Creating an evidence base for clinical care: A randomised controlled study examining the efficacy of dietary therapy for the relief of gastrointestinal symptoms in endometriosis

PROTOCOL – study 1a and 1b. Project: 25358

Contents

1. INVESTIGATORS

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- Dr Judy Moore – Research Nurse
- Prof Mark Morrison - Microbiologist
- Prof Jane Fisher - Psychologist
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- Collaborative partners: Endoactive and Endometriosis Australia

2. LOCATION

Central Clinical School, Alfred Centre, Monash University.

3. PURPOSE OF THE STUDY:

To determine the efficacy of the low FODMAP diet in reducing gastrointestinal symptoms in women with endometriosis experiencing gastrointestinal symptoms.
To determine if changes in gastrointestinal and gynaecological microbiome is associated with gastrointestinal symptoms in patient with endometriosis and whether this is modified by the low FODMAP diet.

4. BACKGROUND:

Endometriosis is a common condition that affects more than 700,000 Australian women, although this number is likely to be far higher owing to delays in diagnosis, misdiagnosis and a lack of research into the domestic burden of the disease[1]. It is associated with severe dysmenorrhoea, menorrhagia, (very painful and heavy periods), chronic abdominal pain, and frequently bowel symptoms similar to those typically associated with irritable bowel syndrome (IBS)[2]. The association between IBS and endometriosis is not new, with difficulties distinguishing the two conditions frequently raised as a clinical concern[3]. Many patients with endometriosis experience abdominal bloating, diarrhoea and/or constipation, common symptoms of IBS, which itself affects up to 15% of the population[4]. When a woman presents with chronic abdominal and/or pelvic symptoms, defining the cause – endometriosis, IBS or both - can be challenging. This dilemma may in part contribute to the average delay of between 6 and 11 years before an eventual diagnosis of endometriosis is made [5, 6].

Endometriosis may be asymptomatic, resulting in subfertility (up to 37% of individuals affected)[7], or it can present with chronic, intractable symptoms characterised by debilitating chronic pain; symptom recurrence; compromised fertility; impaired sexual function, and a substantial reduction in quality of life (QOL). It negatively impacts the families and partners of women affected and costs the country an estimated 7.7 billion annually in healthcare costs, absenteeism and reduced economic participation[8]. Gastrointestinal (GI) complaints such as

diarrhoea and constipation are common among women with endometriosis, affecting up to 90% of patients[9]. Psychological co-morbidities are also common. However, there are few evidence-based treatment options (particularly lifestyle therapies) for these. As such, our research will address a gap in knowledge that is of considerable interest to consumers, namely the efficacy of the low FODMAP diet in the management of GI symptoms associated with endometriosis. Despite the lack of evidence, this diet is regularly prescribed by clinicians and used by patients on account of anecdotal reports of efficacy. Our randomised controlled trial (RCT) of the low FODMAP diet in women with endometriosis and gastrointestinal symptoms will provide high-quality evidence that will inform clinical practice and improve patient outcomes.

There are no RCTs looking at the role of diet in endometriosis, and of the few studies that have looked at food, most were animal or epidemiological studies that examined diet as a risk factor for the development of endometriosis[10]. Only three interventional studies examined diet as a therapeutic intervention in endometriosis. In one, fish oil contributed no difference in recurrence rates compared to placebo[11]. In another, a gluten free diet showed a benefit, although this improvement may have been attributable to the concomitant reduction FODMAP intake[12]. Finally, our team examined the efficacy of a low FODMAP diet in 116 women with IBS +/- endometriosis[13]. This study is described in greater detail below.

Pioneering research from our team that has been replicated by groups world-over has definitively shown that a low FODMAP diet reduces GI symptoms in the majority of IBS patients. FODMAP is an acronym (Fermentable Oligo- Di- and Mono-saccharides And Polyols) that represents a group of short-chain carbohydrates that are poorly absorbed and rapidly fermented in the intestine. These actions promote water movement into the bowel, gas production, and secondary changes in bowel habit and intestinal distension[14]. A FODMAP diet restricts intake of short-chain carbohydrates.

With growing recognition of the overlapping symptoms between endometriosis and IBS; the preponderance of IBS in people with endometriosis (and vice versa); and observations that visceral hypersensitivity (a hallmark feature of IBS) is also present in endometriosis, our team conducted a retrospective, observational study which showed that women with both endometriosis and IBS were more likely to report at least a halving of bowel symptoms after 4 weeks on a low FODMAP diet[13]. While these results were impressive, they were limited by the retrospective design, the lack of laparoscopically confirmed disease and recruitment of patients primarily with IBS symptoms. To improve the diagnosis and treatment of endometriosis, there is also an urgent, unmet need to understand the pathophysiological mechanisms underlying GI symptoms in endometriosis. While GI symptoms may be secondary to extra-genital endometriosis, only 7% of patients have bowel endometrial deposits, suggesting that other pathologies more often predominate[15]. However, at present,

aetiological mechanisms remain elusive.

Alteration of the GI microbiota is considered a key aetiopathological factor in the development of IBS, and there is an increasing interest in the role that intestinal and/or vaginal dysbiosis may play in the pathogenesis of endometriosis.

Differences in gut microbiota have been seen with an interventional low FODMAP diet[19](Halmos 2015), in patients with GI symptoms, but what the influence of this diet would be on microbiota in a woman with both endometriosis and GI symptoms remains to be seen. If intestinal dysbiosis is associated with GI symptoms and endometriosis, will changes be seen in microbiota in these women with the application of the low FODMAP diet?

5. **HYPOTHESES**:

Study 1a; The low FODMAP diet will be efficacious in relieving GI symptoms in women with endometriosis.

Study 1b; Microbiome structure and function will change in response to the low FODMAP diet in women with endometriosis and GI symptoms.

6. **PARTICIPANTS:**

Thirty-two women aged from 18 and over, are pre-menopausal, with endometriosis and concurrent inadequately controlled GI symptoms will be recruited via advertisements, including at gynaecological consultation rooms such as the Monash Health Department of Obstetrics and Gynaecology, The Mercy Health Service, and via support groups such as Endometriosis Australia and Endo-active.

7. INTERVENTION AND STUDY DESIGN:

The study will be a double-blinded, randomised crossover design. Given symptoms are known to vary across the menstrual cycle, baseline data will be collected for the 7 days preceding the due date of their period (days -7 to 0) unless menstrual cycles are hormonally suppressed. If women are hormonally suppressed, data will be collected for the 7 days prior to randomisation and commencement of the study. Participants will complete the symptom and QOL measures as described below. In addition, a daily food and symptom diary and bowel diary will be completed.

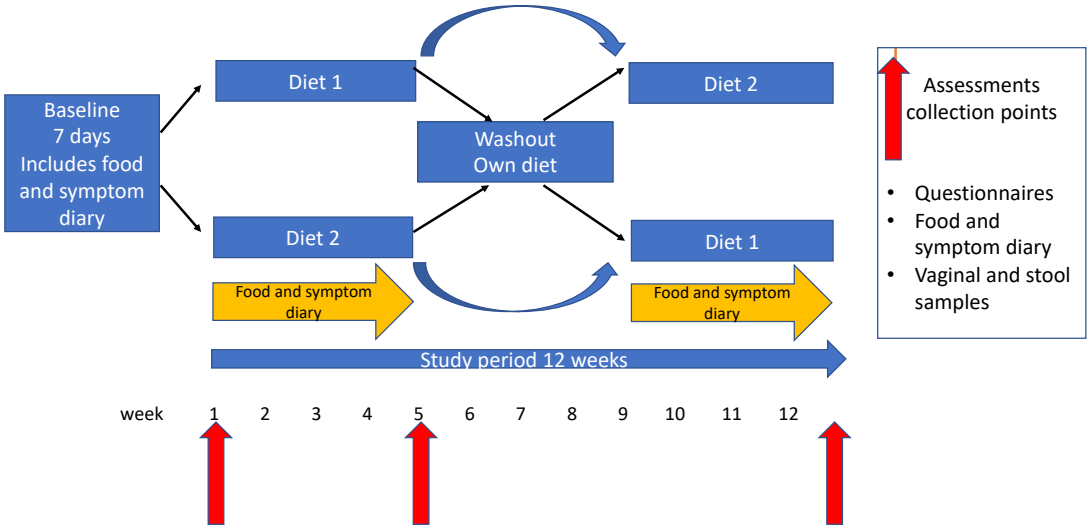
A low FODMAP diet and a control diet will be provided to participants according to the study

design. The 2 test diets will be identical in nutritional needs. The low FODMAP diet will limit oligosaccharide, fructose in excess of glucose, and polyol content to less than 0.5 g per sitting based on previously published data[20]. The control diet will represent a 'typical Australian diet' and mimic the average FODMAP intake of Australians based on a previously validated food frequency questionnaire[21]. To assist with compliance, all food will be prepared by our research chef and dietitian and supplied to the subjects to heat and consume at home. FODMAP containing foods will be masked in the supplied meals to assist with blinding.

Prior to randomisation, following informed signed consent, potential participants will complete the Patient Reported Outcome Measures Information System-Gastrointestinal Symptom Scale (PROMIS-GI) questionnaire, Women's health symptom questionnaire; Endometriosis Health Profile (EHP-30) overall symptom severity Visual Analogue Scale (VAS) Gastrointestinal Quality of Life measure (GIQLI), and the Depression, Anxiety and Stress Scale (DASS – 21) questionnaires. On day 0, eligible participants will be randomised in a 50:50 ratio to a low FODMAP diet or control diet for 28 days (day 0-28). To overcome difficulties with blinding (the low FODMAP diet is well known in Australia) all food will be provided to participants for days 0 – 28 and days 57 – 84. Participants will undergo a washout between days 29 to 56, during which they will consume their habitual diet. Participants will then cross over to the alternate diet, either low FODMAP or control for a further 28 days (day 57 - 84). Participants with hormonally suppressed menstrual cycles can commence the study at any time. Dietary compliance will be assessed using food diaries (proportion of prepared meal consumed and additional food consumed), recorded daily throughout the study. Participants will be given a list of appropriate snacks and drinks that will not interfere with the different diets. Also, throughout the study participants will be instructed to complete a daily bowel habit and symptom diary. On day 28 and day 84 participants will complete the questionnaires listed above again except for the Women's health symptom questionnaire which is for baseline data only. Also on days 28 and 84 participants will collect fresh stool and a vaginal swab which will be immediately frozen for subsequent analysis (see study 1b). Stool and vaginal samples will be collected into Omnigene collection tubes to stabilise microbial DNA (see section 1b below). Detailed instructions on how to collect these samples will be provided.

Analyses of the stool and vaginal microbiota will be undertaken using DNA extracted from these samples by Professor Mark Morrison's group at the University of Queensland (UQ).

Figure 1: Design of Study 1a and 1b.



8. **OUTCOME MEASURES:**

Primary outcome: GI symptom severity as compared at baseline and at the end of each dietary intervention. (symptom VAS score)

Secondary outcomes:

- Specific GI symptoms (PROMIS GI)
- Effect of endometriosis symptoms (EHP-30)
- Quality of life (GIQLI)
- Psychological status (DASS 21)
- Stool microbiota dynamics (study 1b)
- Vaginal microbiota dynamics (study 1b)
- Daily bowel and symptom diary

9. INVESTIGATIVE TECHNIQUES:

Questionnaires

- Overall symptom severity VAS (0-100 where 0 = no symptoms and 100 worst possible)

- PROMIS GI questionnaire (NIH, Spiegel et al 2014)

This validated questionnaire is the *Patient Reported Outcome Measures Information System Gastro-Intestinal Symptom Scale* (PROMIS GI) where overall initial symptom scores will be assessed on the 7 days prior to randomisation.

- Endometriosis Health Profile - (EHP-30)

A validated questionnaire that explores how symptoms of endometriosis affect day to day life

- GIQLI

This is a comprehensive questionnaire on overall GI Quality of Life Indicator as validated by….

- DASS 21 (OEI et al 2014)

Psychological status will be measured by this Depression, Anxiety and Stress Scale; a validated assessment of stress levels.

Pathology (study 1b)

- Stool sample

A fresh stool sample will be collected by the participant into an Omnigene collection tube and immediately frozen for subsequent analysis

- Vaginal swab

A clean vaginal swab will be collected by the participant and placed into an Omnigene tube, and frozen as per stool sample.

10. INCLUSION CRITERIA:

- Women with an existing diagnosis of endometriosis with inadequately controlled gastrointestinal symptoms
- Over age 18, regular periods with a cycle between 24 and 30 days, or on hormonal therapy for endometriosis symptoms
- Women need to show inadequate GI symptom control by answering "no" to the screening question "*Over the past week were your bowel and gut symptoms adequately controlled*?"
- Mean overall symptom VAS score of >30mm.

11. EXCLUSION CRITERIA:

- Women with significant food intolerances and food allergies, e.g. nuts; an overly restricted diet, vegan, or a current history of an eating disorder. Significant concurrent health issues such as diabetes, recent laparoscopic surgery in the last 3 months, past bilateral salpingo-oopherectomy, (removal of both ovaries) coeliac disease and/or other gastrointestinal disease such as inflammatory bowel disease (IBD), bowel resection, malnutrition and active major psychological illness.
- An erratic menstrual cycle.
- Women taking antibiotics and/or probiotics for 4 weeks prior to and/or during the proposed study period.
- Women who are pregnant or planning to become pregnant during the study period.
- Insufficient symptom score in VAS of <30mm symptom severity in baseline week.
- Women already on a low FODMAP diet that are not willing to cease using this diet. (At recruitment women will not be told of the involvement of FODMAPs)
- Insufficient English comprehension requiring use of translator
- Women already undertaking a restricted diet (i.e Vegan, Gluten Free)

12. SAMPLE SIZE CALCULATION AND STATISTICAL ANALYSES

Study 1a and 1b: Data analysis and interpretation: A sample size of 24 will be sufficient to detect a change in overall gastrointestinal symptoms. This number was based on data from studies performed in our department in patients with IBS that produced a standard deviation in overall symptom response of 19mm. Assuming a drop-out rate of ~30% a total of 32 will need to be recruited. Comparisons of measured end-points across treatment periods will be assessed by one-way analysis of variance (ANOVA). Bioinformatics on the microbial results will be conducted at UQ by Professor Morrison's team. The threshold for statistical significance will be set to $p < 0.05$ for all the analyses and corrections for multiple testing by false discovery rate (FDR) with values < 0.05 also considered to be statistically significant. Bonferroni corrections will also be applied to produce adjusted p-values as needed.

13. ETHICAL AND SAFETY RECOMMENDATIONS:

Given the nature of the conditions being examined, and required samples collected it is possible that participants will feel embarrassed discussing their symptoms. Consequently, all interviews will be conducted by a medical professional with detailed knowledge of both endometriosis and gastrointestinal disorders in a private, non-threatening environment.

The diet supplied representing the typical Australian diet may cause GI symptoms, similar or the same as they have been experiencing.

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