemiological data, a questionnaire was applied in both groups, before ultrasonographic evaluation. Data were analyzed using a significance level of 5% ($p \leq 0.05$), applying the Pearson's Chi-square test and Posthoc's test. Of the total of 282 pregnant women, 19.86% (56/282) reported use of medicinal plants. Of these, 62.5% (35/56) are pregnant women with malformations and 37.5% (21/56) are pregnant women with structurally normal fetuses. Statistical differences were obtained regarding the use of medicinal plants such as camomile ($p = 0.02$) and Passiflora ($p = 0.03$). The misuse of medicinal plants are risk factors for fetal morphology. Identifying the plants used in gestation can contribute to the planning of programs for enlightenment for pregnant women and continuing education for health professionals.
Keywords: Pregnancy, medicinal plants, phytotherapy, fetal development.

RESUMO: Plantas medicinais, fitoterápicos e gravidez: efeitos na morfologia fetal. Para desenvolver estratégias de políticas públicas alternativas, tem-se a necessidade de conhecer quais as plantas e fitoterápicos mais utilizados, principalmente pelas gestantes, garantindo uso adequado. O estudo teve por objetivos identificar o perfil sociodemográfico e detectar quais as plantas medicinais e/ou fitoterápicos mais utilizados e os possíveis riscos para morfologia fetal. Estudo do tipo caso-controle, realizado entre julho de 2017 e outubro de 2018. Para a avaliação dos dados clínicos e epidemiológicos, foi aplicado um questionário em ambos os grupos, antes da avaliação ultrassonográfica. Os dados foram analisados adotando um nível de significância de 5% ($p \leq 0,05$), aplicando-se o teste do Qui-quadrado de Pearson e Posthoc. Do total de 282 gestantes, 19,86% (56/282) relataram uso de plantas medicinais. Destas que fizeram uso, 62,5% (35/56) são gestantes de fetos com malformações e 37,5% (21/56) são gestantes de fetos estruturalmente normais. Foram obtidas diferenças estatísticas quanto uso de plantas medicinais como a camomila (p=0,02) e Passiflora (p=0,03). O uso indevido de plantas medicinais são fatores de risco para a morfologia fetal. Identificar as plantas utilizadas na gestação pode contribuir com o planejamento de programas de esclarecimento para as gestantes e educação continuada para os profissionais da saúde.
Palavras-chave: Gravidez, plantas medicinais, fitoterapia, desenvolvimento fetal.

INTRODUCTION

Several times in history, medicinal plants usage has been widely present in society. However, with the arrival of industrialization, its usage had a considerable decline. Nowadays, due to biodiversity and sustainable development worrying, this topic has gained prominence again in the global scenario, being that, in Brazil, the Integrative and Complementary Practices in the Unified Health System (SUS), encourages phytotherapy and medicinal plant research, intending to develop alternative and complementary therapeutics (Brazil 2015).

Phytotherapy strengthening in SUS is important for the development of public policies. In Brazil, phytotherapeutic products must present effectiveness and safety proof, in addition, to the gestation period and breast-feeding. However, due to

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biodiversity lavishness, chemical and pharmaceutical profiles were not thoroughly elucidated by the scientific community, beyond ethical matters. Only Rio de Janeiro State, has specific legislation (Resolução da Secretaria de Estado de Saúde/RJ Nº 1757) for the usage of medicinal plant by pregnant women (Duarte et al. 2017).

Medicinal plants are used mainly by the female population, which use them to increase fertility, induce abortion, treat menstrual disorders, relieve pain and bleeding during o menstrual period or postpartum, increase lactation, treat mastitis, and during pregnancy, use them oftentimes to decrease nausea, dyspepsia, anxiety, insomnia, constipation, influenza, colds, urinary infections. These pregnant women make use of them believing that being "natural", won't cause any harm. Likewise, it happens with allopathic medicine, one ought to evaluate the risk-benefit factor for its use (De Boer and Cotingting 2014).

There are few clinical studies in correlation to safety in the use of medicinal plants and pregnancy. The lack of evidence concerning toxicity, abortion, and teratogenicity, induces contraindication, mainly in the first trimester of pregnancy. Accentuating, in this matter, the importance of family planning, because plants widely used by the population present risks, such as aloe vera (*Aloe* spp.), peppermint (*Mentha piperita* L.), anise (*Foeniculum vulgare* Mill.), gorse (*Baccharis trimera* (Less.) DC.), chamomile (*Matricaria recutita* L.), cascara buckthorn (*Rhamnus purshiana* DC.), hibiscus (*Hibiscus rosa-sinensis* L.), boldo (*Peumus boldus* Molina), and guaco (*Mikania glomerata* Spreng.) (Lamxay et al. 2011).

The abortive effect is the most common association to the medicinal plants, although it is not emphasized the possibility of the same plant being abortive, teratogenic, and/or embryotoxic. As exemplified by, boldo, peppermint (*Mentha* x *piperita* L.), and gale of the wind (*Phyllanthus amarus* Schumach. & Thonn.), are teratogenic and studies have demonstrated its abortive action. It must also be noted the gestational period in which the plant is used, the dosage and effect, the preparation method, and maternal-fetal genotype. In such manner, health care professionals have great importance for successful public policies, guiding appropriately, pregnant women about the risks, better preparation methods, and usage time. Allowing so, an elaborative analysis over the risks and benefits (Rodrigues et al. 2011).

In the given context, the study aimed to identify the socio-demographic profile and detect which medicinal plants and/or herbal medicines are most used and the possible risks for fetal morphology.

MATERIALS AND METHODS

This was a quantitative, observational, field study, of the case-control type, conducted between July 2017 and October 2018, in a fetal medicine service located in the capital of the central region of Brazil with a population of approximately 1.300.000.

A non-probabilistic sample was used, being that, according to the statistical data of the hospital, 200 pregnant women are admitted annually to prenatal care checkups performed by the fetal medicine service. The test span was 80%, the margin of error was 6%. Therefore, a sample of 267 patients was estimated.

The population in the study was formed by pregnant women who were directed by primary health care to tertiary health care, after being diagnosed with a high-risk pregnancy, mainly with structural congenital anomalies. The criteria for inclusion were: (i) pregnant women admitted in the tertiary fetal medicine service care at the time of study and (ii) pregnant women who answered thoroughly the questionary form applied in the research. The criteria for exclusion were: (i) pregnant women who had a chromosomal disorder diagnosis, Zika virus and infections such as toxoplasmosis and cytomegalovirus, when responsible for malformation, and (ii) pregnant women who answered the questionary form applied in the research incompletely.

The care of the referred pregnant women occurs once a week and after the first care they are followed up monthly until the end of the pregnancy. The majority of the pregnant women get to the unit after the 11th week of gestation, because in this period, from 11th to 14th weeks, the Nuchal Translucency (NT) exam is done by ultrasonography, being able to introduce the first indicatory data to any alteration. Pregnant women who were directed previously to this period had a malformation background in previous gestations or risk factors, such as diabetes, congenital infections, or multiple pregnancies. In the first appointment at the unit, each pregnant woman was invited, in a private room to avoid embarrassment, to participate in the research. The main researcher explained the objectives, benefits, and risks of the study. Upon agreement, the Free, Prior, and Informed Consent form (FPIC) was delivered, and the pregnant woman answered the questionary form, which was filled in by the researcher in charge. The data was collected before the ultrasound exam performed by the doctor in charge. After handing the questionary form, the patients were conducted to the fetal ultrasound exam. After the ultrasonographic diagnosis, the result was properly noted. Later, according to the diagnosis, the pregnant women who had a fetus with structural morphological anomalies were included

in the case study group, and in the control group were included the ones who had a fetus structurally normal.

The denouement over the alteration in fetal morphology was obtained through the ultrasonographic diagnosis and the analysis between both groups made it possible to determine possible associated risk factors.

The independent variables analyzed were biological (age, ethnicity), obstetric background (gestation number, abortion background), socio-demographic (schooling - formal education, income, marital status), and the medicinal plants/ phytotherapics most used by both groups. All ultrasound exams were performed by the same physician and the same equipment LogiqP6 (Ge Healthcare®).

The data were analyzed with the assistance of IBM SPSS Statistics 23.0. The sample description according to the type of gestation was performed by absolute frequency (n) and relative frequency (%) applying Pearson's Chi-square and Posthoc Chi-square test. The significance level established was 5% ($p \leq 0,05$).

The research was approved by the Research Ethics Committee under protocol number 2.160.584 and all partakers signed the Free, Prior, and Informed Consent (FPIC).

RESULTS

During the analyzed period, 310 pregnant women were identified. After the criteria of exclusion, the sample was formed by 282 patients who, over time convenience, were split into two groups, according to the ultrasonographic diagnosis. The case group was formed by 202 pregnant women who exhibit a fetus with structural morphological

TABLE 1. Characterization of the demographic profile of pregnant women who used medicinal plants according to the type of pregnancy.

	Gestation n (%)		Total	*p**
	Malformation 35 (62,5)	**Normal 21 (37,5)**		
Age group				
Until 18 years old	5 (14,3)	0 (0,0)	5 (8,9)	
19 - 35 years old	29 (82,9)	20 (95,2)	49 (87,5)	0,18
> 35 years old	1 (2,9)	1 (4,8)	2 (3,6)	
Schooling				
Primary school	5 (14,3)	5 (23,8)	10 (17,9)	
Secondary school	6 (17,1)	3 (14,3)	9 (16,1)	0,68
High school	21 (60,0)	10 (47,6)	31 (55,4)	
Higher education	3 (8,6)	3 (14,3)	6 (10,7)	
Marital status				
Married	11 (31,4)	14 (66,7)	25 (44,6)	
Divorced	1 (2,9)	0 (0,0)	1 (1,8)	0,03
Single	23 (65,7)	7 (33,3)	30 (53,6)	
Ethnicity				
White	7 (20,0)	2 (9,5)	9 (16,1)	
Black	3 (8,6)	1 (4,8)	4 (7,1)	0,47
Brown/dark skin	25 (71,4)	18 (85,7)	43 (76,8)	
Family income				
≤ 1 minimum wage	11 (31,4)	8 (38,1)	19 (33,9)	
1000 - 2000	15 (42,9)	9 (42,9)	24 (42,9)	0,80
> 2000	9 (25,7)	4 (19,0)	13 (23,2)	
Gestations				
Multiparous	23 (65,7)	17 (81,0)	40 (71,4)	0,03
Primiparous	12 (34,3)	4 (19,0)	16 (28,6)	
Abortion				
No	25 (71,4)	15 (71,4)	40 (71,4)	1,00
Yes	10 (28,6)	6 (28,6)	1628,6)	

*Pearson's chi-square

TABLE 2. Comparison of medicinal plants usage and gestation type.

	Gestation		Total	*p**
	Malformation	Normal		
Phytotherapic				
Boldo	3 (5,8)	2 (6,9)	5 (6,2)	0.84
Cascara buckthorn	5 (9,6)	3 (10,3)	8 (9,9)	0.92
Chamomile	9 (17,3)	0 (0,0)	9 (11,1)	**0.02**
Cinnamon	11 (21,2)	2 (6,9)	13 (16,0)	0.09
Citrus aurantium	0 (0,0)	2 (6,9)	2 (2,5)	0.06
Lemon balm	14 (26,9)	10 (34,5)	24 (29,6)	0.48
Hibiscus	4 (7,7)	1 (3,4)	5 (6,2)	0.45
Passiflora	1 (1,9)	4 (13,8)	5 (6,2)	**0.03**
Plumeria lancifolia Müll.Arg.	0 (0,0)	2 (6,9)	2 (2,5)	0.06
Senna	5 (9,6)	3 (10,3)	8 (9,9)	0.92

*Posthoc chi-square; * Cumulative frequencies: the same pregnant woman can use more than one type of medicinal plant and/or herbal medicine.

TABLE 3. Medicinal plants and phytotherapics most used by pregnant women.

Common Name	Scientific name	% of usage	Indication	Adverse effects
Lemon balm	*Melissa officinalis* L.	29,6	Carminative, antispasmodic, and sleep disorders, aids in lowering blood pressure	Drug interactions with CNS depressants and thyroid hormones
Cinnamon	*Cinnamomum zeylanicum* Blume	16,4	Carminative, expectorant, spasmolytic, and diuretic action	Abortivive
Chamomile	*Matricaria recutita* L.	11,12	Antispasmodic, topical anti-inflammatory, digestive disorders, and mild insomnia	Uterine relaxant, increased risk of bleeding, and reduced iron absorption
Senna	*Cassia angustifólia* Vahl	9,87	Constipation, helps with weight loss	Abdominal discomfort, loss of electrolytes and water
Cascara buckthorn	*Rhamnus purshiana* DC.	9,87	Constipation, helps with weight loss	Interaction with thiazide diuretics, hypokalemia, increased blood pressure
Boldo	*Peumus boldus* Molina	6,17	Anxiolytic, mild insomnia, sedative	Teratogenic and abortifacient effects
Passiflora	*Passiflora incarnata* L.	6,17	Anxiolytic, mild insomnia, sedative	Tachycardia, nausea, potentiates other CNS depressants
Hibiscus	*Hibiscus sp.*	6,17	Helps in weight loss, anxiolytic, aids in digestion and blood pressure control, anti-inflammatory and antibacterial	Abortive, may alter fertility, emmenagogue
Citrus aurantium/ Plumeria lancifolia	*Citrus* x *aurantium* L./ *Plumeria lancifolia Müll.Arg.*	4,63	Menstrual flow irregularities, menopausal disorders, dysmenorrhea, antispasmodic, uterine inflammation, and bleeding	Teratogenic, may potentiate the effects of sedatives, and anticoagulants

*CNS: Central Nervous System

Table 4. Description of malformations and use of Chamomile.

Description of the malformation		Chamomile		Total
		No	Yes	
Cardiac	Score	11	0	11
	% of Chamomile	5,7%	0,0%	5,4%
Ovarian cyst	Score	2	0	2
	% of Chamomile	1,0%	0,0%	1,0%
Skeletal	Score	4	1	5
	% of Chamomile	2,1%	11,1%	2,5%
Face	Score	8	1	9
	% of Chamomile	4,1%	11,1%	4,5%
Hydropsy	Score	4	0	4
	% of Chamomile	2,1%	0,0%	2,0%
Multiples	Score	25	1	26
	% of Chamomile	13,0%	11,1%	12,9%
Others	Score	7	0	7
	% of Chamomile	3,6%	0,0%	3,5%
Abdominal wall	Score	21	0	21
	% of Chamomile	10,9%	0,0%	10,4%
Renal	Score	45	2	47
	% of Chamomile	23,3%	22,2%	23,3%
Respiratory	Score	4	0	4
	% of Chamomile	2,1%	0,0%	2,0%
CNS	Score	62	4	66
	% of Chamomile	32,1%	44,4%	32,7%

Regarding Passiflora and the most common malformations, CNS malformations also prevailed (Table 5).

anomalies, and in the control group, 80 patients with a structurally normal fetus.

Of the 282 pregnant women interviewed, 56 reported phytotherapic and/or medicinal plants usage during gestation. Firstly, the listing of these 56 patients was made, both in the case group and control group as well (Table 1).

The medicinal plants and phytotherapics most used by the patients according to the gestation type are listed in Table 2.

The most used medicinal and herbal plants, their scientific name, indications, and adverse effects are listed in Table 3 (Madaleno 2011; Lorenzi and Matos 2008).

Among the malformations found, the ones from the Central Nervous System (CNS) prevailed among 44.4% (4/9) of pregnant women using chamomile. All are reported in Table 4.

DISCUSSION

The most used medicinal plants and/or phytotherapics were fennel, cinnamon, chamomile, senna, cascara buckthorn, boldo, passiflora, hibiscus, and citrus aurantium/plumeria lancifolia. Chamomile obtained a statistically significant difference.

Independent of the Brazilian region, the use of medicinal plants is present in the culture of the country. However, its use may vary due to cultural diversity, the cultivation method, and investment in public policies. In a study carried out by Araújo et al. (2016) in a city in northeastern Brazil, 30,9% of medicinal plants were used during pregnancy, with a total of 178 pregnant women, between 18-42 years old, married, up to 1 minimum wage of income and the most used plants were boldo, fennel, lemon balm, chamomile, and mint. In the study by Veiga Júnior (2008) conducted in the state of Rio de Janeiro, boldo and chamomille were the most listed. In Macena et al. (2012) study, in Mato Grosso, boldo, lemongrass, and mint were more relevant. In

TABLE 5. Description of malformations and use of Passiflora.

Description of malformations		Passiflora		Total
		No	Yes	
Cardiac	Score	11	0	11
	% of Passiflora	5,5%	0,0%	5,4%
Ovarian cyst	Score	2	0	2
	% of Passiflora	1,0%	0,0%	1,0%
Skeletal	Score	5	0	5
	% of Passiflora	2,5%	0,0%	2,5%
Face	Score	8	1	9
	% of Passiflora	4,0%	100,0%	4,5%
Hydropsy	Score	4	0	4
	% of Passiflora	2,0%	0,0%	2,0%
Multiples	Score	26	0	26
	% of Passiflora	12,9%	0,0%	12,9%
Others	Score	7	0	7
	% of Passiflora	3,5%	0,0%	3,5%
Abdominal wall	Score	21	0	21
	% of Passiflora	10,4%	0,0%	10,4%
Renal	Score	47	0	47
	% of Passiflora	23,4%	0,0%	23,3%
Respiratory	Score	4	0	4
	% of Passiflora	2,0%	0,0%	2,0%
CNS	Score	66	0	66
	% of Passiflora	32,8%	0,0%	32,7%

this study conducted in Goiás, 19.86% made use of medicinal plants, being the most used by pregnant women with malformed fetuses, lemon balm, cinnamon, and chamomile. In the group of pregnant women with normal fetuses, the use of lemon balm, passiflora, cascara buckthorn, and senna prevailed.

Santos et al. (2018) demonstrated in his study the prevalence of married women, age between 29 to 39 years old, graduated from high school, income up to 2 salaries and the most used medicinal plants were: lemongrass, fennel, lemon balm, boldo, chamomile, and mint. In a similar manner, a study carried out in a city in Paraíba, highlighted the use of boldo, lemon balm, and cinnamon (Carvalho and Araújo 2007). In Tocantins, the most listed plants were lemon balm, chamomile, lemongrass, and fennel (Beserra et al. 2014).

In this study, statistical differences were obtained regarding the use of chamomile and passiflora between both groups. Regarding chamomile, Arruda et al. (2013) analyzed the effects of aqueous chamomile extract (*Chamomilla recutita* L.) in the pregnancy of rats and in the development of the pups, no toxic effects or changes were obtained. However, because of the postural interference and orientation in the treatment, its use is not safe in human pregnancy. Arcanjo et al. (2013) highlights the relaxing action of the uterine muscles but does not report malformations, toxicity, or abortion. However, it may alter fetal neurological reflexes, in addition to preterm birth and low birth weight, with daily use of chamomile tea. In studies conducted, *in vivo* and *in vitro*, with mice in Londrina-PR, treated with passiflora (P. incarnata), no problems were detected regarding toxicity during pregnancy and lactation, an increased total antioxidant capacity has been described (Boll et al. 2014).

In the study carried out in the United Kingdom (McLay et al. 2017), the most used medicinal plants were: ginger and chamomile. It was highlighted in this study that the concomitant use of chamomile and Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), may increase the risk of bleeding during pregnancy, in addition to interaction with medications such as diazepam, propranolol, diclofenac, and chlorpromazine, which can increase the levels of these drugs in the body and cause depression in the Central Nervous System (CNS) and psychomotor impairment. Cuzzolin et al. (2010), highlighted the danger of chamomile and licorice

in relation to premature birth and the threat of miscarriage. In this study in Goiás, chamomile was widely used by pregnant women with malformed fetuses.

According to Rangel et al. (2009), boldo has one of the most toxic oils and very irritating compounds. High doses can lead to renal changes and in pregnant women, the degree of safety is not known. In animals, studies with dried leaf extract and the alkaloid boldine had abortive and teratogenic action.

In general, the literature indicates as the most cited plants, chamomile in the first place, mint in second place, melissa in third place, and boldo in fourth place. All contraindicated in pregnancy and lactation. However, the identification of the plant, dosage, plant part used, preparation method, and usage method must be taken into account (Menezes et al., 2014).

In order to combat common symptoms during pregnancy, such as nausea, vomiting, and constipation, pregnant women use various plants without knowing the risks. Other plants that were not mentioned in this study, but also widely used and that deserve to be highlighted for use with caution or out of great need, can be mentioned garlic (*Allium sativum* L.), European horse-chestnut (*Aesculus hippocastanum* L.), gorse (*B. trimera*), St. John's-wort (*Hypericum perforatum* L.), ginger (*Zingiber officinale* Rosc.), ginkgo biloba (*Ginkgo biloba* L.), Luffa operculata (*Lufta operculata* L.), artichoke (*Cynara scolymus* L.), rhubarb (*Rheum rhabarbarum*), pomegranate (*Punica granatum* L.), rue (*Ruta graveolens* L.), o clove (*Syzgium aromaticum* L.), rosemary (*Rosmarinus officinalis* L.) e o eucalyptus (*Eucalyptus globulus* Labill.). These plants can lead to interaction with drugs, causing bleeding, inducing abortion, toxicity, and malformations, in addition to exposing the pregnant woman to severe complications. (Nicoletti et al. 2007).

Of the seven plants reported in this study, six (senna, boldo, hibiscus, chamomile, cascara buckthorn, and lemon balm) are contraindicated in Resolution nº 1757, of February 18, 2002, from Rio de Janeiro, for use during pregnancy, and/or lactation. Anhesi et al. (2016), highlight that in Brazil, cinnamon, rue, chamomile, and boldo are the medicinal plants most consumed by pregnant women, and all are contraindicated during pregnancy. Cinnamon tea can cause blood constriction and uterine contraction and rue is an emmenagogue, uterine stimulant, and abortifacient.

The medicine that has the medicinal plant as raw material is what is called phytotherapic, which are industrialized. As they do not have strict criteria like traditional medicines, contamination, and undeclared substances can occur in their production and offer a false impression that they are totally safe (Lisha and Nisha 2015). Among the relationship highlighted by the pregnant women in this study, seven were medicinal plants and two were phytotherapics. Passiflora and citrus aurantium/ plumeria lancifolia (commercial name, Saúde da Mulher), highlighted its use among pregnant women with normal fetuses. Especially passiflora, which obtained a statistical difference, its use is also not indicated during pregnancy, as it can cause uterine stimulation.

Among the most reported malformations are those of the CNS (Gomes et al. 2018), in this study the prevalent malformations were of the CNS, followed by malformations of the Genito-Urinary System (GUS). Pregnant women who used passiflora detected facial alterations and those who used chamomile CNS and SGU alterations.

Germany is one of the countries where pharmacovigilance has made the greatest advances. For this reason, the detection of risks and the standardization of terms provide the safest and most rational use of medicinal and herbal plants. In Brazil, due to the great biodiversity, pharmacovigilance services still need adjustments (Silveira et al. 2008). Therefore, knowing the plants used in pregnancy, by region, can contribute to the planning of information programs for pregnant women and continuing education for health professionals.

Therefore, due to social and ecological needs, the consumption of medicinal plants and herbal medicines has increased. However, because of lack of knowledge and lack of family planning, there is a need for greater investments in the pharmacovigilance program, the inclusion of disciplines on medicinal plants and herbal medicines in the curricula of health courses that deal directly with patients, stricter regulation, and adaptation to local needs, in addition to better establishing safety criteria, which have technical and ethical difficulties.

CONCLUSION

The socio-demographic profile obtained from pregnant women who are followed up in this fetal medicine service in Goiás, who made use of medicinal plants and/or phytotherapics, is for women between 19-35 years old, graduated from high school, brown skin, with income between 1000-2000 reais, multiparous women and no history of abortion.

The most used medicinal and herbal plants were lemon balm, cinnamon, chamomile, senna, cascara buckthorn, boldo, passiflora, hibiscus, and citrus aurantium/plumeria lancifolia. Chamomile obtained a statistically significant difference.

All the compounds mentioned have

contraindications during pregnancy, which can cause fetal alterations, abortions, toxicity, and maternal complications.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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