"Natural" relief of pregnancy-related symptoms and neonatal outcomes: above all do no harm

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ABSTRACT

Ethnopharmacological relevance: In the South of Italy the use of herbal remedies to alleviate pregnancy-related symptoms is very common.
Objectives: To investigate the proportion, prevalence of use, attitude and knowledge base in a sample of Italian pregnant women in the South of Italy. To explore the possible influence and risks of herbal consumption on pregnancy and neonatal outcomes.
Methods: A retrospective observational study was conducted during the study period November 2010–September 2013. Six hundred and thirty expectant mothers were interviewed within three days after childbirth in a public Hospital in the South of Italy.
Results: Due to a lack of data, a total of six hundred interviews were considered. Four hundred and eighty six women (81%) reported to have constantly used at least one herbal product throughout the pregnancy period. The study enrolled mostly women between 31 and 40 years of age, with a middle-high level of education, married and employed. The most commonly used herbal products, taken by oral route and for the entire period of pregnancy, were chamomile, fennel, propolis, cranberry, lemon balm, ginger, valerian and mallow. The most relevant source of information for the majority of participants was the doctor (95%), and most of the women (72%) informed their doctors about their use of herbal remedies.
Conclusions: The regular chamomile consumption resulted in a higher risk of pre-term delivery, lower birth weight and lower length of the newborn. Also a regular use of fennel resulted in a shorter gestational age. Finally, ginger intake resulted in a shorter gestational age and in a smaller circumference of the newborn's skull.

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1. Introduction

In addition to conventional medicine, the use of herbal remedies has become increasingly common in many developing and industrialized countries. In particular, the use of herbal medicines plays a significant role in the management of both minor and major illnesses (Gardiner et al., 2007). Moreover, the use of herbal remedies is often influenced by patients' dissatisfaction with allopathic drugs in term of effectiveness and/or safety and by the perception that herbal medicines are intrinsically safe. Several more complex reasons for preference of herbal medicines exist and are associated with cultural and personal beliefs, philosophical views on health and life (Ernst and White, 2000).

Several studies showed that women represent alternative medicine users to a greater extent than men (Brett and Keenan, 2007; Trabace et al., 2011). Interestingly, patients who are likely to be at a major risk from adverse side effects of herbal medicines include specifically fetus and infants, as well as pregnant women.

Some women continue to resort to these therapies when they become pregnant based on their concerning about their unborn child's well-being. Indeed, the use of herbal products has been favored by the popular perception that pharmaceuticals are dangerous in these specific conditions. Herbal remedies may especially appeal to pregnant women since these substances are often considered as "natural" and "safe" alternatives to conventional drugs. Thus, women may turn to unconventional therapies rather than prescription medication in the belief that this kind of remedies are absolutely preferable products, for safety, to synthetic drugs (Holst et al., 2009).

Moreover, it should be taken into account that maternal physiology undergoes many changes during pregnancy, and a variety of conditions, such as morning sickness, fatigue, constipation, stretch marks appear, all of which are usually self-treated.

In this regard, few studies on the pattern of use of herbal extracts during pregnancy showed that herbal therapy was common among expectant mothers in Finland, Norway and Australia (Forster et al., 2006; Hemminki et al., 1991; MacLennan et al., 2002; Nordeng and Havnen, 2004). Also among Italian women, the use of herbal products has been documented to be frequent (Cuzzolin et al., 2010; Facchinetti et al., 2012; Zaffani et al., 2006).

However, results from studies conducted in Italy are available only from population resident in the northern Italy, totally missing data from the rest of the country.

Despite the widespread popularity and the large use of these herbal medicines, up to now little is known about effects and especially the safety of the most used herbal remedies during the pregnancy. Their use remains poorly documented and certainly inadequately studied. Actually, in contrast to prescribed and newer over-the-counter medications, herbal products usually are marketed without the benefit of rigorous scientific support to demonstrate either safety or efficacy. In addition to that, few data exist on safety and even less on pregnancy and/or neonatal outcomes. In this regard, hypertensive activities have been reported for a number of herbs that are used during pregnancy including blue cohosh, ginger, licorice (Newall and Beedles, 1996). Besides, hyperglycemic conditions that could complicate gestational diabetes have been shown after licorice and ginseng use. Coagulation disorder during pregnancy has been precipitated by the use of alfalfa, dong quai and chamomile (Johns and Sibeko, 2003).

It has been demonstrated that some herbal products may be teratogenic in human and animal models, such as Asparagus racemosus or fennel (Dugoua et al., 2008; Goel et al., 2006; Ostad et al., 2004; Pakrashi and Bhattacharya, 1977; Seely et al., 2008). Nevertheless, data on the extent of women's use of herbal medicines during pregnancy is scanty, probably also because the legislation for distribution and purchase of herbal medicines is not as stringent as it is for conventional medicines.

In this contest, using an interview approach, the first aim of this study, which was intended to serve as a pilot study, was to investigate the proportion, prevalence of use, attitude and knowledge base in a sample of Italian pregnant women in the South of Italy. Additionally, a further aim of the present study was to explore the possible influence and risks of herbal consumption on pregnancy and neonatal outcomes.

2. Methods

2.1. Study population

The survey was conducted at the maternity wards of Gynecology and Obstetrics Clinic of the University Hospital OORR of Foggia, during the study period November 2010–September 2013.

A total of six hundred and thirty women fulfilled our study inclusion criteria and were interviewed after hospitalization or within 3 days after childbirth at the postnatal ward.

Only women of Italian nationality were included in our study, because the use of natural products is strongly affected by the different traditions of the own culture. Therefore, immigrant women were excluded and all of them were at last 18 years old. Pregnant women were excluded from the study if they were users of conventional therapies or other substances that could affect the results.

Interviews were performed once a week. Participants received oral information about the study and written informed consent was obtained before the interview. The women were informed that all the collected information was saved anonymously, and that no prior knowledge of natural products was necessary to participate in the present study.

The study was approved by the local ethics committee (n. 34/CE/2010).

2.2. Data collection

Data were collected via a pre-structured questionnaire administered by a trained pharmacist, who was assisted and accompanied by a trained gynecologist using a face-to-face approach. Each interview lasted approximately 15 min.

We have chosen an interviewer-administered questionnaire because this methodology provides more reliable and complete information than a self-administered questionnaire which is often associated with lower adhesion, inappropriate compilation and misinterpretation of the questions (Kelsey, 1996).

The questionnaire was composed of close and open-ended questions, divided into three sections.

The first section regarded the basic background data for sociodemographic characteristics and lifestyle of the interviewed subjects, including place of residence (urban or rural area), age, marital status, parity, education level, occupational status, smoking status before and during pregnancy, physical activity.

The second section investigated on the health status of the women and therapies during pregnancy. Specifically, the type of product consumed, administration form, duration and time of administration (I, II, III trimester), the reason for its use, their source of information and adverse reactions observed.

The last section focused on the beliefs of pregnant women about the safety and efficacy of the products and the non-conventional therapies used.

In addition to the interview, we consulted certificates of delivery care of the interviewed women to collect information about pregnancy outcome and the characteristics of the newborn at birth. These data included gestational age, birth-weight, length and head circumference of the newborn, Apgar score and presence of congenital malformations or neonatal complications after delivery.

All of the collected information were anonymous and each pregnant woman was assigned an identification code registered in a database. Only study investigators and those who carried out the interview had access to the information.

2.3. Data analysis

Data were stored and analyzed using a Epi Info professional study program. To verify any associations between the variables investigated, an univariate analysis was performed, by using double-entry contingency tables and computing chi square (X^2) and Odds Ratios (OR) with 95% Confidence Intervals (95% CIs), considering as significant P values < 0.05. The assessment of the significant differences between the continuous variables means (age, week of gestation, birth-weight, Apgar score, etc.) was performed using the Student's t-test and one-way ANOVA test considering statistically significant P values < 0.05. To assess the distribution of the variables, the Bartlett's test was used. Data analysis was performed using the STATA software-MP 10.1 for Mac OS X.

3. Results

There were 630 interviews of mothers available for the study. All the women invited to participate to the present research

Table 1
Socio-demographic characteristics of women involved in the study (% in parenthesis).

	Total ($n=600$)	Users ($n=484$)	Non-users ($n=116$)	P-value
Age (years)				
≤ 30	265 (44.2)	210 (43.4)	55 (47.4)	NS
31–40	315 (52.5)	259 (53.5)	56 (48.3)	
> 40	20 (3.3)	15 (3.1)	5 (4.3)	
Level of education				
Primary school	8 (1.3)	8 (1.7)	0 (0)	NS
Secondary school	156 (26.0)	127 (26.2)	29 (25.0)	
High school	288 (48.0)	223 (46.1)	65 (56.0)	
Degree	148 (24.7)	126 (26.0)	22 (19.0)	
Marital status				
Married	493 (82.2)	393 (81.2)	100 (86.2)	NS
Single	107 (17.8)	91 (18.8)	16 (13.8)	
Employed				
Yes	321 (53.5)	269 (55.6)	52 (44.8)	$X^2=4.3$
No	279 (46.5)	215 (44.4)	64 (55.2)	$P=0.0371$
Parity				
≥ 1 priorchild	308 (48.7)	248 (51.2)	60 (51.7)	NS
Nullipara	292 (51.3)	236 (48.8)	56 (48.3)	
Physical activity				
Yes	189 (31.5)	158 (32.6)	31 (26.7)	
No	411 (68.5)	326 (67.4)	85 (73.3)	NS
Smoking				
Before pregnancy	125 (20.8)	105 (21.7)	20 (17.2)	NS
During pregnancy	23 (3.8)	21 (4.3)	2 (1.7)	
No	452 (75.3)	358 (74.0)	94 (81.1)	

Table 3
The most commonly used herbal products by pregnant women.

Herb	N (%)
Chamomile	225 (37.5)
Fennel	94 (15.7)
Propolis	42 (7.0)
Cranberry	16 (2.7)
Lemon balm	14 (2.3)
Ginger	9 (1.5)
Valerian	9 (1.5)
Mallow	6 (1.0)

The most commonly used herbal products are listed in Table 3. The most frequently reported were chamomile, fennel, propolis, cranberry, lemon balm, ginger, valerian and mallow. In particular, chamomile, fennel and ginger were taken regularly for the entire period of the pregnancy.

The most common reasons for beginning to take this kind of remedies were symptoms related to pregnancy condition, such as nausea, vomiting, stomach discomfort, constipation, anxiety, sleep disturbances and stretch marks. In some cases, the use was due to different problems, mainly migraine or influenza. All remedies were taken by oral route.

No side effects were reported, except in one case, where worsening of stomach ache was communicated to the gynaecologist after the occasional consumption of a sirup containing melissa, psyillium and glucomannan.

Our study population learned about herbal products from a variety of sources including friends, relatives, magazines and television. However, the most relevant source of information for the majority of participants was the doctor (95%), and most of the women (72%) informed their doctors about their use of herbal remedies.

Although there is no scientific basis for that belief, the decision to start to use herbal remedies was mainly based on the conviction that the "natural world", and then the natural products, would be safer than traditional therapies during the pregnancy (92%), even if less efficacious (63%).

The following pregnancy and neonatal outcomes were considered in the present study: the course of pregnancy (physiological or pathological course), abnormalities in foetal growth, type of labor (spontaneous or induced labor), gestational age, birth weight, small for gestational age, Apgar score, circumference of the skull and newborn's length.

By examining separately each herbal remedy, as shown in Table 4, *t*-test revealed that women who consumed chamomile every day throughout all pregnancy period were at higher risk of preterm delivery (38.8 ± 1.8 weeks versus 39.2 ± 1.6 weeks; $P < 0.002$) with respect to non-users. The use of chamomile was also associated with an increased risk for low birth weight (3230.4 ± 498.6 g versus 3322.4 ± 511.2 g; $P < 0.02$) and for lower length of the newborn (49.6 ± 0.9 cm versus 49.9 ± 1.6 cm; $P < 0.05$).

A regular consumption of fennel throughout the pregnancy resulted in shorter gestational age compared to non-users (38.8 ± 2.2 weeks versus 39.1 ± 1.6 weeks; $P < 0.05$). Moreover, the

agreed to be involved, with a response rate of 100%. A total of six hundred interviews were considered, because thirty questionnaires were excluded due to a lack of data. We considered only healthy women, to avoid possible interactions between herbal products and drugs (chronic diseases, concurrent pharmacological therapies).

Table 1 shows the socio-demographic characteristics of participants, according to herbal remedies use during the current pregnancy. The study enrolled mostly women between 31 and 40 years of age (52.5%), with a middle-high level of education (48% high school and 24.7% university degree), married (82.2%) and employed (53.5%). Compared to non-users, users were more frequently employed (OR: 1.5, 95% CI 1.0–2.4; $P < 0.05$). Fifty-one per cent were primiparae. The majority of participants declared they performed physical activity (68.5%) and they did not smoke (75.3%).

Four hundreds and eighty four out of six hundred women (80.6%) reported to have used at least one herbal product during the current pregnancy period. Moreover, ANOVA revealed no significant differences among numbers of herbal products taken during each trimester of the pregnancy (Table 2).

Table 2
ANOVA among mean number ($\pm$ SEM) of herbal remedies used in the three different periods of pregnancy.

Trimester						F	P
1st	**2nd**	**3rd**	**1st and 3rd**	**2nd and 3rd**	**1st, 2nd and 3rd**		
1.0 ± 0.03	1.3 ± 0.07	1.2 ± 0.04	1.1 ± 0.03	1.2 ± 0.04	1.1 ± 0.02	2.58605	0.07733

Table 4
Pregnancy and neonatal outcomes according to *chamomile* use *(values are mean ± SD).*

	Users	Non-users	P-value
Gestational age at birth (weeks)	38.8 ± 1.8	39.2 ± 1.6	0.0012
Birth weight (g)	3230.4 ± 498.6	3322.4 ± 511.2	0.0183
Length of the newborn (cm)	49.6 ± 0.9	49.9 ± 1.6	0.0428

Table 5
Pregnancy and neonatal outcomes according to *fennel* use *(values are mean ± SD).*

	Users	Non-users	P-value
Gestational age at birth (weeks)	38.8 ± 2.2	39.1 ± 1.6	0.0256
Birth weight (g)	3261.6 ± 608.9	3292.5 ± 486.6	0.2974
Length of the newborn (cm)	49.5 ± 2.6	49.9 ± 1.2	0.0653

frequency of lower length of the newborn resulted relatively higher in users, although this did not reach statistical significance (49.5 ± 2.6 cm versus 49.9 ± 1.2 cm; $P=0.06$; Table 5).

As far as ginger intake, among the regular users, we observed a shorter gestational age (38 ± 3.3 weeks versus 39.1 ± 1.7 weeks; $P < 0.05$) and a smaller circumference of the newborn's skull (32.1 ± 3.5 cm versus 34.2 ± 1.8 cm; $P < 0.002$) when compared with non-users (Table 6).

None of the remaining evaluated outcome variables were significantly influenced by the mother's consumption of the examined herbal products, such as chamomile, fennel and ginger.

Finally, none of the infant characteristics studied were significantly influenced by the mother's use of the remaining examined herbal remedies during the pregnancy.

4. Discussion

The present study shows that, in a region of the South of Italy, the use of herbal products in pregnancy was very common (80.6%). More interestingly, we also shed light on possible neonatal consequences of such use. In particular, along with gestational age, birth-weight, Apgar score and presence of congenital malformations or neonatal complications after delivery, our survey included, for the first time in the literature, length and head circumference of the newborn. After a regular use of chamomile, we highlighted a shorter gestational age at birth and a reduced length of the newborn, along with a lower birth weight. Moreover, the regular use of fennel resulted in a higher incidence of newborn small for gestational age at birth. Finally, among the regular users of ginger, we observed a shorter gestational age and a smaller circumference of the newborn's skull.

Even if data were collected from women of the same regional provenance, these findings deserve particular attention, especially if we consider that the most relevant source of information for the majority of participants was the doctor (95%), and most of them (72%) informed their doctors about their use of herbal remedies.

Although few previous studies showed the prevalence of use of herbal remedies among Italian pregnant women, to our

Table 6
Pregnancy and neonatal outcomes according to *ginger* use *(values are mean ± SD).*

	Users	Non-users	P-value
Gestational age at birth (weeks)	38.0 ± 3.3	39.1 ± 1.7	0.0336
Birth weight (g)	3146.2 ± 736.9	3289.5 ± 504.6	0.2145
Newborn's skull circumference (cm)	32.1 ± 3.5	34.2 ± 1.8	0.0011

knowledge, this is the first report examining the prevalence of use, attitude, knowledge and pregnancy outcomes in a sample of pregnant women in the South of Italy.

We performed our research through a face-to-face interview, during a study period of three years. We chose this method aware of the fact that self-administered questionnaires or national registries represent a relatively rapid method of collecting information from a large group in a standardized way. However, there is no possibility to remove any doubt or clarify something unclear and the quality of the information obtained is therefore less precise. In this regard, this kind of data collection methods are limited by the participants' knowledge of herbal remedies. On the other hand, in person interviewing generally secures high response rates. Accordingly, in our study we obtained a response rate of 100%. It also provides more flexibility because the interviewer is better able to sense when the respondent is confused, distracted, or otherwise unable to understand what is being asked.

Our data, obtained from six hundred interviewed Italian women, confirm other previous epidemiological surveys demonstrating that herb use is common among pregnant women. In this regard, it has been reported, for example, that the prevalence of herbal use in pregnancy ranges from 48% in Norway, 52% in Australia to 58% the United Kingdom (Frawley et al., 2013; Holst et al., 2011; Nordeng et al., 2011). In particular, in the United Kingdom, among complementary and alternative medicines, herbal products were the most frequently cited (Pallivalappila et al., 2014).

Surprisingly, our findings also revealed that women from a region of South of Italy seem to be more willing to use herbal remedies than other part of Italy. In this regard, in a study conducted at the Maternity wards of two Hospitals in the Northern Italy, Authors showed that one hundred and nine out of 392 women (27.8%) reported to have been taking one or more herbal products during pregnancy (Cuzzolin et al., 2010). Moreover, a recent multicentre cohort study showed that, of the 700 subjects enrolled from three general Hospitals located in Northeastern Italy, 297 (42%) reported that they had taken herbal remedies during the pregnancy (Facchinetti et al., 2012). In a different study conducted in an urban university general Hospital in the Northeast of Italy, it has been also shown that 47% of the investigated women used at least one herbal product (Zaffani et al., 2006) and, similarly, a survey conducted in two different general Hospitals in the North of Italy reported a prevalence of use during pregnancy of 48% (Lapi et al., 2010). These differences could be important for health care professionals in that they should be aware of probable cultural and traditional different attitudes with respect to herbal remedies use during the pregnancy.

Besides the prevalence of use, in our study we found that sociodemographic characteristics of participants are in agreement with the findings reported in other studies. Similarly, they tend to be older (age between 31 and 40 years), having a higher level of education, non-smokers, married and having their first child with respect to non-users. Moreover, a statistically significant difference among users and non-users was found only in relation to employment: the prevalence of herbal remedies was higher in employed women, thus confirming other previous Italian reports (Menniti-Ippolito et al., 2002; Zaffani et al., 2006), as well as results of studies performed in other countries (Hameen-Anttila et al., 2014; Holst et al., 2008; Kennedy et al., 2013).

In the present research, the proportion of women who used herbal remedies did not change during all over the pregnancy period. This might be explained by the concerns about side effects related to the use of standard pharmacological therapies, and by the belief that these remedies provided safe alternatives.

We found that the most commonly used ingested herbal remedies, as reported in other papers, were chamomile, fennel, propolis, cranberry, lemon balm and ginger (Broussard et al., 2010;

Holst et al., 2011).

Interestingly, although no relevant side effects related to these substances were reported during the pregnancy by the participants, substantial findings were drawn from our investigation when the attention was focused on neonatal outcomes of the pregnancy.

In particular, the regular use of chamomile by our women resulted in a lower birth weight. Our observation was in agreement with that reported by other Authors, who showed that regular users of chamomile were at higher risk of low birth weight when compared with non-users, although the results did not reach statistical significance, probably because of the limited numbers of enrolled chamomile users (56 subjects; (Facchinetti et al., 2012)). By contrast, Moussally and Bérard reported a lack of lower birth weight increased risk in pregnant users of chamomile (Moussally and Berard, 2012). However, the difference may be due to the fact that in this paper, Authors evaluated chamomile use during the last two trimesters of pregnancy, while in our study we considered the whole pregnancy. Then, the reported risk could be underestimated.

In addition, our results have highlighted a shorter gestational age at birth and a reduced length of the newborn after a regular use of chamomile. Even though a shorter gestational age, and then a preterm birth, is a multifactorial condition whose etiology is still poorly understood, our results seem to suggest that chamomile use could be considered as a risk factor, especially if we consider that the women enrolled in our study underwent a physiological pregnancy where pathologies, conventional drugs or other risk factors were absent.

Indeed, other reports have discouraged the use of chamomile during the pregnancy. In this regard, oxytocic and uterine stimulating herbs that may potentially induce spontaneous abortion include, among others, the chamomile (Johns and Sibeko, 2003). Additionally, chamomile has been reported as a potential trigger of severe anaphylaxis. A case report described the case of a previously healthy woman with a life-threatening anaphylactic reaction to an enema containing an oily extract of chamomile flowers during labor, resulting in asphyxia of the newborn (Jensen-Jarolim et al., 1998), thus suggesting that chamomile may also give rise to immediate-type I reactions (Reider et al., 2000). In this regard, it is known the potential hazard of allergenic proteins present in chamomile extracts and it is known that immediate-type hypersensitivity reactions to chamomile or other members of the *Compositae* may occur (Benner and Lee, 1973; Casterline, 1980). Subiza and coworkers reported a case in whom ingestion of a chamomile-tea infusion precipitated a severe anaphylactic reaction (Subiza et al., 1989). Similarly, the presence of a type-I allergy to orally ingested chamomile was confirmed in a man who developed an episode of severe anaphylaxis (Andres et al., 2009).

It should also be considered that the use of plants containing coumarin-derivatives, such as chamomile, could represent a potential hazard for those women suffering coagulation disorders during pregnancy (Johns and Sibeko, 2003). In fact, potential drug interactions with chamomile have been suggested. Coumarin may interfere with the blood coagulation processes, thus potentiating the effects of warfarin administration (Heck et al., 2000; Miller, 1998). Accordingly, in a different report, Senegal and Pilote suggested that patients should be educated about the potential risk of using herbal products in general, and chamomile products in particular, while being treated with warfarin (Segal and Pilote, 2006). In the same way, coumarin may interfere with aspirin effects or other anti-inflammatory drugs when used at the same time (Abebe, 2002). Moreover, because of its sedative effect, chamomile might interact with other central nervous system depressive agents, such as alcohol, antidepressant or anxiolytic drugs (Larzelere and Wiseman, 2002). Finally, from a pharmacokinetic

interaction point of view, it has been also shown the inhibitory effects of the essential oil of chamomile and its major constituents on human cytochrome P450 enzymes (Ganzera et al., 2006).

Therefore, although no conclusive results seem to exist at present, taking into account all the above reported evidences, our data further emphasize that, due to the lack of evidence for efficacy and to the risk of side effects, chamomile should not be recommended during pregnancy (Jensen-Jarolim et al., 1998; Subiza et al., 1989), and appropriate warnings should be labeled on chamomile-containing products, especially for pregnancy use.

The second most widely used product in our study was the fennel. We found a higher incidence of newborn small for gestational age at birth among regular users.

Fennel has been used as an estrogenic remedy for thousand years. It has been suggested to promote menstruation, alleviate the symptoms of the female climacteric, facilitate birth and enhance milk secretion (Albert-Puleo, 1980; Hare et al., 1916). Ostad et al. demonstrated that fennel can inhibit contraction of isolated uterus that was induced by oxytocin and PGE2 (Ostad et al., 2001).

The main constituents of the fennel are anethole, dianethole and photoanethole, considered to be active estrogen-like agents (Dhar, 1995; Howes et al., 2002). Thus, the property of this herbal remedy could be considered as biologically significant. In fact, there is a great concern about its potential adverse effect on fetal development. In this regard, it has been observed an in vitro reduction in limb bud differentiation by fennel, thus suggesting toxic effects on fetal cells (Ostad et al., 2004). Moreover, thirteen compounds isolated from the methanolic extract of fennel have been found to possess human liver cytochrome P4503A4 inhibitory activity (Badgujar et al., 2014), thus suggesting potential interactions with other drugs (Smeriglio et al., 2014). However, as suggested by Gori et al. (2012), to establish the effective risk for consumers, data about all constituents should be fully considered, when used as basis for statements about a herbal remedy.

Recently, in the absence of other secondary sex characteristics, a breast development in a prepubertal girl related to fennel tea consumption has been described and the Authors emphasize the importance of awareness of fennel tea as a preventable cause of premature thelarche (Okdemir et al., 2014). Accordingly, a striking and frequent cause of premature thelarche in children was identified in the regular use of *Foeniculum vulgare*, thus suggesting that public awareness of these observations should be recommended (Turkyilmaz et al., 2008).

Hence, our findings reinforce the assessment reported in the statement adopted by the Committee on Herbal Medicinal Products (HMPC) of European Medicines Agency, that describes the data available on the medicinal use of a herbal substance: "because there have been no tests looking at the effects of fennel medicines during pregnancy or lactation, they should not be used in women who are pregnant or breast-feeding as a general precaution" (EMA/HMPC/411665/2008).

None of the evaluated outcome variables were significantly influenced by the mother's consumption of propolis, cranberry and lemon balm.

Alarmingly, as far as ginger intake among the regular users, we observed a shorter gestational age and a smaller circumference of the newborn's skull when compared with non-users.

No evidence in this regard was reported earlier. Our data are in contrast with results reporting that the use of ginger during pregnancy did not alter neonatal outcomes (Heitmann et al., 2013). However, such discrepancies could be due to several reasons. In particular, in the Norwegian Mother and Child Cohort Study, pregnant women reported using ginger before the outcome of the pregnancy was known. Moreover, a low response rate was obtained, thus a selection bias could be raised (Heitmann et al., 2013).

The ginger is increasingly used in Western society, with one of the most common indications being pregnancy-related nausea and vomiting (Dante et al., 2014, 2013). Indeed, ginger is a herbal medicine and thus has a pharmacological action, although its anti-emetic mechanism of action is not completely understood.

Because nausea and vomiting associated with early pregnancy is experienced mainly during the first trimester when organogenesis occurs, teratogen effects become a concern. Its risk-benefit profile has only recently started to come to light and, despite the widespread use of ginger, evidence-based findings on the safety of use during pregnancy are limited and controversial to some extent. This is certainly due to the fact that pharmacovigilance is not required for herbal remedies. In this regard, taking into consideration the limited number of studies considered, variable outcome reporting and low quality of evidence, in a recent review Viljoen and colleagues reported potential benefits of ginger in reducing nausea symptoms during the pregnancy. They suggested that ginger did not pose a risk for side-effects or adverse events during pregnancy, or spontaneous abortion compared to placebo (Viljoen et al., 2014). However, it is widely accepted that absence of evidence is not the same as evidence of absence. Indeed, a higher risk of incidence of stillbirths in the exposed group was found by Choi et al. (2015).

Furthermore, there is an increasing body of evidence regarding the anticoagulant properties of ginger (Jiang et al., 2005; Kruth et al., 2004; Spolarich and Andrews, 2007). On the cardiovascular system, ginger behaves as a hypotensive agent, so expectant mothers prone to the dizziness, as well as those on anti-hypertensive therapy should be warned not to take ginger. Ginger is known to lower blood sugar, then it should be avoided in women with diabetes mellitus (Akhani et al., 2004; Heimes et al., 2009). Ginger is also known to be a stomach irritant and to cause heartburn. In this regard, it is important to underline that the Risk Assessment Unit of the Finnish Food Safety Authority Evira made an assessment on the safety of the consumption of food supplements containing ginger during pregnancy. At this regard, scientific evidence is at present limited and the results of research are inconsistent to some extent. It has been considered that a number of the constituents of ginger could be harmful to foetal development, and some of the chemical constituents have been found to cause cell mortality. The assessment suggested, then, that the consumption of ginger products as well as the abundant or long-term consumption of ginger tea should be avoided during pregnancy. For this reason, Evira considered it appropriate in accordance with the precautionary principle that pregnant mothers should be warned of the consumption of ginger products by separate labeling. Accordingly, the Finnish Authority suggested that the consumption of ginger products during pregnancy should always be discussed with a maternity clinic nurse, a doctor or a nutritionist (Evira Finnish Food Safety Agency. Warning label to be added on food supplements containing ginger as well as on ginger tea, and corresponding drink powders; www.evira.fi/portal/en/food; 2009. 2nd July 2010). Similarly, Denmark issued warnings to women during the pregnancy about the high levels of ginger in a particular product, GraviFrisk, which has been prohibited in 2008 (Jacobsgaard, 2008; Sondergaard, 2008).

Our study is the first one showing that ginger use during pregnancy increases the risk of prematurity and the risk of a smaller circumference of the newborn's skull. However, although our preliminary results are encouraging, further studies should be performed to make more definite conclusions about safety. Certainly, there is a pressing need for further research into safety to balance the evidence we already have on its efficiency.

5. Conclusion

In conclusion, it appears essential to underline the potential risk of the confidence in the "natural world". In this regard, it could be stated that evidence of effectiveness for herbal remedies is not the same as proof of safety. These are not synonyms, and it is irresponsible for healthcare physicians to preserve the unjustified belief that a "natural" remedy is "safe" e or at least "safer" than conventional drugs. All pregnant women should realize that each herbal product has different biological activities and their adverse effects are still unknown. Therefore, they can be potentially harmful. Thus, because of the expanding market of herbal remedies, formalized studies, with the accumulation of rigorous evidence are warranted. Moreover, pregnant women who choose herbal therapies need to be properly informed about which product has undergone reliable clinical studies to deserve a recommendation for use during pregnancy and instead which rely more on traditional story for their efficacy and safety data. Where evidence is available, licensed herbal remedies should be clearly labeled to allow a better informed decisions during pregnancy.

Conflicts of interest

The authors report no conflict of interest.

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