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Our aims are to better understand endometriosis-associated pain, improve diagnosis, develop new non-hormonal treatments, and predict response to existing treatments

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Q1 Could you start by telling us about your professional journey and what has driven your long-standing commitment to improving care for women with endometriosis and pelvic pain?

I was born in Edinburgh, went to school there, and later studied at the University of Edinburgh, UK. After I qualified and began working in obstetrics and gynaecology, I realised that if I didn't leave then, I'd end up stuck there. So, I moved to Dublin, Ireland, to work at the Rotunda Maternity Hospital, which was a fantastic experience, and then to London, UK, where time in a large IVF unit at the Hammersmith Hospital sparked my interest in research. I went on to complete a PhD on endometrial biology in the context of infertility at Imperial College London.

When I returned to Edinburgh for a clinical lectureship, my early research focused on ectopic pregnancy and abnormal embryo implantation. But as I finished my training, it became clear to me how poorly we were managing patients with pelvic pain, with or without endometriosis. That realisation led me to set up a multidisciplinary pelvic pain service, and my research evolved alongside it.

Around that time, I met Philippa Saunders, an eminent discovery scientist, based at the University of Edinburgh. Together, we established a research group called EXPPECT Edinburgh, which is a multidisciplinary team focused on endometriosis. Our aims are to better understand endometriosis-associated pain, improve diagnosis, develop new non-hormonal treatments, and predict response to existing treatments. That's how my career has evolved towards endometriosis and pelvic pain.

Q2 Do you still work as a clinician at the moment?

Yes. In the last couple of years, I've become Director of the MRC Centre for Reproductive Health in Edinburgh, UK, which is both a management and strategic role. As a result, I've reduced my clinical sessions, and I now do about a day and a half of clinical work per week, purely focused on endometriosis and pelvic pain.

Q3 Your primary clinical focus is pelvic pain, but do you also see or work with patients whose main issue is infertility related to endometriosis?

We do as a BSGE-accredited endometriosis centre, but we bring in infertility experts for that. We have bi-monthly multidisciplinary meetings where all complex cases are discussed, and fertility specialists are always involved.

I do see patients whose concerns include fertility, but my main focus is pain associated with endometriosis rather than infertility. That said, pain and infertility often go hand in hand, so I inevitably address both.

Q4 Your research spans metabolic therapies, immunomodulation, cannabinoids, diet and lifestyle interventions, biomarker development, and surgical trials. How do you prioritise which strategies to pursue? Or do you see them as complementary parts of a broader strategy?

I see them as complementary. If we can diagnose endometriosis better, we still need to manage it better to improve patients' overall quality of life. Diagnosis and treatment need to move forward together.

To help prioritise our research, about 7 or 8 years ago, we set up a UK and Ireland James Lind Alliance (JLA) Research Priority Setting Partnership for Endometriosis. This was an initiative that brought patients and clinicians together to identify research priorities using a structured process. We generated a top 10 list of research priorities, published them, and shared them widely. Since then, we've used those priorities to guide our research programme.

The main messages from that exercise were the urgent need for better diagnostics and better non-hormonal treatments for endometriosis. That has been the key driver of our work.

> **"If we can diagnose endometriosis better, we still need to manage it better to improve patients' overall quality of life"**

Q5 At the moment, laparoscopy is still the only way to definitively diagnose endometriosis. Are you aiming to move away from surgical diagnosis entirely?

Exactly. The goal is to move away from surgery for diagnosis towards something much less invasive, ideally advanced imaging and/or biomarkers. Ultimately, I suspect it will be a combination: a blood test plus imaging, allowing us to completely dispense with surgery purely for diagnostic purposes.

Q6 You mentioned that your primary research focus is on non-hormonal treatments. One of the major strands of your work is dichloroacetate (DCA). What first convinced you that cellular metabolism might be the 'Achilles heel' of endometriosis lesions? And what have you learned so far from the early studies and feasibility trials?

This started with a PhD student of mine, Vicky Young. She was formally working on a different project but always came with new ideas. One day she said: "I think we should look at metabolism in the context of endometriosis." Her project evolved in that direction.

We began by collecting samples from patients undergoing surgery for endometriosis and comparing them to patients without the disease. We looked at the endometriosis lesions, the peritoneum adjacent to the lesions, and the peritoneal fluid. That's when we identified changes in the metabolic drivers of aerobic glycolysis and, importantly, that peritoneal mesothelial cells in patients with endometriosis produced more lactate than those in women without the condition.

The idea to target lactate came from that observation. We decided to go down a drug repurposing route rather than starting from scratch with a new molecule. We searched the literature for drugs that were already used clinically or in trials to modify lactate levels. Dichloroacetate had been around for 15–20 years as a treatment for rare metabolic disorders in children. It wasn't widely used, but there were safety data. It had also been trialled in other conditions with elevated lactate, such as cardiomyopathy.

> **Our preclinical work focused on women with superficial peritoneal disease**

Because of this, we could move more quickly into an exploratory trial than we would have with a completely new drug. We tested DCA in an initial cohort of 30 patients with endometriosis and saw encouraging results. On the strength of that, we are now exploring it in a randomised, two-centre clinical trial of 100 patients with endometriosis.

Q7 Are you planning to test DCA in a larger sample after this 100-patient trial?

Yes, absolutely. A trial with 100 women will not give a definitive answer. If we continue to see a signal of efficacy in those 100 patients, we will need to move to a multicentre trial across the UK, likely involving around 400 patients, to properly determine whether DCA is effective. So, there is still a long way to go, and it takes time, but that is the trajectory.

Q8 Do you mainly enrol women with Stage I–II endometriosis, or do you also include more advanced disease?

Our preclinical work focused on women with superficial peritoneal disease for two main reasons. First, it's the most common form of endometriosis (accounts for 80%). Second, I actually think it's the most challenging to treat. Many patients who have surgery for superficial peritoneal disease either don't improve or experience recurrence of symptoms.

These patients need alternative treatment options. Interestingly, there is no correlation between the extent of peritoneal disease and symptom severity; someone can have a tiny lesion and very severe symptoms. That suggests that, in this subtype, the lesions are likely more a manifestation of a systemic condition rather than the sole driver of symptoms.

This fits with the idea of endometriosis as a whole-body, systemic condition that may require medical therapy rather than surgery alone. For ovarian and deep endometriosis, surgery often makes more sense, with excision of the disease and potentially medical treatment alongside to reduce recurrence. But for now, our DCA work is focused on superficial peritoneal disease. If it proves effective there, we would then look at ovarian and deep disease as well.

Q9 Beyond the larger trials, what are the key steps required to move DCA from experimental therapy into something that could be offered routinely in clinical practice?

If we demonstrate efficacy in around 400 women in a well-designed trial, that should be sufficient to support incorporation into national guidelines and routine practice.

One challenge is that, because DCA is a repurposed drug, it's less attractive to pharmaceutical companies: the commercial returns are lower, as they don't own the original intellectual property. So we'll need to identify an industry partner willing to support translation into practice.

One strategy might be to pair DCA with a novel vaginal delivery system to reduce systemic side effects. That could create new intellectual property and make it more commercially attractive, while potentially improving tolerability. But before that, we need robust data in the oral formulation.

Q10 What are the main side effects you have seen with DCA?

The main side effect patients reported was tingling in their fingers, a peripheral neuropathy-type symptom. We investigated whether this correlated with DCA levels in the blood and found that it does: the higher the DCA level, the more likely patients were to experience this side effect.

What's particularly interesting is that individuals can be 'slow' or 'fast' metabolisers of DCA, depending on their genotype. This means we can genotype patients and tailor the dose to reduce side effects.

In the next trial, led by my colleague, Lucy Whitaker at the University of Edinburgh, all patients will be genotyped and then prescribed either a lower or higher dose accordingly. The hope is that efficacy will be preserved while the side effect burden is reduced.

The most striking thing was that, in the first exploratory trial, we, as investigators, were more worried about the tingling than the patients were. They generally described it as a mild nuisance rather than a major problem. It resolved when treatment stopped, and there wasn't really a way to relieve it otherwise. But when you compare it with the side effects of some current endometriosis treatments, which can induce menopausal symptoms like hot flushes, night sweats, vaginal dryness, and mood changes, the patients felt that mild

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tingling was relatively minor. Still, we'd like to minimise it through personalised dosing.

Q11 Alongside DCA, you're also evaluating macrophage-targeted immunotherapies, cannabinoids, tinctures, and other approaches. When you look across these programmes, what do you see as the most promising future treatment landscape for patients? How realistically can we move towards mechanism-based therapy?

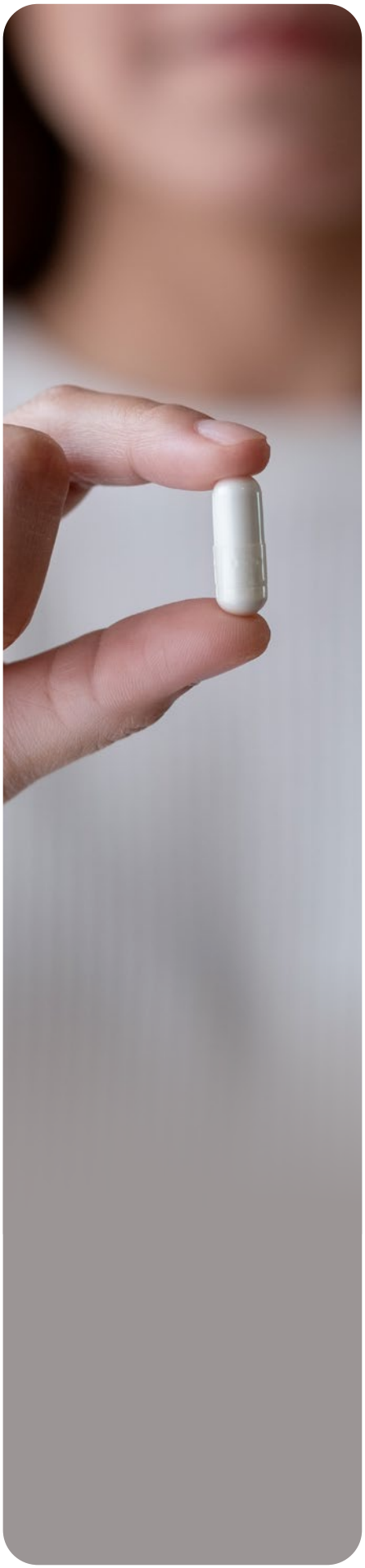
Starting with cannabinoids, our interest began with a large international survey of patients with endometriosis. We were asking primarily about diet and supplements, but we discovered that nearly a third of respondents were using cannabinoids in some form to manage their pain, and many reported good effects.

We then examined whether cannabinoid receptors are expressed in endometriosis lesions and found expression of both CB1 and CB2 in tissue samples. We have a mouse model of induced endometriosis. Mice don't spontaneously menstruate or develop endometriosis, so the Edinburgh team first developed a menstruating model and then injected menstrual tissue from these mice into recipient mice. Those recipients developed lesions very similar to human endometriosis.

Using this model, we tested a CB2 agonist that a pharmaceutical company provided. In mice, it reduced lesion volume and attenuated pain-like behaviours. The drug had originally been developed for rheumatoid arthritis but had not shown sufficient efficacy in late-stage trials. Again, we were exploring repurposing.

Unfortunately, the company then withdrew from women's health altogether, so that route closed. We spent about 18 months looking for alternatives and eventually found a company producing a cannabinoid tincture. Cannabinoids include tetrahydrocannabinol (THC), which causes the 'high', and cannabidiol, which has different mechanisms of action and is now licensed for childhood epilepsy. The tincture we're using contains minimal THC, because we don't want to impair patients' ability to drive or function day-to-day.

We hope this tincture will help with pain and possibly be disease-modifying. The clinical trial design is similar to the DCA study: a two-centre, randomised, placebo-controlled trial in 100 patients. We're aiming to start in February next year and are currently working through regulatory approvals.



Q12 Could you walk us through the macrophage-targeted approach you're now exploring?

We know macrophages play a key role in the development of endometriosis and likely in pain generation. In endometriosis, macrophages take on a phenotype very similar to tumour-associated macrophages, pro-repair rather than pro-inflammatory. In cancer, several therapies are being developed to repolarise macrophages.

We looked at that field and tested a drug called RRx-001, which can repolarise macrophages and also behaves differently in normoxic versus hypoxic environments, both relevant to endometriosis pathology.

Together with my collaborator Erin Greaves at the University of Warwick, UK, we evaluated RRx-001 in a mouse model of endometriosis and found that it reduced disease burden and altered pain-like behaviours. On the back of that, we received funding from the Scottish Government for an early clinical trial.

This will be a small, dose-finding study in 36 patients with endometriosis. It involves weekly intravenous infusions over 6 weeks, each lasting about 2 hours, so it's a high-burden trial in terms of patient time and logistics. We'll be looking closely at tolerability and side effects.

The reassuring thing is that RRx-001 has been tested in head and neck cancer trials, and patients tolerated it well with minimal side effects. We're hopeful that, apart from the inconvenience of regular infusions, patients with endometriosis will also tolerate it well. But it is at a much earlier stage than the DCA and cannabinoid programmes.

Q13 Which of these, DCA, macrophage therapies, or cannabinoids, do you currently see as the most promising?

At the moment, we have the strongest evidence for DCA. Many patients in the initial DCA study reported significant benefits and were very keen to continue the treatment, although, of course, we cannot yet prescribe it outside trials without stronger evidence.

Cannabinoids are also promising, especially since so many patients are already using them informally and reporting benefits. It may be that, in the future, combinations of therapies, metabolic, immunomodulatory, and neuromodulatory, turn out to be most effective.

Q14 Let's switch to diagnostics. There's growing work on biomarkers, wearable sensors, and machine learning approaches to shorten the time to diagnosis. You are recruiting patients into the Endo 1000 project. Can you tell us more about this study and how you think big data can help women receive earlier, better-targeted care?

Endometriosis has historically suffered from a lack of financial investment, which has limited large-scale research. Many studies have been small and underpowered. We need big data to identify patterns that might improve diagnosis and predict treatment responses.

Our ENDO1000 project is designed to address that. We approached this project in a slightly different way than a traditional grant-funded study. From the outset, we wanted it to be an awareness-raising and fundraising campaign, as well as a research project. ENDO1000 is linked to a social media campaign called 'Let's Talk Endo', and we've recruited a number of ENDO1000 ambassadors, including well-known figures from UK radio, television, and sport. Together, we've been raising awareness of endometriosis and the project.

Our financial target is 1 million GBP to fund ENDO1000. We've just passed the halfway point, 500,000 GBP, which has allowed us to start. As the name suggests, we aim to recruit 1,000 individuals with endometriosis and follow them closely for 2 years.

Participants will use our bespoke ENDO1000 app to record detailed information on their symptoms, including pain, bowel symptoms, menstrual cycles, medications, surgeries, and any changes in health. They'll also log self-management strategies, such as dietary changes.

Alongside this, they'll wear a smartwatch to track activity and sleep. We'll send postal kits so they can provide saliva (for genetics), blood (for inflammatory profiling), urine, faeces, and vaginal swabs (to study the microbiome and metabolome). All of this will feed into a large bioresource.

Once we've collated these data, we'll use AI and machine learning to identify patterns that could help us speed up diagnosis and, crucially, predict who is likely to respond to different treatments: surgery, medical therapies, or self-management strategies.

We've just enrolled our first participants, essentially piloting the app over the festive period to ensure everything works smoothly before we publicise more widely.

The initial response has been overwhelming. When we first announced it, we received over 300 emails from patients wanting to take part.

Q15 You recently co-presided over the 15th World Congress on Endometriosis in Edinburgh. Looking back, what themes or shifts in thinking from that meeting excited you most, and which directions do you hope the global community will prioritise over the next decade?

It was a very positive, energising meeting. We'd just emerged from the pandemic, and the community hadn't met in person for some time; the previous Congress had been entirely online. So, there was a real sense of reconnection.

One of the most striking aspects was how multidisciplinary it was: there were sessions on physiotherapy, psychology, and other disciplines, reflecting more holistic approaches to endometriosis care.

The breadth of research was also impressive. There was a lot of emerging work on the microbiome and its potential role in endometriosis, as well as diet. Imaging was another big theme: both novel imaging modalities and more advanced use of transvaginal ultrasound to improve diagnosis. There were also important advances in our understanding of the aetiology and genetics of endometriosis.

That meeting was followed by another major conference led by the World Endometriosis Society (WES) in Sydney, Australia, in May, and we're keeping that momentum going. I've just become President of WES, and we'll be hosting the next major conference in Istanbul, Türkiye in June 2027. The aim is to maintain that sense of progress, share new ideas, and keep the global community connected.

Q16 In your own clinic, what do you currently offer when a patient with suspected endometriosis comes to see you? Is it still mainly hormonal treatments?

At the moment, broadly speaking, we offer analgesics and a range of different hormonal options. Some of these are very effective, but patients often have to try several different treatments to find one that works for them and has acceptable side effects. We also offer surgery where appropriate, particularly for deep and ovarian disease, and we incorporate non-pharmacological approaches such as physiotherapy and psychological support.

Again, this is where a project like ENDO1000 may help us in the future by identifying which treatments are most likely to be effective, and best tolerated, in particular groups of patients, so we can move towards more personalised care.

Q17 Finally, looking ahead, what are the next big research questions for your group? How do you hope your current and future work will change what you can say to a woman sitting in your clinic in 5 to 10 years' time?

We're currently developing a project called ENABLE with the University of Oxford, UK, that will compare seven different hormonal treatments for endometriosis. It's not funded yet, so we're in the process of convincing funders. The idea is to run a large, multicentre trial across the UK.

Traditionally, hormonal treatments have been tested individually against placebo, but rarely head-to-head. Our aim is to compare them directly to determine which are most effective and, just as importantly, which have the fewest side effects. A primary outcome will be Patients' Global Impression of Change (PGIC), their overall assessment of how the treatment affects them.

This would be a very large trial, likely involving over 2,000 patients. The challenge will be both securing funding and delivering such a big study, but we think it's essential.

Looking ahead 5–10 years, my hope is that when a woman sits in front of me with suspected or confirmed endometriosis, I'll be able to offer her non-hormonal, mechanism-based treatments with good evidence behind them, and that I'll be able to personalise her treatment using biomarkers and big-data insights to minimise side effects and improve outcomes. Just as importantly, I want us to reach the point where we can diagnose endometriosis earlier and without surgery, so women are no longer waiting years for answers.

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