Protocol A

Raspberry leaf for use in pregnancy

Scientific Background
Raspberry leaf (*Rubus idaeus*) extract is said to have beneficial effects in pregnancy and labour by toning uterine muscle due to its active constituent, the phytochemical *fragarine*. It may thus shorten labour and reduce the need for medical or surgical intervention during labour/delivery. It is recommended by doctors, midwives, and herbalists in pregnancy-related publications, on websites, and in clinical practice in Australia. However, its claimed efficacy is based largely on popular belief and anecdotal reports, rather than on sound research data. In view of this, we decided to undertake a clinical study to gain more evidence for its benefit during labour.

Aim
To determine if raspberry leaf extract shortens labour and makes labour ‘easier’.

Method
The study will be publicised by means of information leaflets at local GP Practices and two large teaching hospitals in Central England. Volunteers must be aged 18 to 40 years, currently pregnant with a singleton pregnancy, willing to complete a follow-up questionnaire after delivery, and agree to have their hospital records inspected for pregnancy outcome.

Following a pre-enrolment telephone interview by the investigator to explain the study in more detail, check eligibility, and obtain her verbal consent, the woman will be sent a supply of raspberry leaf tablets (1.2 g per tablet) and advised to take two tablets per day, starting from 32 weeks gestation and continuing until the onset of labour. Further supplies will be posted to her as required.

After delivery, the woman will be sent a questionnaire for completion, asking about: the duration of labour; the date, type and quality of delivery (e.g. forceps delivery or caesarean section); and the type of analgesia used, if any (e.g. oral, epidural). Other questions will relate to: whether the trial medication was taken regularly; whether the duration of labour was as she had expected, or longer/shorter; whether she would consider the overall experience of labour to have been ‘easy’, ‘acceptable’ or ‘difficult’; and whether she would use raspberry leaf extract in possible future pregnancies. The investigator will then inspect the woman’s hospital records to verify the outcome of her pregnancy and delivery-related information.

Analysis and Interpretation
The women’s responses to questions relating to the duration, and the overall quality of labour will be analysed, and if the majority women reported satisfaction, it demonstrates that raspberry leaf extract can make a positive contribution to women’s child-bearing experience.
Protocol B

Mefenamic acid for Pain Control in IUD (Intra-Uterine Device) Fittings

Scientific Background
Although approximately 50% of women experience little or no pain during the insertion of an intrauterine contraceptive device, it can be painful for some women, especially if nulliparous. Various strategies to alleviate IUD insertion-related pain have been explored, including non-steroidal anti-inflammatory drugs (NSAIDs), local cervical anaesthetics, para-cervical block and cervical ripening agents. These are usually administered at the time of or after IUD insertion, and have shown varying degrees of success. It would be of interest to determine if NSAIDs given in advance of IUD fitting would be of help.

Aim
To determine whether the administration of mefenamic acid prior to IUD insertion alleviates insertion-related, and/or immediate post-insertion, pain.

Method
Following Research Ethics Committee approval, and distribution of written information about the trial via specialist clinics and GPs, healthy women requesting their first ever IUD will be referred-to and recruited at a large Women’s Health Clinic in Central London. To be eligible, women have to be age 18 and over and free from the usual contraindications to IUDs and mefenamic acid (including past or current pelvic infection, acute cervicitis, and gynaecological abnormalities such as fibroids distorting the uterine cavity). Nulliparous and parous women will be eligible to join. Previous research suggested that 200 participants will be required. At the pre-insertion visit, women will receive further details about the trial, have their eligibility checked, their written consent obtained, and undergo a gynaecological examination. They will be taught how to complete visual analogue scales (VAS) for documenting the degree of pain experienced, where 0 indicates no pain at all and 10 the worst pain imaginable.

On the day of IUD fitting, patients will be seen 1 hour prior to the procedure by a research nurse, who will issue the patient with a trial number, and after opening a corresponding envelope that contains the assignment code chosen at random by computer-generated randomisation charts, administer 500 mg of mefenamic acid or a placebo. Both the trial medication and the placebo will be presented in identical-looking single-product containers, to maintain blinding. All IUD fittings will be carried out in the first 10 days of the menstrual cycle by one of four doctors, highly experienced in this speciality, using a standard Copper-IUD (TCu 380S), a standard insertion procedure, and a tenaculum forceps for stabilizing the uterus. Patients will complete VAS scores prior to IUD insertion (to indicate their anticipated degree of pain), immediately after the IUD is inserted, and at 1 minute and 10 minutes thereafter.

In addition, the doctors will complete a VAS, to indicate their perception of the degree of pain experienced by the patient during the IUD insertion. Further analgesics, if required, will be recorded as will insertion-linked adverse events e.g. vaso-vagal reaction.

Analysis and Interpretation
The VAS scores for the mefenamic acid group, documented at each of the time points specified above, will be compared with those in the placebo group and the differences tested for statistical significance. In addition, the VAS value recorded at the time of insertion will also be compared with that recorded pre-insertion.
Protocol C

Evaluating the net effects of extending the age range for breast screening in the NHS breast screening programme in England from 50-70 years to 47-73 years.

**Background:** Currently women between 50 and 70 years are invited for mammography screening. The government has been committed to extending the age range for a long time, and were persuaded to convert the extension to a randomised controlled trial, which this protocol summarises.

**Aim:** To evaluate the net effects of extending the age range for breast screening in the NHS Breast Screening Programme in England from 50-70 years to 47-73 years.

**Method:** As part of the routine breast screening process, the NHS BSP system creates screening invitation batches and invitations to attend for breast screening are sent out at the same time to all the women in such a batch. In this study invitations will be extended to form batches of women aged 47 to 49 years and 71 to 73 years. One of these batches will be randomly allocated to be invited for screening and the other will not. (Women in either batch will be able to request screening if they would like it.) Existing breast cancer registrations will be obtained in order that women with a breast cancer diagnosis prior to screening invitation can be excluded.

**Data collection:** Relevant data items held on the National Breast Screening System (NBSS) will be downloaded annually for all study participants. Items will include the patient identifiers needed for tracing women on the NHS Central Register (NHSCR) and for women invited for screening, information on screening, assessments and outcomes. All study participants will be traced and flagged at the NHSCR in order to find subsequent breast cancer incidence and mortality.

**Patient information and consent:** As 100% coverage is essential for the scientific validity of the study, the following procedure will be adopted. All women of any age invited for screening will receive an information leaflet about the study enclosed with their invitation for screening and the standard NHS breast screening information booklet (“The Facts”). The leaflet will say that the phasing-in of the age extension is randomised and that researchers will be analysing the results on behalf of the NHSBSP. Consent is implied for those who attend for screening because of the standard procedures of the NHSBSP which uses implied consent, and the information leaflet.

**Outcome:** The outcome will be mortality from breast cancer by age 60 for women having an additional early screen and by age 80 for those having an additional later screen.
Protocol D

Cranial osteopathy for childhood colic.

Scientific Background: All body tissues are constantly going through very subtle rhythmical changes of shape, which are normal and healthy. The skull is capable of accommodating the involuntary motion of the brain but if healthy brain movement is hindered or blocked this can cause problems in the head and in organs and systems anywhere in the body. Through the involuntary motion in the tissues, cranial osteopaths are able to detect the buried traumas and stresses in the body and treat them in a gentle and effective way.

Aim: To compare cranial osteopathic manipulation with no treatment for infants suffering from infantile colic.

Method: The study has been approved by the Local Research Ethics Committee. It is a prospective, randomized, open, controlled trial comparing cranial osteopathic manipulation with no treatment. Infants and their parent(s) will be seen weekly over a 4-week period (total of 5 visits) at a single centre with all treatments given by the same osteopath following his usual clinical practice/management. Eligible infants will be between 1 and 12 weeks of age, no previous osteopathy, have signs of infantile colic and there is no other disease. Infantile colic will be defined as at least 90 min of inconsolable crying per 24 h on 5 out of the previous 7 days (as reported by the parents), with normal behaviour outside of these periods. Inconsolable crying during a colic attack will be when the infants cannot be comforted by being held, rocked or walked, or being soothed in any way. In addition, each infant is required to have displayed typical signs of colic: loud gurgling noises from the abdomen (borborygmi), knees drawn up to the chest, fists clenched and backward bending of the head or trunk.

A written explanation of the objectives of the study will be given to each parent and written consent obtained. The infant can be withdrawn from the study at any time and, if randomized to the control group, osteopathic treatment can be made available, if required, at the end of the study. Parents will keep a daily diary to record the amount of inconsolable crying in every 24 h, the total time spent sleeping, and the time the infant was being held or rocked (taken as an indication of low-level colic). Parents are asked to continue with bringing their infant to the clinic and completing the diary card even if the symptoms of colic resolved during the 4-week period.

Eligible infants will be randomized (using a random number table) into a control and test group. All infants will be brought to the osteopathic clinic once a week for 4 weeks. Equal time will be spent with all participants/parents over the study period. The initial visit and interview will last an hour. Infants in the control group will be given a brief examination with minimal touch. Those in the treated group will receive cranial osteopathic manipulative therapy as required (week 0). Treatment will be individualized, according to clinical findings, and involve standard cranial osteopathic techniques until a palpable release of tensions and dysfunction is achieved. At the four subsequent half-hourly sessions (weeks 1–4), infants in the control group will receive no physical intervention; osteopathic manipulation in the treatment group will be dependent on findings at each visit. All parents will be able to ask questions, discuss their problems and receive counselling from the osteopath at each visit.

Analysis and Interpretation: The two main endpoints are the mean number of hours/24 h spent with colicky crying and the mean number of hours/24 h spent sleeping. For each infant, the difference in these parameters (daily average over the previous week) from weeks 1 to 4 will be calculated and the mean change for each group separately tested for significance using Student’s t-test (paired). In addition, the difference between the means for the two groups will be compared using a two-sample t-test.