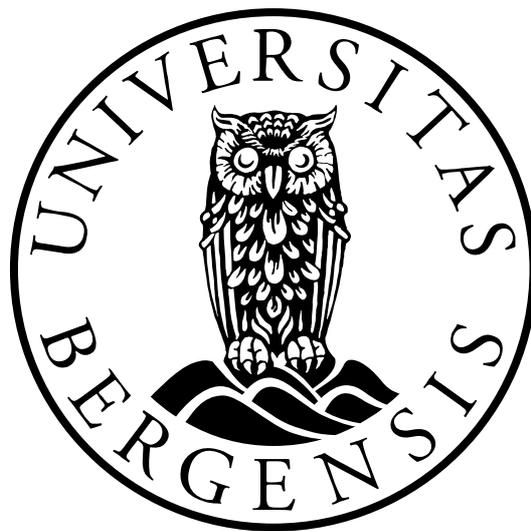


Use of herbal products during pregnancy

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Dissertation for the degree philosophiae doctor (PhD)
at the University of Bergen

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Preface

This thesis is submitted for the degree Philosophiae Doctor (PhD) at the University of Bergen. The work has been carried out at the Department of Chemistry and the Centre for Pharmacy at the University of Bergen, at the School for Chemical Sciences and Pharmacy at the University of East Anglia, Norwich, UK and at the Antenatal Clinic and Antenatal Ultrasound Department at the Norfolk and Norwich University Hospital, Norwich, UK. The thesis consists of five papers.

The aim of the work was to study use of herbal remedies during pregnancy. It was the intention to:

- Describe the users.
- Identify the types of herbs used and the extent of use.
- Identify the indications for use.
- Identify the sources of information about herbs used by the women.
- Review the literature on safety and efficacy of the herbs used.
- Gain a better understanding of women's reasons for use of herbs – their attitudes and feelings.

Chapter 1 gives an introduction to the topics herbal products, their use in pregnancy, pregnancy as such and pharmacoepidemiology. Chapter 2 presents the methods used, Chapter 3 the main results, Chapter 4 a general discussion of the results and Chapter 5 conclusions and future perspectives.

All plants will be mentioned by their English name in the text but a table of English, Norwegian and Latin names of mentioned plants is given below. Plants only mentioned in Appendix B are not included. Latin names according to Barnes et al¹ except from those marked ^A or ^B. A refers to Heinrich et al² and B to Blumenthal³.

Table 1 Names of plants discussed in this thesis

Latin	English	Norwegian
<i>Arctostaphylos uva-ursi</i> (L.) Spreng.	Bearberry	Melbær
<i>Carum carvi</i> L. ^A	Caraway	Karve
<i>Matricaria recutita</i> L. or <i>Chamaemelum nobile</i> (L.) All.	Chamomile	Kamille
<i>Vaccinium macrocarpon</i> Aiton	Cranberry	Tranebær
<i>Taraxacum officinale</i> Weber	Dandelion	Løvetann
<i>Echinacea purpurea</i> (L.) Moench	Echinacea	Solhatt
<i>Echinacea pallida</i> (Nutt.) Nutt.	Coneflower	
<i>Echinacea angustifolia</i> DC.		
<i>Foeniculum vulgare</i> P. Mill. ^A	Fennel	Fennikel
<i>Frangula alnus</i> Mill.	Frangula	Trollhegg
<i>Zingiber officinale</i> Roscoe	Ginger	Ingefær
<i>Panax ginseng</i> C.A. Meyer	Ginseng	Ginseng
<i>Aesculus hippocastanum</i> L.	Horse chestnut	Hestekastanje
<i>Equisetum arvense</i> L. ^B	Horsetail	Kjerringrokk Åkersnelle
<i>Melissa officinalis</i> L.	Lemon balm	Sitronmelisse
<i>Mentha x piperita</i> L. A	Peppermint	Peppermynthe

<i>Rubus idaeus</i> L.	Raspberry	Bringebær
<i>Senna alexandrina</i> L.	Senna	Sennes
<i>Hypericum perforatum</i> L.	St. John's wort	Prikkperikum, Johannesurt
<i>Valeriana officinalis</i> L.	Valerian	Valeriane

Acknowledgements

My interest in pharmacognosy arose when I was a pharmacy student in Copenhagen in 1982-1988. The most interesting (though challenging) lab courses and some very keen lecturers – especially Lene Gudiksen - were part of the explanation.

I want to thank all the people who have influenced my PhD work somehow, especially my supervisor Svein Haavik who believed in me and gave me the chance to do this work. He has helped and supported me in all my ideas, discussed and brought perspective to things and made me think once again whenever needed. I will also thank my co-supervisor Øyvind Andersen who accepted me as a Ph.D. student even though I was not the most obvious fit for his research group and who gave valuable comments to the manuscript for this thesis.

Hedvig Nordeng at the University of Oslo introduced me to the “pregnancy”-track by offering me to visit Bengt Källén in Sweden instead of her. This resulted in my first published paper. She also let me use and modify her interview guide for my questionnaire and she did a great job as co-author on my papers. Bengt Källén helped me with the data from the Swedish Medical Birth Register.

Part of my work was done in Norwich at the University of East Anglia and the Norfolk and Norwich University Hospital. This would not have been possible without David Wright who was my supervisor there. He helped me with loads of practical details and had time and enthusiasm enough for me on top of all the other projects he runs. He and his wife, Debi, welcomed my family as well and gave us a good time there.

The ante-natal clinic and ultrasound department at Norfolk and Norwich University Hospital let me hand out my questionnaires there. I want to give a special thank to the receptionists without whom the project would not have been possible. All employees were kind and helpful and made me feel welcome but I want to give a special thank to Alice Lince who took good care of me.

Many colleagues at the University of Bergen and the University of East Anglia have shown supportive interest in my work – especially Monica Jordheim who has shared office and thoughts with me and even looked after my guinea pigs while I was in Norwich and Kjersti Bakken who has always been there when I needed someone to discuss things with.

All my friends outside the University have probably considered my job a little bit odd and difficult to understand but they have all shown interest and supported me. Thank you.

Last but not least I want to thank my family. My parents in Copenhagen – they have always encouraged and supported me – even when I decided to move to Norway. My husband, Thorbjørn and my son Klaus - they had to put up with a wife and mother who had irregular working hours and who moved them to England for 4 months. Thank you ever so much for coming with me over there – I could not have done it alone.

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Abstract

Background: The use of herbal remedies is gaining popularity in the western world though little scientific documentation for safety and efficacy is available. Women are found to be more frequent users of herbs than men and studies from North America, Australia and Europe have shown widespread use among pregnant women.

Objective: The major aim of the work was to study use of herbal remedies during pregnancy in two different populations and by different methods.

Methods: One study was performed as a survey among 578 pregnant women at the Norfolk and Norwich University Hospital between November 2007 and February 2008. Use of herbal remedies and treatment of various ailments were studied. Six women from this study population also participated in a focus group discussion about the results of the survey and their reasons for herb use in pregnancy. Another study was performed in the Swedish Medical Birth Register. Data on the use of herbal remedies during pregnancy were obtained from 860215 pregnant women during the period 1st July 1995 to end of 2004. Outcome variables studied were prematurity, birth weight, Apgar score, number of infants in delivery and congenital malformations.

Results: The usage of herbal remedies during pregnancy was 57.8% in the UK study and 0.9% in the Swedish study. This very big difference is probably mainly due to the different methods of data collection. Ginger, cranberry and raspberry leaf were the most commonly used herbal remedies in the UK study while Floradix®, ginseng and valerian were most commonly reported in the Swedish study.

Family and friends were the most used source of information about herbs used in pregnancy in the UK study and 75% of the herb users did not inform their doctor or midwife about the herb use. Potentially harmful herbs or herbs for which the documentation for safety in pregnancy is inadequate were used by 41.2% of the participants. Forty one different herbs were reported used and 96 different indications were given for the use but 46 of those indications could not be confirmed in literature as “traditional use”.

The focus group discussion showed that users of herbal remedies expected health care personnel to disapprove of herb use and thus did not reveal use to them. They found it difficult to find a reputable alternative practitioner but they wanted the National Health Services to include alternative therapists in the public healthcare system.

Conclusion: Use of herbal remedies is common among pregnant women while documentation of safety and efficacy is limited. Health care personnel should be able to give evidence based information about herbs but more research is necessary to enable this.

Future perspectives: Studies are necessary to document as well safety as efficacy of herbs during pregnancy. Controlled clinical trials are preferred but will probably be difficult for practical as well as economical and ethical reasons so prospective observational studies regarding herbal remedy usage and pregnancy outcome are warranted to determine safety. Communication of scientific data about herbal safety to the public is a challenge because it is a general belief that herbs are safer than pharmaceuticals. Though some women acknowledge that some herbs may have side effects, they still believe that the herbs they use are safe. Another challenge for the future is to introduce more education about herbal remedies in the training of health care personnel. As this education needs to be evidence based, this challenge is linked to the need for more research in the field.

Abbreviations

ATC	Anatomical Therapeutical Chemical (classification system for drugs)
BMI	Body mass index
CAM	Complementary and alternative medicine
CI	Confidence interval
CNS	Central nervous system
EMA	European Medicines Evaluation Agency
EU	European Union
INR	International normalized ratio
LGA	Large for gestation age
MA	Marketing authorisation
NHS	National Health Services
NMA	Norwegian Medicines Agency
NVP	Nausea and vomiting in pregnancy
OR	Odds ration
OTC	Over the counter
SGA	Small for gestation age
SPC	Summary of product characteristics
UTI	Urinary tract infections
WHO	World Health Organisation

List of publications

Paper I

Use of herbal drugs during early pregnancy in relation to maternal characteristics and pregnancy outcome. Holst L, Nordeng H, Haavik S. *Pharmacoepidemiology and Drug Safety* 2008; 17:151-159.

Paper II

The use and the user of herbal remedies during pregnancy. Holst L, Wright D, Haavik S, Nordeng H. *The Journal of Alternative and Complementary Medicine*. Accepted 01.01.09.

Paper III

Safety and efficacy of herbal remedies in obstetrics – review and clinical implications. Holst L, Wright D, Haavik S, Nordeng H. *Midwifery*. Accepted 20.05.09.

Paper IV

Use of herbal preparations during pregnancy: Focus group discussion among expectant mothers attending a hospital antenatal clinic in Norwich, UK. Holst L, Wright D, Nordeng H, Haavik S. *Complementary Therapies in Clinical Practice*. Accepted 18.02.09.

Paper V

Raspberry leaf – should it be recommended to pregnant women? Holst L, Haavik S, Nordeng H. *Complementary Therapies in Clinical Practice*. Accepted 11.05.09.

1. Introduction

1.1 Herbal remedies – regulations, safety and efficacy

The use of herbal remedies is increasing worldwide and has been for years⁴. In 1996, the *British Medical Journal* published the news “Complementary medicine is booming worldwide”⁵. Women are found to be more frequent users of herbs than men^{5,6}. A population based survey from England in 1998 found that 20% of 2669 adults had used OTC herbal remedies during the last 12 months and that 31% had used them sometime during their lifetime while only 1% had visited a medical herbalist during the last 12 months and 4% sometime during their lifetime⁷. It is a common misunderstanding that herbs are natural and thus safe and this may lead people to use herbs instead of pharmaceuticals^{8,9}. This is especially appealing to pregnant women who are concerned about not only their own health but also the health of their unborn baby.

1.1.1 The regulation of herbal products in Norway and in the EU

Manufacturers of pharmaceuticals must apply for a “Marketing Authorisation” (MA) for their products before they can bring them to the market. In this process documentation for the quality, safety and efficacy of the product is evaluated by either the national authorities in one EU country (in Norway: The Norwegian Medicines Agency, NMA) or by the European Medicines Evaluation Agency (EMA). In addition the product information aimed at health care professionals (the Summary of Product Characteristics, SPC) and consumers (package inserts) are approved.

Regulation of herbal products is different. Until recently there has been no common regulation in the EU. The NMA has had an “Herbal medicines” (“Naturlegemidler”) scheme since 1995. The application procedure has been simpler than for pharmaceuticals – equal for quality documentation but no requirement of

toxicological, pharmacological and clinical documentation (safety and efficacy) if “the product was intended for self treatment of conditions which the user could diagnose and treat without medical supervision” and if “the applicant could refer to scientific publications regarding the contents of the product and their traditional use in Europe and/or North America for at least 30 years, it has a well known effect and is acceptably safe”. If the symptoms could be caused by a serious condition, the product label or insert should state that the user should seek medical advice to rule out this before taking the product. The NMA had the right to give directives with respect to label and insert.

In 2005 the EU directive 2001/83/EC as amended in 2004/24/EC was intended to be implemented in all EU countries. Work on developing monographs for herbal ingredients is ongoing in the EU and in Norway the new regulations will enter into force from 30.4.2011. All products with a MA according to the established regulations will need a new MA to remain on the market. In the new regulations, two different procedures will be available for herbal medicines: “Well-established herbal medicinal products” and “Traditional herbal medicinal products”. For both categories the necessary quality documentation is similar to that for pharmaceuticals. For the well-established herbal medicinal products the safety and efficacy can be documented in the same way as for those pharmaceuticals where MA is sought based on bibliographic documentation based on well established use. For traditional herbal medicinal products safety and efficacy can be made probable from all of the 4 points below:

1. Medicinal use for at least 30 years, whereof at least 15 in the EU.
2. A bibliographic review of all available safety documentation and an expert report on this.
3. Indication suitable for self-treatment.
4. For oral, topical or inhalation use.

If an EU monograph for the herb is available or if the herb is on the EU list, this and an expert report stating that the EU documentation is valid for the relevant product is

accepted as documentation. The intentions of the directive are to acquire better safety for the consumers, to give easier access to traditional herbal products of a documented quality, to ascertain that safety and indications are based on long experience and to give a full declaration, a package insert and an SPC.

In Norway as well as in the EU many products are legally sold without a MA. They can be sold as “Food supplements” as long as they don’t contain herbs regulated as “medicinal” according to “Lov om legemidler” (Act relating to medicines). In Norway they are regulated by “Lov om matproduksjon og mattrygghet mm” (Act relating to food production and food safety. etc.). In that case no documentation of quality, safety or efficacy is reviewed before the product is marketed. The only request is a notification. In addition there are regulations for the labelling and advertising. It is illegal to claim that a food supplement can “prevent or treat disease, symptoms thereof or pain” and that “a balanced and varied food intake gives insufficient amounts of vitamins and minerals”. A committee, “Syse-utvalget”, was appointed to give recommendations on legal or illegal claims about food supplements¹⁰. The committee established a list of claims and decided whether they are “medicinal claims” which are only to be used about pharmaceuticals, “legal health claims” which can be used about food supplements or “illegal health claims” which can not be used at all. The list is supposed to show examples and new claims must be evaluated according to that.

Herbal practitioners and other alternative practitioners mix and sell herbs to their clients. In medical herbalism it is common to use a mixture of herbs, made up for the individual patient. As long as the herbs are not listed as “medicinal” according to “Lov om legemidler” this is also legal and unregulated.

In conclusion it is possible to sell herbal products without applying for a MA and thus without the products being evaluated for quality, safety and efficacy.

1.1.2 Quality issues

The lack of quality control of food supplements (see 1.1.1) represents a potential risk to the users. Mistaking one plant for another, microbial disintegration or contamination of plant material and deliberate forgery are actual problems. One case of contamination of a herbal “internal cleansing cure” with *Digitalis lanata* was described in 1998. The product was said to contain “plantain” (*Plantago* sp.) but the raw material was contaminated from the supplier and caused heart symptoms in a patient¹¹. Contamination of Chinese herbal medicines with aristolochic acid is well known^{12,13}. This leads to nephropathy (commonly known as “Chinese herb nephropathy”) and often to life-long treatment with dialysis. More than 100 women were affected by this in Belgium in the 1990es as they used a slimming treatment. The latest development is “Herbal Viagra” or herbal aphrodisiacs shown to contain analogues of sildenafil (active constituent of Viagra®) or other similar substances¹⁴.

1.1.3 Pharmacovigilance

Associated with a MA for a pharmaceutical is a demand for pharmacovigilance. Pharmacovigilance has been defined by the World Health Organisation (WHO) as “*the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems*”¹⁵. As well the manufacturer as the authorities collect and analyse reports of side effects. The aim of this is to identify risks and risk factors in the shortest possible time and in this way also identify previously unsuspected adverse effects or adverse effects in special patient groups (pregnant women, children, elderly) where clinical trials are often not

performed before the MA is granted. This information, if used effectively, allows for evidence-based use of medicines.

In many countries like Norway and the UK reporting of adverse effects is spontaneous. It has commonly been done by health care personnel (doctors, dentist and pharmacists) but lately some schemes, like the UK Yellow Card Scheme¹⁶, have opened for reports from patients. The spontaneous reporting schemes are also open for reports on adverse effects of herbal remedies but the Norwegian authorities state in their annual report from 2007 that this group of adverse effects is underreported¹⁷. An explanation for this is suggested by Barnes who describes the situation from a UK point of view¹⁸. Herbal remedies are often recommended by family and friends or by the popular media and they are bought OTC from a pharmacy, from a herbal shop or on the Internet¹⁸. Professional advice is not commonly sought and herb use is often not disclosed to health care personnel¹⁸. For this reason adverse effects are not disclosed either and are thus not reported¹⁸. The new EU legislation on "Well-established herbal medicinal products" and "Traditional herbal medicinal products" will require manufacturers to comply with provisions of pharmacovigilance.

1.1.4 Safety of selected herbs in pregnancy

Safety data for herbal remedies used in pregnancy is mainly based on experience over time as few clinical trials are performed so the evidence base is minimal. Herbs commonly used in pregnancy and for which some clinical documentation is available include: Ginger, cranberry, raspberry leaf, echinacea and St. Johns wort. When choosing herbs for use during pregnancy one should always evaluate the need against the risk.

1.1.4.1 Ginger

Ginger is probably the herb most studied in pregnant women. It has been used traditionally to treat nausea for centuries. Nine clinical trials and one prospective study were found (see Appendix A)¹⁹⁻²⁸. The doses tested in the clinical trials were between 0.5 g and 1.5 g a day for 3 – 21 days^{19-22,24-28} except from one study giving 6 g a day for 4 days²³. No adverse effects on pregnancy outcome were reported, but the studies were small (14 – 146 women in the treatment group) and thus might not reveal uncommon effects.

It has been hypothesised that ginger can influence testosterone metabolism in the foetus²⁹ but no clinical or experimental data to suggest or contradict this concern were found³⁰. Some concern has been expressed about the mutagenicity of gingerol but a study from 1987 found that while gingerol was mutagenic in a test on *Salmonella typhimurium* zingerone suppressed the mutagenic activity³¹.

Interestingly however GraviFrisk® (translates to something like “PregnaWell” and equating to a daily dose of 6g of dried ground ginger) which was advertised for pregnant women in Denmark was withdrawn from the market in February 2008 due to fear of effect on the metabolism of testosterone in the foetus and thus on the development³². The Danish Veterinary and Food Administration stated that it is not dangerous to consume food containing ginger, but that the amount in different herbal products is too high³².

A sound conclusion seems to be that ginger can be used in amounts not greatly exceeding the amounts used in food or drink.

1.1.4.2 Cranberry

One study of multiple daily doses of cranberry showed no difference between the treatment and control groups with regard to obstetric or neonatal outcomes (see Appendix A)³³. Another study has shown that patients at risk for nephrolithiasis (whether pregnant or not) should not take concentrated cranberry products

(tablets/capsules)³⁴. If cranberry is used to treat urinary tract infections (UTI) it might not be effective (see 1.1.5.2). Twenty to 30 % of untreated cases of UTI are expected to lead to acute pyelonephritis. This may result in low birth weight, premature delivery, and, occasionally, stillbirth^{35,36}. For this reason it is important that UTI during pregnancy are treated with antibiotics.

It seems sensible to conclude that cranberry can be used in amounts not greatly exceeding the amounts used in food or drink but is not recommended as sole treatment for UTI.

1.1.4.3. Raspberry leaf

One double blind, randomised, controlled trial and one retrospective study of raspberry leaf was found (see Appendix A)^{37,38}. The dose tested in the controlled trial was 2 x 1.2 g a day, from 32 weeks until labour. No adverse effects were seen but the study was small with only 96 women in the test group. Doses varied between one and eight cups of tea/tablets a day in the retrospective study. Duration of use varied between 1 and 32 weeks and started as early as week 8. No adverse effects were seen.

No firm conclusions can be drawn on this basis and thus raspberry leaf should not be used during pregnancy until further documentation is available.

1.1.4.4 Echinacea

No clinical trials were found on the safety of echinacea during pregnancy but one prospective study was available (see Appendix A)³⁹. The doses varied: Tablets 250 – 1000 mg a day, tincture 5 – 30 drops a day. The duration was 5 – 7 days. The treatment group consisted of 206 women. No significant differences in spontaneous abortions or malformations were seen between treatment and control groups.

No firm conclusions can be drawn on this basis and thus echinacea should not be used during pregnancy until further documentation is available.

1.1.4.5 St John's wort

No clinical trials were found on the safety of St. John's wort during pregnancy. One single case report⁴⁰ was found (see Appendix A). Two cases are mentioned but only one is followed through delivery and one month after. No unwanted effects were described.

Due to the lack of safety data, St. John's wort should not be used during pregnancy.

1.1.5 Efficacy of selected herbs used in pregnancy

Efficacy data for herbal remedies used during pregnancy is mainly based on use over time and on a few clinical trials and prospective studies just like the safety documentation.

1.1.5.1 Ginger

Two clinical trials of 1 g ginger daily and one of 6 g found ginger more effective against nausea than placebo, two trials comparing 1 resp. 1.5 g ginger to Vitamin B6 found the products equally useful, two trials comparing 1 resp. 2 g ginger to Vitamin B6 found ginger more effective and one study of 1 g ginger found that ginger may be useful in some pregnant women. One trial comparing ginger to dimenhydrinate found the products equally effective. A prospective study with various doses found that ginger capsules were better than other ginger forms but that almost half of the women found ginger totally ineffective (see Appendix A)¹⁹⁻²⁸.

1.1.5.2 Cranberry

The use of cranberry juice or tablets/capsules to prevent recurrent UTI gets some support from a Cochrane review⁴¹. The conclusion is that there is some evidence that cranberry juice may decrease the number of symptomatic UTI over a 12 month period but that a large number of dropouts/withdrawals indicate that cranberry juice may not be acceptable over long periods of time. Neither optimum dose nor preferred method of administration is clear. Conversely another Cochrane review considering cranberry for treatment of UTI concludes that there is no good quality evidence to support that it is effective⁴². One pilot study of the preventive effect of cranberry juice against asymptomatic bacteriuria in pregnancy concludes that the results suggest that there may be a protective effect, but the data did not show statistical significance (see Appendix A)³³.

1.1.5.3 Raspberry leaf

One study showed that raspberry leaf did not shorten the first stage of labour, but the second stage with 9.59 min³⁸. A lower rate of forceps deliveries was also seen³⁸. The retrospective study showed some effect on shortening and less “mechanical assistance”³⁷. None of the described differences between treatment- and control group were statistically significant^{37,38}.

1.1.5.4 Echinacea

Efficacy of echinacea has not been studied during pregnancy. A Cochrane review of publications on the efficacy in prevention and treatment of common cold with echinacea has found that no studies show preventive effect better than placebo but

that there is some evidence that preparations based on *Echinacea purpurea* might be effective for the early treatment of colds in adults⁴³.

1.1.5.5 St. John's wort

Efficacy of St. Johns wort has not been studied during pregnancy. A Cochrane review of 29 publications on the efficacy of St. Johns wort on major depression shows that the herb is superior to placebo, similarly effective to standard antidepressants and causes fewer side effects but that studies from German-speaking countries come to more positive conclusions than others⁴⁴.

1.1.6 Risk of interactions between the above mentioned herbs and various pharmaceuticals

Herbs contain a complex mixture of chemical constituents and can affect pharmacokinetic and pharmacodynamic properties of pharmaceuticals⁴⁵. Various herb-drug interactions are described in the literature. Herb-users are often not aware of the risk of interactions and do not always inform their doctor about herb use. Doctors – even if they are told – do not always have the necessary information or knowledge to evaluate the risk of interactions when prescribing drugs to a herb-user⁴⁶.

1.1.6.1 Ginger

The most commonly described interaction involving ginger is with warfarin and other anticoagulants. Ginger has been found to inhibit thromboxane synthetase and might thus cause a prolonged bleeding time⁴⁷. Theoretically this may add to the effect of ingested anticoagulant and thus increase the international normalized ratio (INR).

Until more is known, it is recommended to monitor INR closely in patients taking significant amounts of ginger⁴⁸. Ginger may also enhance the effect of CNS depressants⁴⁹.

1.1.6.2 Cranberry

Contradictory evidence on the effect of cranberry on warfarin is found. Some studies show an increase of the international normalized ratio (INR) in patients taking cranberry and warfarin simultaneously while other studies show no significant effect^{50,51}. The Committee on Safety of Medicine (UK) reported 12 cases in 2004 and has concluded that there is sufficient evidence of an interaction for formal advice to be issued⁵². The Committee recommends that patients taking warfarin should avoid taking cranberry juice or other cranberry products⁵².

1.1.6.3 Raspberry leaf

Raspberry leaf contains tannins. When iron and tannin containing herbs are taken simultaneously, the tannins may interfere with the absorption of the iron and even if this is not a serious problem, it should be taken into account in anaemic patients^{53,54}.

1.1.6.4 Echinacea

Echinacea is reported to have immunostimulant activity and can therefore theoretically decrease the effect of immunosuppressive therapy⁴⁹. Neff et al describe 2 patients taking echinacea after a liver transplantation⁵⁵. Both experienced elevation of aminotransferase levels (indication of rejection) which resolved with discontinuation of the herb⁵⁵.

1.1.6.5 St. John's wort

St. John's wort is found to induce specific CYP450 enzymes and thus have the potential to affect the effect of drugs metabolised by those⁵⁶. Many different drugs (ex: cyclosporine, midazolam, amitriptyline, tacrolimus, digoxin, warfarin and antidepressants) are mentioned in the literature indicating the importance for doctors to ask about herb use and for patients to reveal their use⁴⁵.

1.1.7 Limited knowledge about herbs among health care personnel

The knowledge among health care personnel about herbs, their use, toxicity and possible interactions with pharmaceuticals is limited. No studies of the knowledge about herbal safety in pregnancy were found, but some general studies are available. Suchard et al 2004 studied doctors' knowledge regarding the toxic effects and drug interactions of herbal remedies by distributing questionnaires at educational meetings of emergency medicine and internal medicine doctors⁴⁶. A total of 142 questionnaires were completed – among those 26 from medical students. The mean subject score on the quiz determining the knowledge was only slightly higher than would have been from random guessing. The difference was statistically significant but was not considered clinically relevant as it equalled less than 4% of the total possible score. As many as 74% rated their own knowledge as “poor” and none rated it as “good” or “excellent”. Nine percent of the participants had previous formal instruction regarding herbal remedies (therapies, toxicities and/or interactions). They all rated their knowledge as “fair” but did not get a significantly better quiz score than those rating it as “poor”. The authors conclude that “a great deal of education will be necessary”.

Another study of 1268 doctors, pharmacists, nurses, dieticians and students of those professions showed a slightly better result⁵⁷. The survey was performed prior to the participants' enrolment in an online course about herbal and dietary supplements.

The mean score on the knowledge test was 66 %. Doctors, pharmacists and dieticians had a significantly higher score than nurses and all categories of students. The study also tested “confidence” and “communication”. Users of herbs and dietary supplements were more confident than non-users and dieticians and doctors more confident than the other groups. Dieticians and doctors were also better at communicating information about herbal remedies. The authors conclude that all categories of health care personnel would benefit from learning more about herbal and dietary supplements and about communication.

Giveon et al found that 70% of 165 primary care doctors claimed little or no knowledge about herbal remedies⁵⁸. Sixty percent of the 165 doctors expected 10% of their patients to use herbal remedies, which is too low an estimate according to the authors.

One study evaluated the effect of a tutorial about uses, contraindications and drug interactions of common herbal medicines on the knowledge among doctors⁵⁹. The participants were tested pre- and post-tutorial and showed a statistically significant rise in knowledge score from 30% pre-tutorial to 64% post-tutorial. This indicates that there is a room for improvement and that it is possible to achieve.

Nurses do not show better knowledge than doctors. A survey among 149 registered nurses about use, purpose, side effects and interactions of ginkgo, St. John’s wort, ginseng, garlic and echinacea showed that the nurses neither used nor recommended the remedies. They were relatively unfamiliar with the five commonly used herbs and more unfamiliar with side effects and interactions than with purpose of use. The median number of correctly identified purposes was 28% while for side effects it was 14% and for interactions only nine percent.

A study among 164 pharmacists showed similar results; the pharmacists knew more about uses of herbal remedies than about possible adverse effects, drug interactions and necessary precautions⁶⁰. The average score on the knowledge test was 42% and

pharmacists with previous continuing education or access to information about herbal remedies at their practice site had a significantly higher score than those without.

The studies indicate that health care personnel need more knowledge about herbal remedies and they are all aware of it. The teaching should preferably be part of their basic education and not left to continuing education courses.

1.2 Studies identifying herbal remedy use in pregnancy in the western world

Studies identifying herb use in pregnancy in the western world are given in Appendix B^{8,61-72}. Thirteen studies were identified. Eight were performed in antenatal clinics, two in postnatal ward and three in other settings. Seven used self completed questionnaires, six were interview studies. The amount of herb users varied between 7 and 56%. Two studies did not specify amount of herb users but only users of CAM (Complementary and Alternative Medicine) where herbs are just a part of this. One study showed 96% of herb users but in this study purposeful sampling was used so the percentage is not relevant for comparison.

The most used herb varied between the studies. Raspberry leaf and echinacea were the most frequently used herbs in three studies each and ginger in two. Peppermint, chamomile, cranberry and St. John's wort also had more than 10 % users in at least one study each and many other herbs were used. Nordeng mentions use of as many as 46 different herbs⁷⁰.

Some authors try to characterise "the most common herb user". Forster et al from Australia describe her as older, tertiary educated, English speaking, non-smoker and primiparous⁷². Other Australian and US authors^{61,63,67,71} also mention primigravida, tertiary education and higher age but Nordeng⁷⁰ found fewer users than non-users in the group of 36 years or older and no other significant differences. The profile of the typical user is not well defined.

It is a common belief that herbs in general are safer than pharmaceuticals^{8,9,64,69}. They are described as not really drugs, milder, more natural, simpler, more familiar or having fewer side effects. Hepner et al found that only 14% of the 1203 women studied considered herbs to be “medications” and that significantly more women in that group discontinued herb use when pregnancy was confirmed⁶³.

Indications for herb use during pregnancy are described in six studies^{8,66-68,70,72} and they are mainly nausea and vomiting (NVP), labour preparation, cold/flu, sleep/relax, urinary tract infections (UTI) and digestion aid. Those are all common ailments in pregnancy except from “labour preparation” and some of them can be treated with OTC pharmaceuticals.

The pregnant women took herbal remedies on their own initiative or got recommendations and information from various sources like family and friends, herbal store, health care personnel, alternative practitioners, books/magazines and the internet. Family and friends turned out to be the most important source of information and health care personnel were in most cases far less important^{67,68,70,72}.

Different methods have been used and different questions asked. This makes comparison between the studies difficult and of limited value. When one study treats herbs, other alternative treatments and pharmaceuticals there is a reason to believe that the information on each topic is more superficial than if the study treats only one aspect of treatment during pregnancy. Thus it would be an advantage if a standardised protocol can be used in various countries to compare different cultures and populations.

The main concern expressed by the authors is the lack of documentation of safety and efficacy of herbal remedies in pregnancy^{61,62,64,65,67,68,70,72}. Another point often

mentioned is that health care personnel should identify and monitor use of herbs as well as pharmaceuticals and be able to give evidence based advice to pregnant women^{61,63,66,68,70-72}. The lack of scientific evidence on many of the used herbs makes this a difficult task and the fact that many pregnant women omit telling their health care personnel about herb use makes a pro-active attitude necessary.

1.3 Pregnancy

Pregnancy is timed from the first day of last menstrual period and normally lasts 37-42 weeks (average 40 weeks). It is split in three trimesters: 1st trimester is week 1 – 13, 2nd week 14 – 27 and 3rd week 28 – 40. Organogenesis takes place in the first trimester making the foetus most sensitive to any compounds ingested by the mother in this period⁷³.

When referring to the condition of a newborn baby, “Apgar score” is commonly used. This is a scoring system for heart rate, respiratory effort, muscle tone, reflex irritability and colour. Each characteristic is assigned a value of 0 to 2 points so the total score is 0 to 10. The newborn is evaluated at 1 and 5 minutes after birth. A score of 7 or more is considered normal, 4-6 compromised and 3 or below medical emergency⁷⁴.

1.3.1 Common ailments and treatments

The numerous physiological changes which occur during pregnancy commonly result in a variety of conditions including morning sickness (70%)⁷⁵, insomnia (66-94%)⁷⁶, heartburn (30-50%)⁷⁷, constipation (11-38%)⁷⁸, ankle oedema (12%)⁷⁹, anaemia (14-52% in 3rd trimester)⁸⁰ and urinary tract infection (UTI) by (1 – 13%)⁸¹ amongst others. Various treatments for most of the ailments are available to the pregnant woman.

1.3.1.1 Treatment with pharmaceuticals

No pharmaceuticals are licensed for use to treat NVP but some products, considered to be safe due to experience over time, are used when the condition reaches a certain level of severity. First choice when dietary and lifestyle measures have turned out insufficient would normally be Vitamin B6. If this also turns out insufficient, metoclopramide will be next in line in some countries⁸² and antihistamines in other (Paper I). If metoclopramide fails to relieve the NVP, ondansetron is recommended⁸². In some cases the NVP develops to *hyperemesis gravidarum*. If that happens, intravenous antiemetics and rehydration therapy will be necessary and in severe cases also total parenteral nutrition.

Insomnia can be expected to occur in the 3rd trimester due to hormonal and mechanical changes in the body and does not normally need pharmacological treatment but rather life style changes with more focus on “sleep-hygiene”⁷⁶. If treatment is necessary, diphenhydramine (an antihistamine) is recommended by Briggs⁸³ but contraindicated in 3rd trimester by Schaefer⁸².

Heartburn can in most cases be relieved with antacids. Aluminium-, calcium- and magnesium-containing antacids and sucralfate are considered safe in recommended doses and are thus first choice⁷⁷. If symptoms persist, histamin₂-receptor antagonists like ranitidine or famotidine can be used according to Richter, Schaefer and Briggs^{77,82,83} though the manufacturers advice to avoid use in pregnancy⁸⁴.

Constipation is according to a Cochrane review from 2001 best treated with fibre supplements⁷⁸. If they turn out inefficient, a stimulant laxative is preferred according

to Jewell⁷⁸ while Schaefer⁸² recommends lactulose before stimulant laxatives like bisacodyl. The manufacturers describe lactulose as a suitable laxative for pregnant women due to minimal absorption. They also state that years of clinical experience have shown that neither the pregnancy nor the foetus nor the newborn are influenced by the mother's use of bisacodyl.

Ankle oedema alone should not be treated pharmacologically in pregnancy⁷⁰. If associated with raised blood pressure it can be an indication of pre-eclampsia but otherwise it is of no danger but only discomfort⁸⁵.

Anaemia is commonly and safely treated with iron supplements⁸². Some women may experience gastrointestinal discomfort from Iron(II) salts and might benefit from hem-iron (haemoglobin bound iron) instead.

UTI are common in pregnancy and should be treated with antibiotics to avoid pyelonephritis (see 1.1.4.2). Penicillins are the antibiotics of choice in pregnancy⁸².

For conditions like NVP and insomnia where dietary or lifestyle changes are recommended before pharmaceuticals some women will find it natural to turn to herbal remedies. The gastrointestinal discomfort of iron supplements might have the same effect as might fear of taking antibiotics and the doctor's unwillingness to treat ankle oedema.

1.3.1.2 Herbal and other alternative treatments

In the treatment of NVP various advices on diet and life style are given by health care personnel. The most common are to eat regular, small meals to keep the blood sugar level stable, to start the day with dry biscuits and eat them whenever nausea comes or to avoid food which triggers nausea. No scientific documentation is available for the efficacy of those methods. The most common herbal remedy is ginger. Ginger is tested in nine clinical trials and considered to be safe in the recommended doses, better than placebo and just as effective as Vitamin B6 (see 1.1.5.1). It is used in different forms like fresh in food or drink, dry for brewing tea or in capsules or as biscuits, ale or beer. Ginger is part of the normal diet in many countries, easily obtained from the supermarket and as such a simple “first choice”. Peppermint tea and chamomile tea are also used but no scientific documentation is available⁸⁶.

Other alternative treatments are acupressure and homeopathy. Acupressure is commonly performed by use of “sea sickness” bands, which are wrist bands working on an acupressure point on the inner wrist but can be performed manually as well⁸⁷. True double-blind trials of acupressure are difficult to perform as a placebo-treatment for comparison is difficult to obtain but reviews from 1998 and 2005 concluded that evidence for beneficial effects was found and that no harm could be done as acupressure points for uterine stimulation are located far from the so called P6 point used for relief of NVP^{30,88}.

Homeopathy is also used but due to the theories of homeopathy, different women might need different preparations and self-treatment is thus not easy⁸⁹. Trials of homeopathy are also difficult to perform due to the theories of individual treatments so no scientific evidence for the effect is available⁸⁹.

Common herbal treatments for insomnia are chamomile tea, valerian and lemon balm. Scientific documentation of the efficacy or safety of chamomile and lemon balm in pregnancy is not available⁴⁸. Like other composite plants chamomile causes a risk of allergic reactions^{90,91}. Two reviews conclude that valerian may improve sleep quality

but methodologic flaws of the included studies limit the value of the conclusions^{92,93}. The safety of the treatment is inadequately documented (see Paper I).

Other alternative treatments are relaxation techniques and homeopathy.

Heartburn and indigestion is also often treated with ginger but no scientific documentation is available. Other undocumented herbal treatments are chamomile, caraway and fennel seeds.

Other alternative treatments are available, but none are very common.

Constipation is best treated with water and fibre. Herbs like senna and frangula are not recommended during pregnancy⁴⁸ and not commonly used either according to the available studies.

Other alternative treatments are available, but none are very common.

Ankle oedema is commonly treated by rest and elevation of the feet. Diuretic herbs like horsetail and dandelion are used by some women and horse chestnut by others. No scientific documentation is available about safety or efficacy of horsetail or dandelion in pregnancy. Horse chestnut seed has been shown to reduce symptoms of chronic venous insufficiency like swelling in the legs⁹⁴ but no data on safety in pregnancy are available. A Cochrane review from 2007 found two small studies showing that compression stockings had no effect on ankle oedema but that reflexology appeared to help improve symptoms better than rest⁸⁵.

The herbal iron supplement Floradix® seems to be well known and used to prevent or treat anaemia in Europe⁷⁰. It is also reported to be recommended by midwives in the US⁹⁵ but no pregnant women have reported use (see Appendix B). Floradix® contains 20 different herbs and fruit juices at very low levels together with iron and vitamins in recommended amounts and consequently it can be used safely in pregnancy⁹⁶.

Urinary tract infections are sought treated with cranberry, dandelion, horsetail or bearberry. Cranberry causes an anti-adherence effect on the bladder mucosa making it difficult for the bacteria to adhere⁹⁷ and can possibly prevent recurrent infections³³ but is not effective as a treatment⁴². The safety in pregnancy is not well documented. The effect of dandelion and horsetail is believed to be diuretic but documentation for safety and efficacy in pregnancy is lacking and a diuretic is not an adequate treatment for UTI. A preliminary study from 1993 showed that a combination of bearberry and dandelion might reduce the recurrence rate of UTI in women⁹⁸ but no further documentation is available and the safety is not documented either.

1.4 Why is it important to study herb use in pregnancy?

Herbs have been used in pregnancy all through history. Knowledge about herbs has been passed on between generations and all times have had their herbal healers. As time went by, the knowledge and experience was collected and books like Culpepper's Complete Herbal and English Physician⁹⁹ or Gerard's herbal¹⁰⁰ came up. Very little evidence based knowledge is available even now.

The challenge in pregnancy is to use only remedies which are safe for both mother and foetus. It is important to get to know which herbs are commonly used and by whom because when more is known about that, it is possible to do research on those herbs and gain evidence of safety and efficacy.

A solution might be to warn against all herb use in pregnancy, but due to long traditions and fear of unwanted effects of pharmaceuticals it is not possible to keep pregnant women from using herbs. It is probably not necessary either but more knowledge is needed before health care personnel can recommend herbs and discuss herb use with pregnant women on an evidence base.

1.5 Pharmacoepidemiology – a brief introduction

Pharmacoepidemiology is the study of the use of and the effects of drugs in large numbers of people¹⁰¹. The major use of pharmacoepidemiology is in post marketing drug surveillance and the subject has developed since the Thalidomide® disaster in the early 1960s. Post marketing surveillance is routinely performed by as well authorities as manufacturers of drugs. The aim is to gain supplementary information about the drug like more precise information about incidence of known adverse and beneficial effects, information from patient groups not studied pre marketing, knowledge about interactions, comparison to other drugs for similar indications, discover new (adverse) effects, effect over time, effect of an overdose.

Pharmacoepidemiology contributes to our knowledge about the safety of drug use by applying the methods of epidemiology to the area of clinical pharmacology.

Pharmacoepidemiology is not widely used when it comes to herbal remedies as post marketing surveillance is not performed to any mentionable extent by authorities or manufacturers.

1.5.1 Study designs in pharmacoepidemiology

The various study designs used in pharmacoepidemiology and their advantages and disadvantages are shown in Table 2¹⁰¹.

Table 2 Study designs in pharmacoepidemiology

Design	Description	Advantages	Disadvantages
Case report	Description of an observed event. Single patient	Raise hypothesis	No hypothesis testing
Case series	Description of: - clinical outcomes from a collection of patients exposed to the same drug or - exposures of a collection of patients showing the same symptoms	Raise hypothesis Quantitate incidents	No hypothesis testing
Trend analysis	Trends in exposure which is considered the cause and trends in a disease considered the effect are compared to see if they coincide.	Quickly get an overview of the probability of a hypothesis	Can not be controlled for confounding

Case-control study	Compares cases (with disease) to controls (without disease) and looks for differences in previous exposure.	Study: <ul style="list-style-type: none">- Multiple exposures- Uncommon diseases	Data are possibly biased as they are collected retrospectively
Cohort study	Identifies subsets (exposed/not exposed, different exposition) of a population and follows them over time to look for differences in their outcome.	Study: <ul style="list-style-type: none">- Multiple outcomes- Uncommon exposures	Prospective is time consuming Retrospective causes bias
Randomised clinical trial	Patients are randomly and blindly allocated to treatment or control groups	“Gold standard” Comparable groups Controls for confounders	Expensive Logistically difficult Ethical considerations

1.5.2 Types of errors

Important issues in the described study designs are sample size and bias.

In statistic tests a significance level of 0.05 (or a 95% confidence interval) is commonly applied. To achieve the significance level, a minimum sample size is necessary. Too small samples may give inaccurate results and too large samples will waste resources. Methods for sample size calculations can be found in relevant textbooks¹⁰¹.

Various types of bias can occur in pharmacoepidemiological studies¹⁰².

Selection bias origins from the method of recruitment into the study or to losses to follow up. It is seen when groups of subjects who differ from those in the target population are selected into the study. One way is if the referral to the study is related to drug exposure status (referral bias). Another is self selection bias which occurs when a participant herself decides to participate in or leave the study (this might be the case in the survey described in Chapter 2 – women using herbal remedies might more easily choose to participate in the survey about herb use in pregnancy because they have a special interest in the topic. This will lead to an over-estimation of the amount of herb users in the population.).

Information and misclassification bias origins from the classification of a participant with respect to exposure or disease. Two kinds of bias are common in this category: Recall bias is important in retrospective studies – for instance, a mother with an impaired baby may give a more thorough description of her drug use in pregnancy than a mother with a healthy child. Or the recall of the drugs used may be more difficult as time passes. Detection bias occurs when for instance the questioning about exposure is more thorough in cases than in controls.

Confounding occurs when the estimate of a measure of association between variable and outcome is disturbed by an extraneous variable (the confounder) – for instance another pharmaceutical used by the patient.

As well selection bias as information bias will have to be dealt with in the design phase of the study since their presence affects the study validity and can not be compensated afterwards. The effect of confounding can be dealt with in both design and analysis phases.

2. Materials and methods

The studies included in this thesis are based on two different study populations. One study is based on the Swedish Medical Birth Register of 860215 women giving birth between 1995 and 2004. The other studies are based on 578 women attending antenatal care at the Norfolk and Norwich University Hospital between November 2007 and February 2008.

2.1 The database study (Paper I)

2.1.1 Aim

To study characteristics of women using herbal remedies in early pregnancy and the possible impact of this use on pregnancy outcome.

2.1.2 Study population

The Swedish Medical Birth Register collects data on antenatal care, pregnancy and outcome of birth from nearly all deliveries in Sweden and the quality of the data has been evaluated at various times^{103,104}. The study includes all births registered between 1st of July 1995 and 31st of December 2004. The register was complete for 2004 at the time of study. In total 860215 women gave birth to 872377 infants during the study period.

2.1.3 Data collection

The data in the register are based on copies of the original medical records which are identical all over Sweden. Swedish women usually come to antenatal clinic before

they are 12 weeks pregnant, and during this first visit they are interviewed by a midwife. Among many questions, they are asked about smoking habits and the use of drugs – specified as prescription drugs, OTC drugs and herbal remedies. This means that the information mainly refers to first trimester use. Drug names are recorded in clear text and are later recoded into therapeutic classes according to the Anatomical Therapeutic Chemical Classification System for drugs (ATC)¹⁰⁵ but as very few herbal products have such codes, the names in the register remain mainly as clear text. Data for maternal education as an indication for social level were obtained by linkage with the Central Register of Education (Statistics Sweden) but were only available for births up to and including 2001. Additional data for congenital malformations were obtained from the Register of Congenital Malformations and from the Hospital Discharge Register.

2.1.4 Variables

The descriptive variables studied were:

- Maternal age at pregnancy (<25, 25-34, ≥ 35 years).
- Maternal parity (a woman having her first infant is said to be parity 1, divided into parity 1, 2, 3, and 4 or more).
- Maternal smoking (unknown, none, <10 cigarettes per day, 10 or more cigarettes per day).
- Previous miscarriages (none, 1, 2, 3 or more).
- Involuntary childlessness (number of years the couple has tried for the woman to become pregnant, none, 1, 2, 3, 4, 5 or more).
- Mother's country of birth (Sweden, other Nordic country, non-Nordic country).
- Maternal BMI (Body Mass Index, < 19.8, 19.8 – 25.9, 26.0 – 29.9, ≥ 30.0, ≥ 26.0).
- Maternal education level (only available up to and including 2001, unknown, ≤ 9, 10 – 13, 14 – 15, ≥ 16 years).

The outcome variables studied were:

- Number of infants in pregnancy.
- Preterm delivery defined as born before 37th week. (Only singleton infants).
- Low birth weight defined as less than 2500 g. (Only singleton infants).
- “Small for gestation age” (SGA) defined as less than 2 standard deviations below expected weight¹⁵. (Only singleton infants).
- “Large for gestation age” (LGA) defined as more than 2 standard deviations above expected weight¹⁵. (Only singleton infants).
- Low Apgar score (< 7) at 5 minutes.
- Congenital malformations (Relative severe malformations means that infants with only the following malformation diagnoses are not counted as malformed: Patent ductus arteriosus in a preterm infant, preauricular appendix, undescended testicle, unstable hip, tongue tie, single umbilical artery, nevus).

2.2. Survey (paper II and III)

2.2.1 Aim

To describe the use and the user of herbal remedies during pregnancy and to evaluate this use with reference to literature. To study the sources of information about herbs used and if possible to identify the most probable users by comparing characteristics for women using herbal preparations during pregnancy to those not using herbal preparations.

2.2.2 Study population

Expectant mothers at least 20 weeks pregnant presenting at the antenatal clinics held within Norfolk and Norwich University Hospital teaching hospital between 26th of

November 2007 and 15th of February 2008 made up the study population. 1037 questionnaires were handed out and 578 were returned.

2.2.3 Data collection

The women were asked by the clinic receptionist if they would care to have a word with the pharmacist about some research while they waited. If they approached the pharmacist in the waiting room, they were explained the aim of the study and given a patient information leaflet, a questionnaire and a stamped addressed envelope.

The survey was based on a questionnaire developed by Nordeng at the University of Oslo, Norway⁷⁰. To clarify what kind of remedies the study was concerned about, the following definition of an “herbal preparation or medicine” was given in the questionnaire: “any kind of product, such as a tablet, a mixture, an ointment or herbal teas which are produced from plants and used to acquire better health”. See Appendix C for original questionnaire.

2.2.4 Variables

The following sociodemographic and lifestyle data were collected:

- Year of birth.
- Number of pregnancies prior to this one.
- Marital status.
- Smoking during pregnancy.
- Medicines taken regularly.
- Education level.
- Occupation (if housewife, partner’s occupation).
- Payment for prescription medicines (as a proxy for social status).

Other variables studied were:

-
- Prior use of herbal remedies with specific questions regarding 9 different herbs:
 - Echinacea (coneflower).
 - Floradix®.
 - Ginger.
 - Chamomile.
 - Valerian.
 - Cranberry.
 - Horsetail.
 - Raspberry leaf.
 - St. John's wort.

These herbs were originally selected because they (except from raspberry leaf) were the ones with an authorisation as herbal medicinal products according to the Norwegian legislation. Raspberry leaf was known to be used especially in pregnancy. For each product participants were asked if they were aware of it and if so – whether they had used it during pregnancy and if so – what condition they had used it for, when during pregnancy (trimester) and for how long time. An open question about other herbal remedies used was also included. Participants who had used herbal remedies were asked about:

- Who recommended it to them.
- Whether or not they had told their doctor about the use.

All participants were asked:

- If they had other children that were breastfed and if so:
 - If they had used herbal remedies to increase milk production.
- Whether they expected to use herbs in the future.
- Where they would go/look for information about herbs in the future.
- Medical conditions experienced during pregnancy, when experienced and how treated:
 - Nausea, vomiting or morning sickness (NVP).

- Fatigue.
- Indigestion or heartburn.
- Common cold.
- UTI.
- Swollen ankles.
- Other conditions – specify condition, time and treatment.

Three statements from the “Beliefs about medicines questionnaire”¹⁰⁶ were included to evaluate the participants’ attitudes towards medicines and herbs. The statements were answered on a 5 point Likert scale from “Strongly agree” to “Strongly disagree”.

- Medicines do more harm than good.
- Natural remedies are safer than medicines.
- If doctors had more time with patients they would prescribe fewer medicines.

2.3 Focus group discussion (Paper IV)

2.3.1 Aim

To gain a better understanding of women’s reasons for use of herbal remedies during pregnancy.

2.3.2 Study population

All participants in the survey were also invited to claim their interest in the focus group discussions by submitting, in a separate envelope, name, address, phone number and information about whether they had used herbs in pregnancy or not.

Thirty four users and 18 non-users were interested in participating. The intention was to have two focus group discussions – one for users and one for non-users. All non-users and 18 randomly selected users were invited for the focus group discussions.

Only one non-user was willing to attend so this focus group discussion never took place. Seven users agreed to attend and six participated.

2.3.3 Data collection

The focus group discussion took place at the University of East Anglia, Norwich, UK. A moderator (Ph.D. student) and her academic supervisor were present.

The discussion was recorded on two digital recorders and transcribed verbatim.

2.3.4 Variables

The attendees were asked to provide explanations for the following results from the survey:

- 57.8 % used one or more herbal remedies during pregnancy compared to non-UK studies which found between 4.1 – 56 %.
- Users of herbal remedies tended to “Disagree” that “Medicines do more harm than good”.
- The most important source of information about herbal remedies actually used during pregnancy was “Family and friends”.
- The use of herbal tea to increase production of breast milk was rare (3.3 % compared to 43.3 % in Norway).
- Only 4.5 % reported taking Iron supplements against fatigue.

Attendees were also asked to clarify the following:

- Is ginger a herbal remedy – why or why not?
- Why use herbal remedies at all when we have lots of medicines available both OTC and on prescription?
 - Safety.

- Efficacy.
- Cost.

2.4 Review (Paper V)

The electronic databases PubMed, ISI Web of Science, Natural Medicines Comprehensive Database and Cochrane Library were searched. The search words: “safety” or “efficacy” in combination with “pregnant” or “pregnancy” in combination with “raspberry” or “*Rubus idaeus*” were used. Articles with focus on safety or efficacy during pregnancy, pharmacology and in vitro tests explaining mode of action were selected. Another search with the words “raspberry” or “*Rubus idaeus*” and “constituents” was performed and articles with focus on constituents in *Rubus idaeus* (not other *Rubus* sp) were selected. References in the literature found were also studied.

The aim of this study was to review the literature about safety, efficacy, constituents and possible modes of action of raspberry leaf in pregnancy.

2.5 Statistic and other methods of analysis used

2.5.1 For the database study

Women who had used herbal drugs were compared to all women who had given birth during the study period. Infants of the first group were compared to infants of the second. Mantel-Haenszel procedure was used to estimate odds ratio (OR) and 95% confidence intervals (95% CI) were determined using Miettinen’s method¹⁰⁷.

2.5.2 For the survey

Chi-square tests were used to analyse univariate associations between variables. A significance level of 0.05 was applied.

Logistic regression was used to study associations between sociodemographic and lifestyle-variables and use of herbal remedies during pregnancy. Forward logistic regression analysis was used to generate models. Variables related to use of herbal remedies with significance level of 0.05 or greater were included into the model. Interaction factors were included in addition to single variables where appropriate.

The statistical analyses were performed using Statistical Packages for Social Sciences (SPSS) version 15.

2.5.3 For the focus group

The transcript was analysed according to Colaizzi's method of content analysis¹⁰⁸.

- Read the transcript to acquire a feeling for it.
- Review the transcript to extract significant statements.
- Formulate meanings for each significant statement.
- Organize the formulated meanings into clusters of themes.
 - Refer the clusters back to the original protocol to validate them.
 - Note discrepancies among and/or between the clusters.
- Integrate the results into a description of the phenomenon under study.

The transcripts and the extracted themes were sent to the participants to validate the interpretation and to obtain further comments.

Four criteria have been suggested as the “gold standard” for establishing trustworthiness of qualitative data: credibility, dependability, confirmability and transferability¹⁰⁹. To achieve credibility each of the members of the focus group were asked to comment on the researcher's interpretation of the data. Co-author David Wright listened to the tape and scrutinised the transcripts to achieve dependability and

confirmability. Transferability was enhanced by including women unrelated to one another and coming from different parts of Norfolk. It was supported by inclusion of verbatim quotes in the manuscript to be published to allow the reader to evaluate.

3. Main results

This thesis is based on three different studies, two of which are related, and a review. One study is based on data from 860215 women in the Swedish Medical Birth Register. The second study is based on a survey among 578 women at the Norfolk and Norwich University Hospital and the third study is based on a focus group discussion between 6 women from the same population.

The main findings in this thesis were:

Data from survey and focus group discussion among women from Norfolk:

- 57.8% (334 women) of the participants 20 weeks or more pregnant had used herbs and the usage was 1-10 herbs pr woman.
- The most commonly used herbs were ginger, cranberry and raspberry leaf, see Figure 1 (numbers according to question 2-11, see appendix C).
- Herbal galactagogues had been used by only 3.3%.
- Family and friends were the most used source of information about herbs used in pregnancy, see Figure 2, and more than 75% did not inform their doctor or midwife about the herb use.
- Nausea and vomiting (NVP) was the condition most commonly treated with herbs and overall the pregnancy-related condition most commonly treated.
- 41 different herbs were reported used, 96 different indications were given for the use and only 50 of those could be confirmed in literature as “traditionally used”. The most used herbs and the reasons for use are given in Table 3 (numbers adjusted according to questions 17-23).
- 41.2% of the participants had used potentially harmful herbs or herbs for which the documentation for safety in pregnancy was inadequate.

- Of all 578 participants 232 (40.1%) had used pharmaceuticals sometime during pregnancy AND herbs sometime during pregnancy. Seventy one (12.3%) used drugs regularly AND used herbs sometime during pregnancy.
- The typical user had been pregnant before and had a university degree.
- Significantly more users (45.2%) than non-users (33.2%) of herbs in pregnancy agreed with the statement “If doctors had more time with patients they would prescribe fewer medicines”.
- The users of herbs expected herb use in pregnancy to be an “underground” thing.
- The users relied on family and friends for information – they did not expect doctors to be interested in or knowledgeable about herbs and found it difficult to evaluate the reputability of alternative practitioners so avoided them.
- The users knew that documentation for safety of herbs was inadequate but considered them to be safer than pharmaceuticals anyway.
- The users wanted the NHS (National Health Service, UK) to be more open minded.

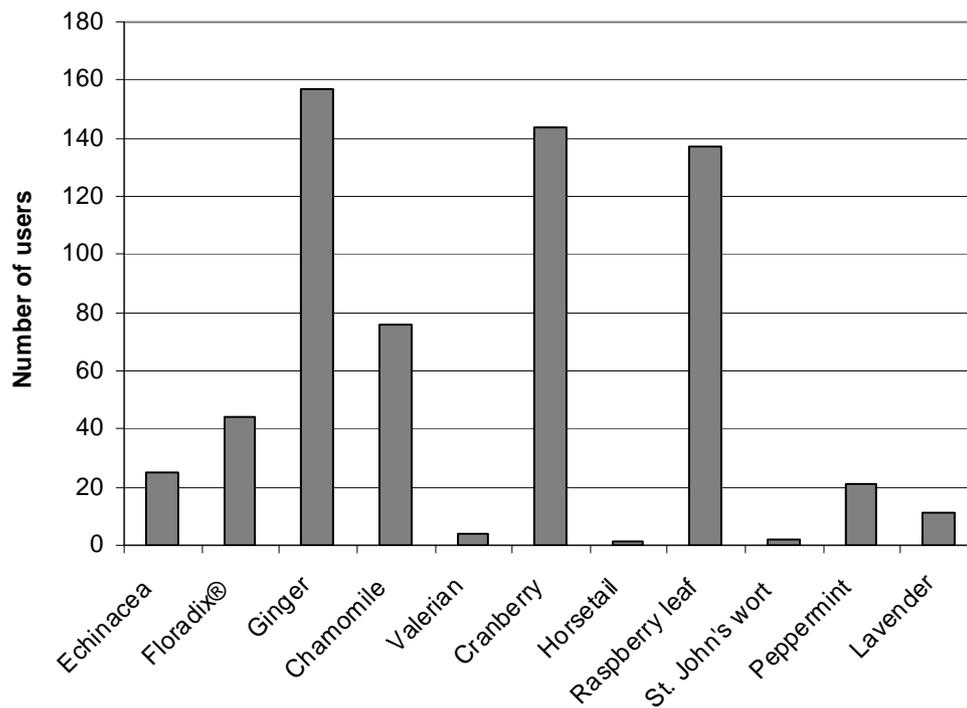


Figure 1. Number of users of the various herbs (survey.)

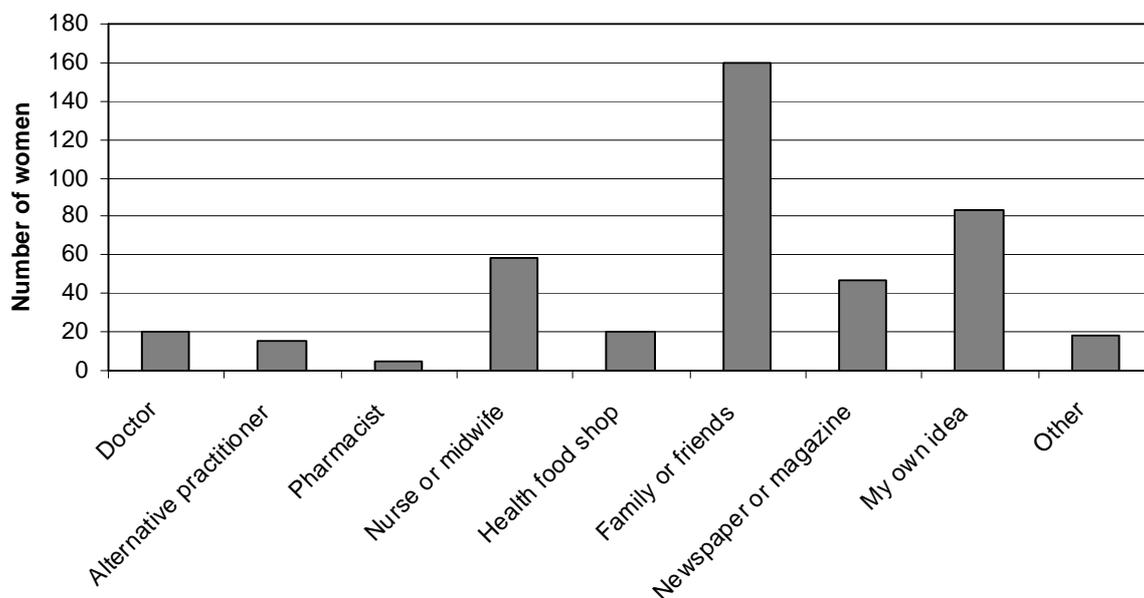


Figure 2. Sources of information used about the herbs used during pregnancy in the survey

Table 3. The most commonly used herbs and the reasons for use (n=578)

Plant	Users	Most commonly reported reasons for use (no)
Ginger (<i>Zingiber officinalis</i>)	194 (33.6%)	Morning sickness (107) Nausea (37) NVP (35) Indigestion (9) Other, confirmed (7) Other, not confirmed (12)
Cranberry (<i>Vaccinium macrocarpon</i>)	146 (25.3%)	Treat UTI (69) Prevent UTI (23) Vaginal thrush* (7) Other, confirmed (2) Other, not confirmed (12)
Raspberry leaf (<i>Rubus idaeus</i>)	137 (23.7%)	Induce and ease labour (59) Tone/prepare uterus for labour (18) Soften/prepare cervix (10) Strengthen uterus (6) Other, confirmed (4) Other, not confirmed (8)
Chamomile, German (<i>Matricaria recutita</i>)	76 (13.1%)	Relax (26) Sleep (14)
And Chamomile, Roman (<i>Chamaemelum nobile</i>)		Calming (7) Other, confirmed (8) Other, not confirmed (2)

*Indications marked with * could not be confirmed in literature. NVP = nausea and vomiting in pregnancy, UTI = urinary tract infections. Numbers may not add up as each person could use one herb for more than one purpose.

Data from the Swedish Medical Birth Register:

- 0.9% (787 women) of the population had used herbs during the first 12 weeks of pregnancy and the usage was 1-3 herbs pr woman.
- The typical user was 35 years or older and had 14-15 years of education (Bachelors degree).
- The most commonly used herbs were Floradix® (iron rich herbs), ginseng and valerian, see Figure 3.
- Concomitant drug use was common.
- None of the infant characteristics studied were influenced significantly by the herb use.

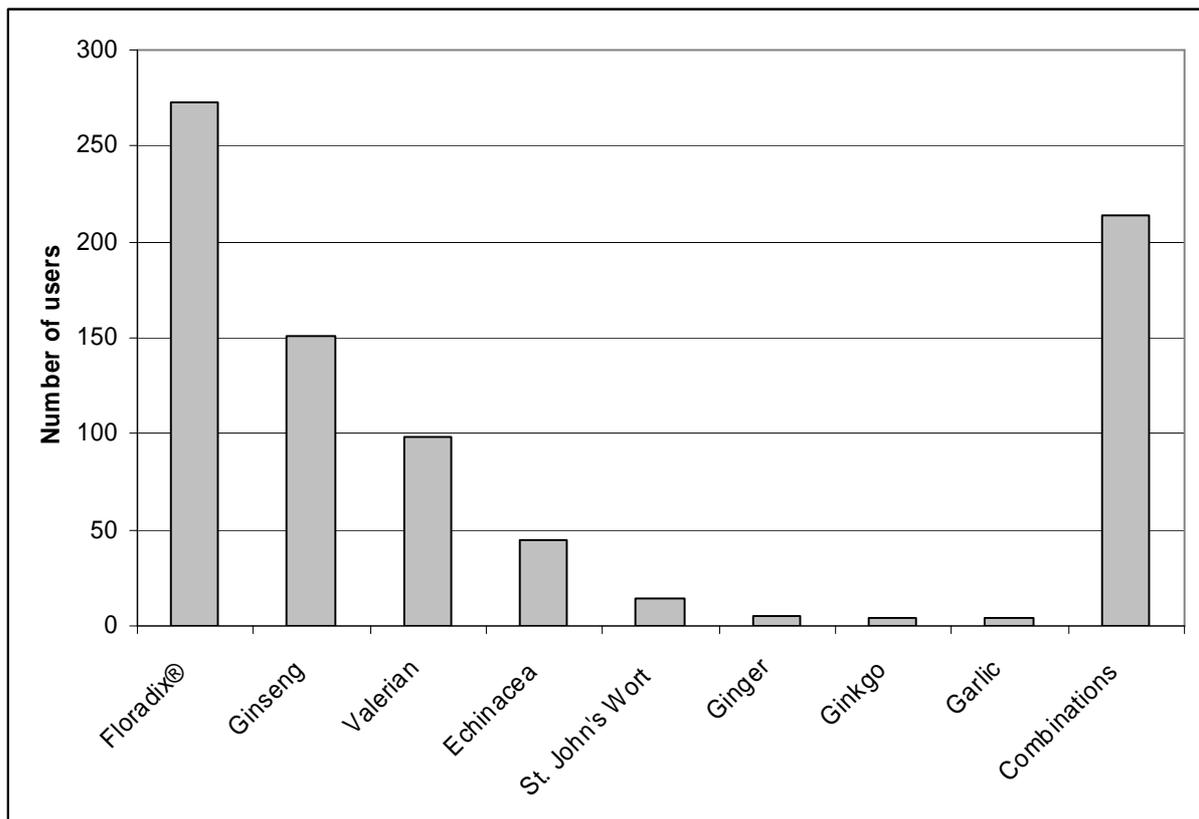


Figure 3. Number of users of the various herbs (database study).

Review

- Raspberry leaf tea has traditionally been used to relieve nausea, strengthen, tone or prepare uterus, soften or prepare cervix and induce or ease labour. This use is described in old herbals.
- The first scientific documentation known is from 1941. It was found that toned smooth muscles were relaxed by raspberry leaf while relaxed muscles were contracted. The active constituent was not identified.
- Even in 2002 neither active constituents nor mode of action are known.
- A retrospective study from 1998/1999 and a clinical trial from 2001/2002 showed no adverse effects on mother or baby but no statistically significant effects either.
- Trend (insignificant) towards reduced likelihood of need for artificial rupture of membranes was discovered in the test group as well as mentionable shorter duration of respectively the first stage and the second stage of labour in the two studies.

4. General discussion

4.1 Comparisons between studies

A list of studies of herb use in pregnancy in the western world from 2001 to 2008 are given in Appendix B. Ten out of the 13 studies are relevant for comparison to the studies in this thesis (see 1.2.1). Eight of those were performed in antenatal clinic, one in postnatal ward and one was a mail survey. Five studies were interview studies and five used self completed questionnaires. Four were from Australia, four from the US, one from Norway and one from Italy. The studies by Nordeng (Norway)⁷⁰ and Forster (Australia)⁷² were the only ones designed specifically to study use of herbs in pregnancy – the other studies also included other alternative treatments, dietary supplements or prescription and OTC drugs. Forster was the only one to look into reasons for herb use in pregnancy⁷². The percentage of users in the studies varied between 7 and 56.

In the database study (Paper I) only 0.9% of the women had used herbs during the first 12 weeks of pregnancy. This number is low compared to the other studies and it does not seem probable that such a big difference should be found between Norway (36% reported use)⁷⁰ and Sweden, but various explanations for the findings can be discussed. One explanation can be that the results describe use early in pregnancy. It can be argued that NVP is common at this time and one would expect more than 0.6% of the women to use ginger to treat it but NVP is commonly treated with antihistamines in Sweden¹¹⁰. This means that the women will not be left with only dietary advice to treat the most common condition in early pregnancy and it is probable that fewer will try herbal remedies. Another explanation can be that though all women were questioned according to a standard national questionnaire, they were questioned by different midwives with different attitudes towards herbs. Reporting of herb use was not the main aim of the questioning and it is not known how detailed the

questioning was (information bias discussed in 4.2.1.2). There is a good reason to believe that the herb use is under-reported in this study and it would be interesting to perform a survey similar to the one performed at Norfolk and Norwich University Hospital in a Swedish hospital.

In the survey (Paper II and III) 57.8% of the women, who were at least 20 weeks pregnant reported use of herbs. This percentage is comparable to other similar studies^{8,66,68} but higher than most. One possible explanation can be selection bias as discussed in 4.2.2.1

The most used herbal remedy in the database study, Floradix®, was used by 34.7% of the herb users compared to 12.8% in the survey, 11.8% in the Norwegian study⁷⁰ and no reports in any other study. National differences and year(s) of data collection can possibly explain part of this finding. Just like all other phenomena in a community, various herbal remedies are popular at various times. Floradix® is a German product and the way to Scandinavia and the UK has probably been shorter and easier than the way to the USA or Australia explaining why this product was used to such a high extent in Sweden between 1995 and 2004, in the UK in 2007-8 and in Norway in 2003-4 while not reported used in the USA and Australia at all at the same time.

A description of “the typical herb user” would be very convenient as it would enable health care personnel to be more alert when interviewing “her” about drug use and herb use in pregnancy but it is difficult to find. In the database study she was 35 years or older and had 14-15 years of education (Bachelors degree) while in the survey she had been pregnant before and had a university degree. Other studies found “the typical user” to be:

- Younger than 36⁷⁰.
- Primigravada, married, having tertiary education⁶⁷.

-
- Prior user of herbs. Trend (not significant): white, at least college education⁶¹.
 - Trend (not significant): 41 – 50 years old⁶³.
 - Higher age, have a degree, English as first language, non-smoker, primigravida⁷².

All together it seems sensible to conclude that higher age and higher education indicate higher probability for herb use in pregnancy but as the Norwegian study⁷⁰ found an opposition to this, all pregnant women should be interviewed closely about their eventual herb use. Unpublished data from the focus group discussion showed that three out of six women used herbs because they were brought up to do it while one got scared of side effects of pharmaceuticals from seeing her mother getting cancer treatment. This also indicates that it can be difficult to describe a typical user from demographic data and thus that all women should be interviewed.

Many different herbs were reported used. The survey showed 41 different herbs which is comparable to the 46 found in the Norwegian study⁷⁰. The use of potentially harmful herbs or herbs for which the documentation for safety in pregnancy is inadequate is also similar in the two studies; 41.2% in this survey and 39% in the Norwegian study⁷⁰. This mainly reflects the lack of safety documentation of herbal remedies in pregnancy and not a documented risk of harm.

Forty eight percent of the reasons given for use of the herbs in the survey were not confirmed in literature on traditional or modern use of herbal remedies^{1,48}. This gives rise to concern because it is impossible to evaluate whether potential benefit outweighs potential risk. The majority of those not described reasons are given by just one or a few women but the use of cranberry to treat vaginal thrush is mentioned by 7 women. Thrush is a fungal infection most commonly caused by *Candida albicans*. A weak effect of cranberry on *Candida albicans* in urine is shown¹¹¹ but nothing is found about bioavailability or effect on vaginal thrush.

Concomitant use of herbs and pharmaceuticals was described in both studies. Such use is also described in other studies^{8,62} and causes a risk of interactions. No potentially serious interactions were identified in the survey but in the database study concomitant use of valerian and psycholeptics was reported by 12 out of 98 users of valerian. This combination may cause excessive sedation¹.

The most important source of information about the herbs used during pregnancy was “family and friends”. This is similar to findings in other studies^{67,68,70,72}. The women in the focus group explained this by the expected lack of knowledge among health care personnel, the difficulty in finding a reputable alternative practitioner and the desire to get information from as many people as possible and then making up their mind (see below).

Herbal galactagogues were used by only 3.3% of the 241 women who had prior children that were breastfed. This is very little compared to the 43.3% reported in the Norwegian study⁷⁰. According to the women in the focus group many British women found breastfeeding inconvenient and gave up early. Some suggested that knowledge about herbal galactagogues would be useful for those women but others in the group thought that it would be considered “a nightmare” because it would somehow force women to continue trying to breastfeed. The effect of herbal galactagogues is not well documented and should not be encouraged according to Nordeng⁷⁰.

The focus group discussion (Paper IV) was performed to get a better understanding of the women’s attitudes towards herbs and reasons for choosing herbal remedies instead of pharmaceuticals. A belief in herbs as natural and thus safe was expressed. The lack of scientific documentation and the fact that anything with an effect can have side effects was acknowledged but the belief in safety was stronger.

The women did not believe that doctors or other health care personnel were interested in herbs or had any particular knowledge about them – they rather expected them to disapprove of herb use and thus did not discuss their herb use with them. The expected lack of knowledge is documented in various studies (see 1.1.7) indicating that health care personnel should learn more about herbal remedies to be able to give advice^{46,57-60}. On the other hand the women found it difficult to find a reputable alternative practitioner due to the lack of regulation of those (only therapists of chiropractic and osteopathy are regulated in the UK by now, but the Department of Health works to regulate acupuncture, herbal medicine and traditional Chinese medicine practitioners as well within a year or two). Still they wanted the NHS to be more open minded and to include alternative practitioners in their services. Though they described doctors as “drug pushers” unwilling to listen to them and discuss treatment alternatives, they seemed to trust the NHS to be able to select reputable alternative practitioners for collaboration. This seems somehow contradictory but is possibly based on a wish to be responsible for own health, be involved in decisions, consider all possible treatments and still feel safe. The NHS is considered the guarantor for this safety.

The literature review in papers III and V show that there is a lack of scientific documentation of the safety and efficacy of many herbs commonly used in pregnancy. This is also described in chapter 1.1. Raspberry leaf has been used in pregnancy for a very long time and some practitioners consider this an adequate documentation for safety; “if it was not safe, we would have known by now”¹¹². Others recommend avoidance of a herb in pregnancy until positive evidence for safety is available⁴⁹. Health care personnel have to give evidence based advice but this is not available for most herbs both due to the lack of clinical trials or other studies of efficacy and safety and due to the lack of pharmacovigilance which is not compulsory for herbal products yet (see 1.1).

4.2 Limitations and methodological considerations

4.2.1 *The database study*

The use of data from an established database in research is common when quantitative data are wanted. The Swedish Medical Birth Register consists of data from standard interviews of pregnant women at their first antenatal visit before they are 12 weeks pregnant. The advantages of an established database compared to a survey are that a large sample is available to ensure the validity of prevalence estimates (in this case more than 800.000 pregnant women) and that money as well as time is saved. A disadvantage is that questions are already asked, so the study must adapt to that and not *vice versa*.

4.2.1.1 Selection bias

na.

4.2.1.2 Information bias

The main concern in the database study is the possible incomplete registration of herb use caused by the varying interest in or concern about herbal remedies among the midwives interviewing the pregnant women. The incomplete registration will cause some exposed women to be registered as unexposed which will bias the associations and risk estimates and thus reduce the potential for identifying an existing association. The large number of women in the study increases the statistical power and might outweigh the bias.

The fact that the interviews are performed before the outcome of pregnancy is known makes exposure information prospective in relation to outcome and eliminates recall bias caused by the outcome.

4.2.1.3 Confounding

Adjustment for confounding factors was performed with respect to maternal age, year of pregnancy, parity, smoking and previous miscarriages according to experience at the Swedish Medical Birth Register.

4.2.1.4 External validity of results

The Swedish Medical Birth Register collects data on antenatal care, pregnancy and outcome of birth from nearly all deliveries in Sweden. The data are based on copies of the original medical records which are identical all over Sweden. Antenatal care is free of charge and nearly all women attend this service. The only disadvantage is that record of herb use is taken at the first visit around 12th pregnancy week and no data are available about use later in pregnancy. This means that the data can not be used as an estimate of the prevalence of herb use. Though the first trimester is the period of organogenesis the bias mentioned above (4.2.1.2) makes conclusions about safety of the used herbs uncertain.

4.2.2 The survey

Surveys generally involve the systematic, structured questioning of a statistically valid sample of people¹¹³. The sample for this survey was calculated from results from a study by Nordeng⁷⁰ showing that 36% of the study population used herbal remedies, an acceptable standard error of +/- 2% and the following mathematics:

$$SE = \sqrt{\frac{p(100-p)}{n}} \text{ (according to Haraldsen}^{114}\text{) showing that a sample size } n = 600$$

would satisfy the conditions.

A survey can be undertaken as a self-completed questionnaire or as a structured interview. It involves no active intervention by the investigator. In this case a self-completed questionnaire was chosen because it was considered an appropriate way to obtain the descriptive information needed, it was less labour consuming and possible

for a person with English as a second language to perform within the dedicated time period.

4.2.2.1 Selection bias

The bias of concern is “self selection bias” – the women in the study have chosen to participate (submit the completed questionnaire) and women using herbal remedies might be more prone to participate in a survey about herb use in pregnancy because they have a special interest in the topic. This will lead to an over-estimation of the amount of herb users in the population.

4.2.2.2 Information bias

Like in the database study, the questionnaires were completed before outcome of pregnancy was known thus eliminating recall bias caused by this. Recall bias caused by time is not considered very important as the period of time is not very long and as both herb/disease specific and open ended questions were asked.

4.2.2.3 Confounding

In paper II, multivariate logistic regression was used to control for confounding. Variables related to use of herbal remedies with significance level of 0.05 or greater were included into the model. Interaction factors were included in addition to single variables where appropriate.

4.2.2.4 External validity of results

Sample size was calculated according to known parameters and statistical methods and should therefore be adequate. The study was carried out in the antenatal clinic of one hospital in one region of the UK and though women from both rural and urban areas come to this clinic the respondents may not be representative of the pregnant

population in the UK. The results may also not be generalisable with a 56% response rate.

4.2.3 The focus group discussion

A focus group discussion is a group interview technique for collection of qualitative data. It is commonly known from marketing research but also useful in other disciplines where knowledge about peoples' views, experiences, concerns and priorities is sought to explain behaviour. It is the intention that participants shall interact with one another in discussing the selected issues and forming opinions like people do in everyday life. In this way points relevant for the issues discussed will come clear as more or less important in the group. It is common to have more than one group discussion on an issue to make sure that all relevant points come up. One advantage of the method is that many different points come up and are discussed but of course some participants might feel less comfortable in the situation and thus not participate as eagerly as others. To compensate for that, focus group discussions are sometimes combined with individual interviews. In this case two focus group discussions were planned but only one was held as the possible participants of the other were unable to attend or no longer interested. This means that the issue is not completely studied, but the points which came up are considered important for the care of pregnant women and should thus be published for health care personnel.

The main concern in the focus group study is the fact that only one focus group discussion was performed. This is a disadvantage (see 2.6.3) and the study must be considered a pilot study.

5. Conclusions and future perspectives

More than half of the women in the survey from the Norfolk and Norwich University Hospital used herbs during pregnancy and more than 75% of the users reported that they did not inform their health care provider about the use. The focus group discussion gave an explanation to why women omit informing health care personnel: The women expected or had experienced a negative attitude to herbs among health care personnel – *“I went to ask mine (midwife) about raspberry leaf and she practically laughed me out of the office”* - and did not expect them to have any knowledge about herbs either.

It is still not possible to describe “the typical herb user” so all pregnant women should be asked about herb use and health care personnel should be able to give evidence based advice on the use. To do this it is necessary to have knowledge about as well traditional use as scientific documentation. Unfortunately; with few exceptions there is still a lack of well-conducted studies on the safety and efficacy of herbs in pregnancy.

Data from the Swedish Medical Birth Register did not indicate any influence on premature birth, birth weight, small or large for gestational age, Apgar score or congenital malformations of the newborn from maternal use of specific herbs during first trimester. The number of registered exposures, however, was low and it is not known how thoroughly the “herbal drug history” was taken in each case so this study does not document the safety of the used herbs and probably not the degree of herb usage either.

The studies performed for this thesis and similar studies in other countries show which herbs pregnant women use and form the base of future work with many

challenges. The first one is to design and perform studies to document as well safety as efficacy of herbs during pregnancy. Controlled clinical trials are preferred but will probably be difficult for practical as well as economical and ethical reasons so prospective observational studies regarding herbal remedy usage and pregnancy outcome are warranted to determine safety.

The existing and relatively new EU legislation allows sale of many herbal products as “food supplements”. This does not prompt further studies of safety or efficacy or the development of evidence based patient information leaflets. When a product can be marketed as a food supplement after a notification to the relevant authorities there are few good reasons for manufacturers to collect documentation or even do clinical trials with all the involved costs, to acquire a marketing authorisation for a herbal product as a traditional or well established herbal medicinal product.

The six women in the focus group were all aware of the lack of scientific safety documentation of their herb use. Anyway they were certain that herbs were generally safer than pharmaceuticals and that even though some herbs had side effects, the herbs they used were safe. Here is another challenge for the future – communication of scientific data to the public. Preliminary data from the survey were presented at the British Pharmaceutical Conference 2008 and a journalist from Daily Mail quoted part of it in the newspaper. Nine comments from readers were added during the first day after publication. They ranged from “More scare stories to get people to give up herbal supplements” to “Herbal remedies can be as potent as pharmacy medicine and should be avoided in pregnancy because unborn babies can be affected by these as much as any other medicine” and included women’s’ own experience as “documentation” for safety. This shows that the way we communicate the results and recommendations is crucial.

The way information is communicated is related to the competence of the person who gives the information. A third challenge for the future is to introduce more education about herbal remedies in the training of health care personnel. For pharmacists this can be done by (re)introducing relevant courses in pharmacognosy in the curriculum and for other groups of health care personnel courses might need to be extended or developed. As the base of this education has to be scientific this leads back to the first challenge; it is necessary to do research to gain more knowledge about the safety and efficacy of herbs in pregnant women.

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APPENDIX A

Clinical trials and other human studies of herbal products used in pregnancy

Author and year of publication	Dose and duration	Number of participants test:control	Safety	Efficacy
Ginger				
Fischer-Rasmussen et al ¹⁹ 1990	1 g dry rhizome a day for 4 days	30 (cross-over)	No side effects.	More effective against symptoms of <i>hyperemesis gravidarum</i> than placebo.
Vutyavanich et al ²⁰ 2001	1 g dry rhizome a day for 4 days	32:38	No adverse effect on pregnancy outcome detected.	More effective against nausea and vomiting than placebo.
Keating & Chez ²¹ 2002	1 g dry rhizome a day for 2 weeks	14:12	No significant side effects (but too few participants to reveal uncommon effects).	May be useful in some patients experiencing nausea and vomiting.
Sripamote & Lekhyananda ²² 2003	1,5 g dry rhizome a day for 3 days	64:64	No significant side effects (but too few participants to reveal uncommon effects).	Equivalent to Vitamin B6 against nausea and vomiting

Willetts et al ²³ 2003	500 mg extract equal to 6 g rhizome a day for 4 days + 4 days (ginger for both groups)	60:60	No significant differences in outcome, but as both groups got ginger for the extra 4 days, there is no untreated control group.	More effective against nausea than placebo.
Portnoi et al ²⁴ 2003	Various doses, in 39% of cases combined with pharmaceuticals, used for 3 days or longer.	187:187 (prospective)	No significant differences in outcome.	Capsules more effective than other forms. Almost half of the women found ginger totally ineffective.
Smith et al ²⁵ 2004	1050 mg dry rhizome a day for 3 weeks	146:145	No differences between groups for complications or outcome.	Equivalent to Vitamin B6 against nausea and vomiting
Chittumma et al ²⁶ 2007	650 mg dry rhizome 3 times daily for 4 days	61:62	No significant difference in number of patients experiencing side effects. Side effects were all minor.	Significantly greater reduction in nausea vomiting score than Vitamin B6

Pongroj paw et al ²⁷ 2007	0.5 g dry ginger 2 times daily for 7 days	85:85		Ginger is as effective as dimenhydrinate in treatment of NVP and has fewer side effects.
Ensiyeh & Sakineh ²⁸ 2008	0.5 g dry ginger 2 times daily for 4 days	35:35	No adverse effects were seen.	Significantly greater reduction in nausea score than Vitamin B6
Cranberry				
Wing et al ³³ 2008	240 ml 27% cranberry juice (special formulation) vs placebo (special formulation), 3 times daily (red. to 2 times), from w16	58:67:63 (3 doses:1 + 2placebo: 3 placebo)	No differences between the groups with regard to obstetric or neonatal outcomes.	Trend towards fewer UTI's with multiple daily doses vs placebo and a weaker trend for a single daily dose.
Raspberry leaf				
Parsons et al ³⁷ 1999	Various doses, duration 1 – 32 weeks	57:51 (retrospective)	No identified adverse effects	Some effect on shortening labour and less “mechanical assistance”.

				(not statistically significant)
Simpson et al ³⁸ 2001	Tablets, 2 x 1.2 g a day, from 32 weeks until labour.	96:96	No adverse effects	Did not shorten first stage of labour, but second with 9.59 min., lower rate of forceps delivery (not statistically significant)
Echinacea				
Gallo & Koren 2000	Doses: Tablets 250 – 1000 mg/day. Tincture 5 – 30 drops/day. Duration 5-7 days.	206:206 (prospective)	No significant difference in abortions or malformations.	na
St. John's wort				
Grush et al 1998	900 mg a day, from 24 weeks until labour	1 (case)	No adverse effects	na

APPENDIX B

Summary of studies identifying herbal medicine use in pregnancy

	Gibson et al 2001	Tsui et al 2001	Hepner et al 2002	Hollyer et al 2002	Pinn et al 2002	Byrne et al 2002	Maats et al 2002
Country	USA	USA	USA	Canada	Australia	Australia	Australia
Location	Antenatal clinic	Antenatal clinic	Mail	Helpline	Antenatal clinic	Antenatal ward	Antenatal clinic
Method	Survey	Survey	Survey	Survey	Survey	Interview	Interview
N	250	150	1203	70	305	48	211
% reported using herbal medicines	9	13	7	61.2 (CAM)	12	56	33.6/20.4/23.2 1 st /2 nd /3 rd trimester
Chamomile	X				2.7	44.4	12.7/30.2/26.5
Peppermint	X					25.9	
Ginger	X	6.7	9.6	50.7	8.1	33.3	59.2/20.9/4.1
Echinacea	X	8.9	36.5		5.4	3.7	2.8/9.3/6.1
Ginseng	X		9.6			3.7	
Pregnancy tea		8.9					
Raspberry leaf		4.4			21.6	18.5	5.6/9.3/34.7
Cranberry			7.7				
Ginkgo			9.6				
Evening Primrose			9.6		8.1		
St. Johns Wort			19.2		8.1	3.7	
Valerian			5.8		2.7	7.4	
Golden seal					2.7		
Barley					2.7		
Miso paste					2.7		

Noni juice	2.7	
Parsley	2.7	
Chinese herbs	13.5	
Slippery elm		3.7
Dandelion		3.7
Tea for sleep		3.7
Unspecified	13.5	3.7
Cocoa butter		
Licorice		
Green tea		
Witch hazel		
Kava kava		
alfalfa		
Blue cohosh		
Broccoli		
Cannabis		
Castor oil		
Coconut oil		
Fenugreek seed		
Nettle		
Oat straw		
Partridge berry		
leaf		
Yellow dock		
Iron rich herbs		
(Floradix ®)		

Horse tail

Elderberry

Almond oil

Propolis

Fennel

Mauve

The percentages given for each herbal product is percent of herb-users using this specific herb unless otherwise indicated. Some women use more than one herb.

Cont.

	Glover et al 2003	Westfall 2003	Nordeng et al 2004	Refuerzo et al 2005	Forster et al 2006	Lapi et al 2008
Country	USA	Canada	Norway	USA	Australia	Italy
Location	Rural obstetric clinic	Various	Post-natal ward	Post-natal ward	Antenatal clinic	Antenatal ward
Method	Interview	Interview	Interview	Survey	Survey	Interview
N	578	27	400	418	588	150
% reported using herbal medicines	45.2	96	36	4.1 (CAM)	36	48
Chamomile	4.6	7.7	9.0		30.1	4.2
Peppermint	39.8	23.1				
Ginger	1.9	23.1	10.4	0.2 ¹	32.1	
Echinacea	3.1	11.5	22.9		8.0	
Ginseng	5.4		X	1 ¹		
Pregnancy tea	17.6		6.9			
Raspberry leaf	2.3	84.6	X		39.2	
Cranberry	28.7	3.8	8.3		24.1	
Ginkgo	3.1			0.5 ¹		
Evening Primrose		7.7			5.2	
St. Johns Wort	1.9		X			4.2
Valerian						
Golden seal						
Barley						
Miso paste						
Noni juice						

Parsley			
Chinese herbs			3.8
Slippery elm			4.2
Dandelion		3.8	
Tea for sleep			
Unspecified	2.7		4.2
Cocoa butter	15.3		
Licorice	6.9		0.5 ¹
Green tea	6.1		
Witch hazel	2.3		
Kava kava	1.1		
alfalfa		15.4	
Blue cohosh		11.5	
Broccoli		3.8	
Cannabis		3.8	
Castor oil		7.7	
Coconut oil		3.8	
Fenugreek seed		7.7	
Nettle		34.6	
Oat straw		3.8	
Partridge berry		7.7	
leaf			
Yellow dock		7.7	
Iron rich herbs			11.8
(Floradix ®)			
Horse tail			5.6

Elderberry	5.6	
Almond oil		27.8
Propolis		19.4
Fennel		15.3
Mauve		

The percentages given for each herbal product is percent of herb-users using this specific herb unless otherwise indicated. Some women use more than one herb.

¹ % of n = 418

APPENDIX C

Questionnaire for the survey

Use of herbal medicines during pregnancy

Project led by Mrs Lone Holst
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Mr Rick Adams Clinical pharmacist, Norfolk & Norwich University
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Guidance for completion

A 'herbal preparation or medicine' is defined as any kind of product, such as a tablet, a mixture, an ointment or herbal teas, which are produced from plants and used to acquire better health.

- The questionnaire has been designed to take no more than 5-10 minutes to complete
- The questionnaire does not require your name for completion
- All responses will be reported anonymously
- Please tick only one box for each question unless requested to do otherwise
- Once you have completed the questionnaire, please place it in the prepaid envelope provided
- If you have any questions then please contact Lone Holst on 01603 593144

Completing and returning the questionnaire constitutes consent to participate in the study.



Section 1 Your awareness and use of herbal preparations/medicines

This section explores your knowledge and use of herbal preparations.

1. Have you ever used herbal preparations or medicines in the past?

Yes No Unsure/don't remember

Below is a list of herbal preparations. For each of the preparations listed below please complete the following questions:

2. Echinaceae (Coneflower)

Have you heard about the preparation? Yes No

If 'No', go to question 3.

Have you used it during pregnancy? Yes No

If 'No', go to question 3.

What condition(s) did you use/take it for?

When during your pregnancy did you use/take it? Please tick all that apply.

During 1st 3 months During 2nd 3 months

How long did you use/take it for? Approximately _____ days.

3. Iron-rich herbs ('Floradix')

Have you heard about the preparation? Yes No

If 'No', go to question 4.

Have you used it during pregnancy? Yes No

If 'No', go to question 4.

What condition(s) did you use/take it for?

When during your pregnancy did you use/take it? Please tick all that apply.

During 1st 3 months During 2nd 3 months

How long did you use/take it for? Approximately _____ days.

4. Ginger

Have you heard about the preparation? Yes No

If 'No', go to question 5.

Have you used it during pregnancy? Yes No

If 'No', go to question 5.

What condition(s) did you use/take it for?

When during your pregnancy did you use/take it? Please tick all that apply.

During 1st 3 months During 2nd 3 months

How long did you use/take it for? Approximately _____ days.

5. Chamomile

Have you heard about the preparation? Yes No

If 'No', go to question 6.

Have you used it during pregnancy? Yes No

If 'No', go to question 6.

What condition(s) did you use/take it for?

When during your pregnancy did you use/take it? Please tick all that apply.

During 1st 3 months During 2nd 3 months

How long did you use/take it for? Approximately _____ days.

6. Valerian

Have you heard about the preparation? Yes No

If 'No', go to question 7.

Have you used it during pregnancy? Yes No

If 'No', go to question 7.

What condition(s) did you use/take it for?

When during your pregnancy did you use/take it? Please tick all that apply.

During 1st 3 months

During 2nd 3 months

How long did you use/take it for? Approximately _____ days.

7. Cranberry

Have you heard about the preparation? Yes No

If 'No', go to question 8.

Have you used it during pregnancy? Yes No

If 'No', go to question 8.

What condition(s) did you use/take it for?

When during your pregnancy did you use/take it? Please tick all that apply.

During 1st 3 months

During 2nd 3 months

How long did you use/take it for? Approximately _____ days.

8. Horsetail

Have you heard about the preparation? Yes No

If 'No', go to question 9.

Have you used it during pregnancy? Yes No

If 'No', go to question 9.

What condition(s) did you use/take it for?

When during your pregnancy did you use/take it? Please tick all that apply.

During 1st 3 months

During 2nd 3 months

How long did you use/take it for? Approximately _____ days.

9. Raspberry Leaf

Have you heard about the preparation? Yes No

If 'No', go to question 10.

Have you used it during pregnancy? Yes No

If 'No', go to question 10.

What condition(s) did you use/take it for?

When during your pregnancy did you use/take it? Please tick all that apply.

During 1st 3 months During 2nd 3 months

How long did you use/take it for? Approximately _____ days.

10. St John's Wort

Have you heard about the preparation? Yes No

If 'No', go to question 11.

Have you used it during pregnancy? Yes No

If 'No', go to question 11.

What condition(s) did you use/take it for?

When during your pregnancy did you use/take it? Please tick all that apply.

During 1st 3 months During 2nd 3 months

How long did you use/take it for? Approximately _____ days.

11. Did you use any other herbal preparations during pregnancy?

Yes No Unsure/don't remember

If 'Yes', please complete the following table.

Product or plant name	Condition used for	When taken (week of pregnancy)	Duration of use (no. of days)

If you have not used herbal preparations during pregnancy, go to question 14.

12. Who recommended the use of herbal preparations to you? Please tick all that apply.

- | | | | |
|-----------------------|--------------------------|-----------------------|--------------------------|
| Family or friends | <input type="checkbox"/> | Doctor | <input type="checkbox"/> |
| My own idea | <input type="checkbox"/> | Alternative therapist | <input type="checkbox"/> |
| Newspaper or magazine | <input type="checkbox"/> | Pharmacist | <input type="checkbox"/> |
| Health food store | <input type="checkbox"/> | Nurse or midwife | <input type="checkbox"/> |
| Other | <input type="checkbox"/> | Please state: | _____ |

13. Did you inform your general practitioner (GP) about your use of herbal preparations during pregnancy?

- Yes No Unsure/don't remember

14. Do you have other children that were breastfed? Yes No

If 'No', go to question 15.

If 'Yes', did you use herb tea or other herbal preparations to increase production of breast milk?

- Yes No Unsure/don't remember

15. Do you think you will use herbal preparations in the future?

- Yes No Unsure

16. If you want information about herbal preparations, where or from whom would you seek this from? Please indicate your choices by numbering as many as are applicable to you, no. 1 being your first choice.

- | | | | |
|-----------------------|--------------------------|-----------------------|--------------------------|
| Doctor | <input type="checkbox"/> | Health food store | <input type="checkbox"/> |
| Alternative therapist | <input type="checkbox"/> | Family or friends | <input type="checkbox"/> |
| Pharmacist | <input type="checkbox"/> | Newspaper or magazine | <input type="checkbox"/> |
| Nurse or midwife | <input type="checkbox"/> | | |
| Other | <input type="checkbox"/> | Please state: | _____ |

Section 2

Medical conditions experienced during pregnancy and their treatment

This section is to identify what medical conditions you experienced during pregnancy and what treatment, if any, you used.

During your pregnancy, did you experience:

17. Nausea, vomiting or morning sickness?

Yes No Unsure/don't remember

If 'Yes', please complete the following, otherwise go to question 18.

When did you experience it? Please tick all that apply.

During 1st 3 months During 2nd 3 months

Please state how you treated it in the box below:

18. Fatigue? Yes No Unsure/don't remember

If 'Yes', please complete the following, otherwise go to question 19.

When did you experience it? Please tick all that apply.

During 1st 3 months During 2nd 3 months

Please state how you treated it in the box below:

19. Indigestion or heartburn? Yes No Unsure/don't remember

If 'Yes', please complete the following, otherwise go to question 20.

When did you experience it? Please tick all that apply.

During 1st 3 months During 2nd 3 months

Please state how you treated it in the box below:

20. Common Cold? Yes No Unsure/don't remember

If 'Yes', please complete the following, otherwise go to question 21.

When did you experience it? Please tick all that apply.

During 1st 3 months During 2nd 3 months

Please state how you treated it in the box below:

21. Urinary Tract Infection? Yes No Unsure/don't remember

If 'Yes', please complete the following, otherwise go to question 22.

When did you experience it? Please tick all that apply.

During 1st 3 months During 2nd 3 months

Please state how you treated it in the box below:

22. Swollen ankles? Yes No Unsure/don't remember

If 'Yes', please complete the following, otherwise go to question 23.

When did you experience it? Please tick all that apply.

During 1st 3 months During 2nd 3 months

Please state how you treated it in the box below:

23. Have you experienced any other conditions during pregnancy?

If 'Yes', please complete the following table to indicate what other condition(s) you experienced and when, and how you treated it/them, otherwise go to question 24.

Yes No Unsure/don't remember

Condition	Week of pregnancy	Treatment

Section 3 Your opinions about medicines in general

Below are some statements about medicines in general (not only herbal medicines). Please indicate the extent to which you agree or disagree with them by ticking the box which most closely reflects your opinion.

24. Medicines do more harm than good

Strongly agree Agree Uncertain Disagree Strongly disagree

25. Natural remedies are safer than medicines

Strongly agree Agree Uncertain Disagree Strongly disagree

26. If doctors had more time with patients they would prescribe fewer medicines

Strongly agree Agree Uncertain Disagree Strongly disagree

Please complete the following information:

27. Your year of birth: _____

28. Number of pregnancies before this one: _____

29. Marital status: Married/cohabitant Single Other

30. Did you smoke during pregnancy? Not at all Now and then Daily

31. Do you take any medicines regularly?
Yes No

If yes, please complete the following table to indicate which medicine(s) you take and for what condition(s).

Medicine	Condition(s) taken for

32. When did you finish your education?

After completing: GCSEs/'O' levels

'A' levels

University degree

Other

Please state: _____

33. What is your occupation? If you are a housewife and have a partner, please give your partner's occupation.

34. Do you pay for your prescription medicines?

Yes No

Thank you for taking the time to complete this questionnaire.

