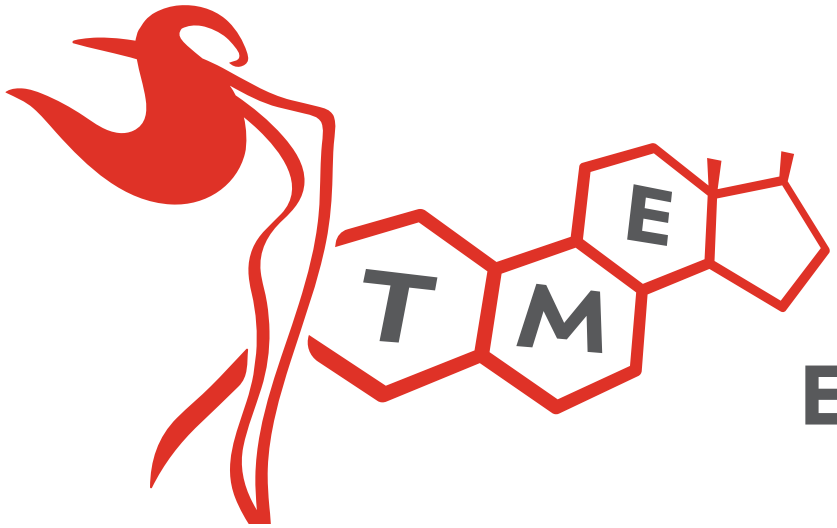

TRANSLATIONAL MOLECULAR ENDOCRINOLOGY

BOOK OF ABSTRACTS 2026

Organized by the Program group P3-0449 of the Faculty of Medicine, University of Ljubljana and the Association of Gynecologists and Obstetricians of Slovenia.

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3. Scientific meeting Translational Molecular Endocrinology

23rd September 2026

Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia

BOOK OF ABSTRACTS

Dear Colleagues,

The annual scientific meetings on Translational Molecular Endocrinology have become a tradition.

We are delighted that, at the 3rd scientific meeting "**Translational Molecular Endocrinology**", a number of renowned speakers from across Europe (Belgium, Finland, South Africa, Sweden, Switzerland, the United Kingdom, the USA, and Slovenia) will share their cutting-edge research. In addition to nine invited talks, the programme includes eight short oral presentations and 11 poster presentations. We are pleased that this year we are introducing the Elsevier JSBMB Award for the best poster, which will be selected by the Poster Award Committee.

The meeting will include four sessions, three scientific and one patient-oriented session. In the first session, **Models for Hormone-dependent Diseases**, different complex models of the endometrium, uterine diseases and ovarian cancer will be presented – from primary cells derived from menstrual blood or ectopic tissue, organoids to patient-derived explants – together with their application in studying decidualisation effects, treatment response and local steroid metabolism.

The second session focuses on the **Molecular Mechanisms of Hormone-dependent Diseases**. The invited talks will cover a broad range of topics, from steroidomics and transcriptomics analyses revealing hormonal regulation in the endometrium, to multimodal profiling for individualised treatment for ovarian cancer, and potential new treatments for polyendocrine metabolic ovarian syndrome. The short oral presentations will include examples of microbiome analysis in patients with adenomyosis, options for drug repurposing in ovarian cancer, lifestyle interventions in polyendocrine metabolic ovarian syndrome, and androgen metabolism focusing on 11-oxygenated metabolites in prostate cancer.

Diagnostic and Prognostic Biomarkers of Hormone-dependent Diseases are the topic of the third session. We will gain new insights into the circulating proteome from blood drops, liquid biopsy in endometrial cancer, the diagnostic potential of altered androgen production in endometriosis, as well as models integrating soluble immune checkpoints and multimodal biomarkers for the prognosis and diagnosis of endometrial cancer, respectively.

In the final session, **Research on Hormone-Dependent Diseases – Patients' Perspectives**, the Daily Centre for Endometriosis at University Medical Centre Ljubljana and the Association Europa Donna, which also supports patients with gynaecological cancers, will be introduced.

The meeting provides a platform for Slovenian, EU and non-EU groups of researchers and clinicians to present their current studies, exchange knowledge in translational molecular endocrinology, strengthen existing collaborations, and establish new contacts that will lead to new high-quality studies in the coming years.

We would like to thank the invited speakers, all presenters, the members of the programme group, and everyone involved in organising this event.

You are cordially invited to attend the 4th Translational Molecular Endocrinology meeting in 2027.

On behalf of the organising committee

Head of the programme group P3-0449.

Prof. dr. Tea Lanišnik Rižner

Scientific Meeting Translational Molecular Endocrinology*

23rd September 2026

University of Ljubljana, Faculty of Medicine, Korytkova 2, 1000 Ljubljana, Slovenia

PROGRAMME

10:00-10:10	**Registration**
10:00-10:10	**Welcome**
	Ksenija Geršak, Dean of the Faculty of Medicine, University of Ljubljana, Slovenia **Borut Kobal**, Head of the Division of Gynaecology and Obstetrics, UMC Ljubljana, Slovenia
10:10-11:20	**Models of Hormone Dependent Diseases**
	Chairs: Maja Pušić Novak
10:10-10:30	**Dharani Hapangama**, University of Liverpool, UK *Complex In vitro Models of the Endometrium and Uterine Disorders*
10:30-10:45	**Polona Šafarič Tepeš**, Northwell Health, New York, USA *A Non-invasive in vitro Endometriosis Model Resolving Decidualization Effects at Single Cell Resolution*
10:45-11:00	**Alejandro Herreros Pomares**, KU Leuven, Belgium *Development of a Patient-derived Explant Platform to Preserve Tumour Microenvironment Complexity and Predict Treatment Response in Ovarian Cancer*
11:00-11:10	**Merve Yildiz**, Research Institute for Oncology & Reproduction, Maastricht University, The Netherlands *Charting Local Steroid Metabolism in Patient-derived Endometrial Cancer Organoids*
11:10-11:20	**Maja Pušić Novak,** Faculty of Medicine, University of Ljubljana, Slovenia *Heterogeneity of Primary Stromal Cells Derived from Peritoneal Endometriotic Lesions*
11:20-12:00	**Coffee break and Poster session**
12:00-13:40	**Molecular Mechanisms of Hormone Dependent Diseases**
	Chairs: Matti Poutanen and Francis Jacob
12:00-12:20	**Matti Poutanen,** Turku University, Finnland *Hormonal Regulation of Endometrial Function as Revealed by Steroidomic and Transcriptomic Analyses*
12:20-12:40	**Francis Jacob**, University Hospital Basel, Switzerland *Biology as a Compass: Multimodal Profiling to Guide Treatment in Ovarian Cancer*
12:40-13:00	**Karl Storbeck**, Stellenbosch University, Stellenbosch, South Africa *AKR1C3 Inhibition Selectively Decreases 11-Oxygenated Androgens in Women: a Potential Treatment for Polyendocrine Metabolic Ovarian Syndrome*
13:00-13:10	**Nika Troha**, University Medical Center Ljubljana, Slovenia *Bacterial Microbiome Analysis of Vaginal, Cervical and Endometrial Samples in Patients with Adenomyosis During the Window of Implantation*
13:10-13:20	**Nika Marolt,** Faculty of Medicine, University of Ljubljana, Slovenia *Transcriptomic and ROS Profiling Reveals Distinct Responses to Medroxyprogesterone Acetate in Ovarian Cancer Cells*
13:20-13:30	**Dzhamilyat Abdulkhalikova,** University Medical Center Ljubljana, Slovenia

	Lifestyle Intervention Modifies the Endometrial Proteome in Women with Polyendocrine Metabolic Ovarian Syndrome and Obesity
13:30-13:40	**Matthew Markgraaff**, Stellenbosch University, South Africa *Distinct Temporal Responses to Classic and 11-oxygenated Androgens are Regulated by Differential Metabolism in Prostate Cancer Cells*
13:40-14:40	**Lunch break and Poster session**
14:40-16:00	**Diagnosis and Prognosis of Hormone Dependent Diseases**
	Chairs: Jochen Schwenk and Jerzy Adamski
14:40-15:00	**Jochen Schwenk,** KTL, Stockholm, Sweden *Unlocking the Circulating Proteome from a Single Drop of Blood*
15:00-15:20	**Jure Knez**, University Medical Centre Maribor, Slovenia *Liquid Biopsy in Endometrial Cancer*
15:20-15:40	**Douglas Gibson**, University of Edinburgh, UK *Steroid Hormone Profiling Reveals a Distinct Adrenal Androgen Signature That Could Support Non-invasive Diagnosis of Endometriosis*
15:40-15:50	**Boštjan Pirš,** University Medical Center Ljubljana, Slovenia *Preoperative Prediction of MMR Deficiency and Lymphovascular Space Invasion in Endometrial Cancer Using Machine Learning Models Integrating Soluble Immune Checkpoints*
15:50-16:00	**Marija Gjorgoska,** Faculty of Medicine, University of Ljubljana, Slovenia *Multimodal Biomarker Integration Enhances Non-invasive Detection of Endometrial Cancer*
16:00-16:20	**Research on Hormone Dependent Diseases – Patients' Perspectives**
	Chair: Vid Janša
16:00-16:10	**Helena Ban Frangež,** Daily Endometriosis Centre, University Medical Centre Ljubljana, Slovenia
16:10-16:20	**Darja Molan**, Europa Donna, Slovenia
16:20-16:30	**Concluding remarks and announcement of the Elsevier JSBMB Best Poster Award**
	Tea Lanišnik Rižner, Program Group Translational Molecular Endocrinology for Women's Health, Faculty of Medicine, University of Ljubljana, Slovenia **Jerzy Adamski**, Editor-In-Chief, Journal of Steroid Biochemistry and Molecular Biology
17:00-18:30	**Social event: Ljubljanica boat tour**

*Organized by the Laboratory for Translational Molecular Endocrinology, Faculty of Medicine, Universtity of Ljubljana and

Association of Gynecologists and Obstetricians of Slovenia.

ZDRUŽENJE GINEKOLOGOV IN PORODNIČARJEV SLOVENIJE

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Lectures

Posters

Models of Hormone Dependent Diseases

Complex In vitro Models of the Endometrium and Uterine Disorders

Dharani Hapangama[1],

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The human endometrium is a remarkable and enigmatic tissue, uniquely capable of undergoing cyclical shedding and regeneration to support embryo-implantation and pregnancy. However, many fundamental aspects of endometrial function remain poorly understood, in part because commonly used laboratory animals do not menstruate and therefore cannot fully recapitulate human endometrial physiology. Furthermore, several major gynaecological disorders, including menstrual disorders such as endometriosis, are uniquely human, highlighting the limitations of conventional laboratory animal models.

Patient-derived, complex three-dimensional in vitro models offer an opportunity to better reproduce the cellular and molecular complexity of the human endometrium and address key gaps in our understanding of health and disease. Recent advances in tissue engineering and microfluidic technologies have further expanded the potential of these models for investigating disease mechanisms and identifying novel diagnostic and therapeutic approaches. In this talk, I will share selected work from our team demonstrating the development and application of complex human in vitro models to study endometrial function and uterine disorders.

Funding: UKRI; MRC (MR/V007238/1); VineHill Trust project grant; Wellbeing of Womens project grant (RG2137); Peter Sowerby Foundation

Invited lecture | I2

Non-invasive in vitro Endometriosis Model Resolving Decidualization Defects at Single Cell Resolution

Polona Šafarič Tepeš[1], Laurianna Frasson[1], Rixsi Hererra[1], Indira Kolenovic[1], Peter Greregsen[1], Christine Metz[1].

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Endometriosis affects 10% of women yet remains dependent on surgical tissue for research. We present ME-eSC — primary endometrial stromal cells from self-collected menstrual effluent — as a non-invasive, cycle-phase-matched, genetically tractable in vitro model for endometriosis decidualization research.

Menstrual effluent (internal cup, 6–12 h) was double-filtered (100→40 µm), cultured to passage 0 and biobanked. Decidualization was assessed at passage 1 by 48 h IGFBP1 ELISA (8-Br-cAMP ± medroxyprogesterone acetate, 96-well). A lentiviral reporter (IGFBP1−900→mScarlet / PRL→mVenus / CMV→mECFP) enabled live single-cell imaging and flow-cytometric sorting. High-resolution respirometry (Oroboros O2k, SUIT Protocol 2) was performed on matched donors under vehicle and decidualized conditions.

In 218 donors, absolute IGFBP1 under cAMP+MPA was significantly lower in surgically confirmed endometriosis (DX 19,581 pg/mL) than in symptomatic unconfirmed women (SX 62,720 pg/mL; p=0.005), with controls intermediate (CT 36,357 pg/mL). After age-matched comparison at 32–33 years, DX secreted 4× less than SX despite identical age — ruling out age as the explanation. Progestin fold-change was identical across groups (CT 1.36×, DX 1.32×, p=0.84): the deficit is in secretory set-point, not progestin receptor sensitivity.

Respirometry revealed that DX cells enter decidualization with their electron transfer chain already at the uncoupled ceiling (PI+II/E: DX 1.06 vs CT 0.64, p=0.017★). Upon decidualization, complex I engagement rose significantly beyond the ceiling in DX cells (PI/E: DX 0.727 vs CT 0.551, p=0.024★). In 6 matched donors, resting ETC load correlated perfectly with absolute IGFBP1 output (Spearman ρ=+1.00, p<0.001), directly linking mitochondrial state to decidualization capacity.

At single-cell resolution, the IGFBP1 promoter reporter drove 4.32% of decidualised cells above the sort gate — exceeding a constitutive CMV control (1.62%) — enabling isolation of responding versus non-responding subpopulations for downstream profiling.

ME-eSC recapitulate the endometriosis decidualization phenotype without surgery, expose a mitochondrial basis for the secretory deficit that fold-change metrics conceal, and support single-cell functional resolution. This platform enables non-invasive, longitudinal, bioenergetically informed endometriosis research.

Funding: Northwell Health -Innovation Award, Katz institute for Women's Health; Endometriosis Foundation of America.

Development of a Patient-derived Explant Platform to Preserve Tumour Microenvironment Complexity and Predict Treatment Response in Ovarian Cancer

Alejandro Herreros-Pomares[1,2], Wout De Wispelaere[1,2], Rossana Benedetto[1], Anne-Sophie Van Rompuy[3], Daniela Annibali[1,2,4], Frederic Amant[1,2,5,6]

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Ovarian cancer (OC) is characterized by marked inter- and intratumour heterogeneity, a complex tumour microenvironment (TME), and frequent development of resistance to platinum-based chemotherapy. Unfortunately, most preclinical models fail to preserve the native architecture, cellular composition and patient-specific context required to functionally study therapy response. We developed and optimized a patient-derived explant (PDE) platform from fresh OC surgical specimens to investigate TME interactions and predict treatment response.

Fresh tumour samples were manually dissected into ~1 mm³ fragments to preserve tissue architecture while allowing diffusion of nutrients and drugs. Fragments from different tumour regions were pooled to capture intratumour heterogeneity and embedded in an artificial extracellular matrix to prevent immune-cell efflux. Culture conditions were optimized by comparing matrix composition, culture medium, serum source and hormone supplementation. Immune, stromal and tumour compartments were analysed over time by flow cytometry, including immune composition, T-cell state and activation, and the presence of myeloid, fibroblast and endothelial cells. Treatment response was monitored using repeated AlamarBlue measurements and ToxiLight cytolysis assays. In parallel, cultured fragments were processed into tissue microarrays to evaluate cellularity, morphology, tumour architecture, proliferation, apoptosis and compartment-specific marker expression after carboplatin exposure.

Embedding did not impair immune-cell function or induce unspecific immune activation. Key immune, stromal and tumour compartments remained stable for up to three days, enabling the analysis of early treatment effects. AlamarBlue revealed strong intra- and intertumour heterogeneity in metabolic reduction capacity. Importantly, fragments from clinically refractory patients showed no treatment-induced differences compared with untreated controls, whereas fragments from potential responders displayed increased cytolysis and a clear decline in reduction capacity after carboplatin exposure. This optimized PDE platform preserves TME complexity and captures clinically meaningful carboplatin-response patterns, providing a patient-proximal ex vivo model to dissect TME-mediated therapy resistance and support personalized treatment selection in ovarian cancer.

Funding: AHP is supported by the Horizon Europe Framework Programme under the Marie Skłodowska-Curie Postdoctoral Fellowship 2021 (#101064216; https://doi.org/10.3030/101064216).

Charting Local Steroid Metabolism in Patient-derived Endometrial Cancer Organoids

Merve Yildiz[1,2], Bert Delvoux[1,2], Sofia Xanthoulea[1,2], Henrica MJ Werner [1,2], Andrea Romano[1,2]

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One of the leading risk factors for developing endometrial cancer (EC) is prolonged estrogen exposure. Locally produced estrogens contribute to this supply as EC cells take up inactive steroid precursors from the bloodstream and convert them by a number of steroidogenic enzymes into metabolites such as the highly active 17B-estradiol. The local action of these steroids regulates endometrial physiology, and its deregulation is involved in the initiation and maintenance of EC. Understanding the local intracrine steroid metabolism is crucial for developing targeted therapies to intervene with the estrogen synthesis pathways in EC cells. Patient-derived EC organoids are a good model that mimic the important tumor characteristics such as hormone sensitivity, and we have established a biobank of different EC grades. We aimed to chart the local steroid metabolism in these organoids to better understand its influence in EC growth.

Fifteen lines of patient-derived organoids were incubated with physiological concentrations of steroid substrates (10^{-7} M progesterone and dehydroepiandrosterone, 10^{-8} M androstenedione, estrone, and 17B-estradiol, 10^{-9} M testosterone) for 24 hours. Organoids and medium were harvested for steroid profiling by liquid chromatography mass spectrometry (LC/MS). Enzyme activities of 17B-hydroxysteroid dehydrogenase types 1 and 2, and steroid sulfatase were measured with high-performance liquid chromatography (HPLC), and estrogen sulfotransferase was determined by LC/MS.

LC/MS data indicated that the incubated substrates were metabolized into their subsequent metabolites by cultured organoids. The progestogens, androgens, and estrogens pathways were active in all grades and 17B-estradiol was mainly produced by low-grade EC organoids. Enzyme activity levels corresponded to these produced metabolites.

This is the first study to show the dynamic activity of steroidogenic enzymes and local production of steroid metabolites in EC organoids. The balance of the steroidogenic enzymes determines the overall steroid metabolism contributing to tumor progression.

Funding: Supported by a grant from the Dutch Cancer Society (KWF) with project number 2022-4 EXPL/14795.

Heterogeneity of Primary Stromal Cells Derived from Peritoneal Endometriotic Lesions

Maja Pušić Novak[1], Maruša Godler[1], Tamara Dokmanović[1], Helena Ban Frangež[2], Tea Lanišnik Rižner[1]

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Endometriosis is a chronic inflammatory gynecological disease affecting approximately 190 million women worldwide. Peritoneal endometriosis (PE) is the most common subtype, yet comprehensive characterization of primary stromal cultures specifically derived from peritoneal lesions and the inter-patient heterogeneity they exhibit remains limited. This study aimed to establish and characterize primary stromal cell cultures from peritoneal endometriotic lesions as patient-specific *in vitro* models and to investigate inter-patient heterogeneity at functional, transcriptomic, and hormonal levels.

PE lesion samples (n=13) were collected from 12 patients undergoing laparoscopic surgery. Primary stromal cells were isolated and characterized by morphology, population doubling time, migration, senescence, mRNA sequencing, spheroid formation, and hormonal responsiveness to estradiol (E2) and medroxyprogesterone acetate (MPA) in 3D models. Immunocytochemistry confirmed stromal identity (vimentin$^+$/cytokeratin$^-$) and endometrial origin (Pax2+).

Isolated primary stromal cultures were successfully established from 11 tissue samples. Functional characterization revealed significant inter-patient variability with population doubling time ranged from 2.2 to 12.2 days and wound closure capacity from 58% to 97% at 102 h. Notably, one culture derived from a black fibrotic lesion consistently showed the lowest proliferative and migratory capacity alongside the highest senescence, whereas a culture from a red active lesion showed the opposite profile across all functional assays, suggesting that the *in vitro* phenotype reflects the biological properties of the lesion of origin. At the transcriptomic level, mRNA sequencing confirmed inter-patient heterogeneity. Principal component analysis and unsupervised hierarchical clustering both revealed partial stratification by lesion color, with donor identity as the dominant source of variance and menstrual phase having no effect. All cultures demonstrated spheroid-forming capacity within 24 hours. Hormonal responses to E2 and MPA in 3D spheroids varied between patients and partially correlated with *ESR1* and *PGR* expression levels determined by RNA sequencing.

We successfully established well-characterized primary peritoneal endometriotic stromal cultures that preserve patient-specific fingerprints suggesting that they can serve as tools for investigating individualized disease pathophysiology and targeted drug responses.

Funding: This research was supported by ARIS grants Z3-4522 to M.P.N. and P3-0499 to T.L.R, and the EU H2020-MSCA-RISE project TRENDO.

Multidimensional analysis of HGSOC cell lines in 2D and 3D culture reveals subtype-aligned molecular and functional heterogeneity

Vesna Kokondoska Grgič[1,2], Gaber Kobal[1], Nika Marolt[11], Aleksandar Janev[4], Jurica Levatić[5], Katja Kološa[3], Ivana Jovčevska[1], Tea Lanišnik Rižner[11]

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High-grade serous ovarian cancer (HGSOC) is frequently diagnosed at an advanced stage and more than 80% of patients eventually develop resistance to platinum-based therapy. Conventional two-dimensional (2D) cultures do not reproduce tumour architecture or drug-resistance mechanisms. We therefore compared molecular and functional characteristics of matched 2D and three-dimensional (3D) models of four genomically representative HGSOC cell lines.

OVCAR-4, OVSAHO, COV362 and Kuramochi cells were grown in 2D, as spheroids in ultra-low-attachment plates, and, for OVSAHO and Kuramochi, as 3D-bioprinted constructs. Models were assessed by morphological analysis, proliferation, invasion, carboplatin sensitivity, cell-cycle analysis, Ki-67 quantification and targeted gene-expression profiling. RNA sequencing of 27 samples was analysed using differential-expression, UMAP, Celligner and gene-set enrichment approaches and aligned with TCGA HGSOC tumour data. Platinum-sensitive and -resistant TCGA tissues were further evaluated by co-expression and survival analyses.

All cell lines formed reproducible spheroids but displayed distinct morphology, proliferation and invasion. Three-dimensional growth induced cell-line-specific EMT, extracellular-matrix, DNA-repair and WNT programmes, while suppressing proliferation in OVCAR-4 and Kuramochi. Carboplatin IC50 values were consistently higher in 3D than in matched 2D models. RNA-seq demonstrated geometry-dependent transcriptomic reprogramming and subtype-aligned relationships between the cell models and HGSOC tumours. Recurrently downregulated genes included RXRG, IMPG2, KIRREL2 and BEX1. In patient tumours, resistant disease showed coordinated EMT–ECM network rewiring; high TWIST2, ZEB2 and WNT11 expression was associated with shorter progression-free survival. Upregulation of WNT11B in 3D OVSAHO and Kuramochi models mirrored this clinical resistance signature.

Two-dimensional and 3D HGSOC models provide complementary information. Integrating functional assays, RNA-seq and patient transcriptomic data identifies model-specific resistance mechanisms and supports deliberate selection of preclinical platforms according to the biological question.

Funding: Slovenian Research and Innovation Agency (ARIS), projects L4-4565 and P3-0108.

Molecular Mechanisms of Hormone Dependent Diseases

Invited lecture | I4

Hormonal Regulation of Endometrial Function Revealed by Steroidomic and Transcriptomic Analyses

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Female reproductive health depends on the cyclic, hormone-driven renewal of the uterine endometrium. This hormone-dependent regulation is governed by the availability of steroid hormones and expression of their receptors. The steroids, including estradiol, progesterone, testosterone, and cortisol, act through distinct nuclear receptors, which show cell-type-specific expression patterns in the human endometrium during the menstrual cycle. These receptor patterns determine which endometrial cell populations are competent to respond to circulating and locally available steroid ligands.

Systemically delivered sex steroids are synthesized mainly in the ovaries and adrenal glands. However, circulating hormone concentrations do not necessarily reflect the steroid milieu within target tissues. In the endometrium, local steroid concentrations may be shaped by steroid-metabolizing enzymes as well as tissue uptake, retention, and binding proteins. This tissue-specific regulation of steroid availability is often referred to as intracrinology, whereby local conversion and metabolism of steroid precursors influence ligand availability at the site of action. Thus, endometrial function is likely regulated not only by systemic endocrine signals, but also by local intratissue steroid dynamics.

Despite the central role of steroid hormones in endometrial biology, matched measurements of serum steroid concentrations, intratissue steroid levels, receptor expression, and transcriptomic responses have remained limited. Such integrated study designs are important because they allow local hormone availability to be directly linked to gene expression programs in the same tissue samples. We have, thus, analyzed intra-tissue and serum steroid profiles in fertile-aged women across the natural menstrual cycle in combination with global transcriptomic analyses. The results reveal distinct, steroid-specific mechanisms by which ligand-receptor interactions, and therefore the downstream signaling, are regulated.

Funding: University of Turku, Sigrid Juselius Foundation, Finnish Cultural Foundation, Yrjö Jahnsson Foundation.

Biology as a Compass: Multimodal Profiling to Guide Treatment in Ovarian Cancer

Francis Jacob[1]

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Current treatment guidelines recommend platinum-based chemotherapy, often combined with PARP inhibitor maintenance, as first-line management for high-grade serous tubo-ovarian carcinoma (HGSC), with benefit largely confined to homologous recombination-deficient (HRD) tumors. Despite these advances, chemotherapy remains the default backbone even for non-HRD patients, who derive limited benefit from current maintenance strategies. To address this unmet need, we integrated up to eleven molecular and functional technologies into a multimodal tumor profiling workflow with a four-week turnaround, demonstrating feasibility for real-world clinical decision-making, changing hypothetical treatment recommendations in 76% of patients, and supporting earlier tumor biology-guided intervention. Building on this, we recently launched OVPrecision (NCT06466382), a nationwide randomized clinical trial testing molecular tumor board–guided therapy at diagnosis in treatment-naïve non-HRD HGSC. First patients in the experimental arm receiving molecular tumor board–guided treatment in a window-of-opportunity fashion show response, with declining CA125 and pathology-confirmed on-tissue response. These early cases support feasibility of alternative first-line treatment recommendations beyond standard chemotherapy. Together, initial data chart a translational path from deep tumor profiling to informed first-line intervention.

Funding: The Swiss Tumor Profiler Study is jointly funded by ETH Zurich, University of Zurich, University Hospital Zurich, and University Hospital Basel. The Ovarian Cancer Research group is additionally supported by the Swiss National Science Foundation, Swiss Cancer Research, and by the University of Basel and the University Hospital Basel.

Invited lecture | I6

AKR1C3 Inhibition Selectively Decreases 11-oxygenated Androgens in women: A Potential Treatment for Polyendocrine Metabolic Ovarian Syndrome

Lina Schiffer[1], Amarah V. Anthony[1], Laura B. L. Wittemans[2,3,4], Angela E. Taylor[5], Imken Oestlund[6], Antonio M.A. Miranda[1], Eka Melson[1,7], Tara McDonnell[8], Punith Kempegowda[5,9], Paul Smith[10], T. Justin Clark[5,10], Martin Wabitsch[11], Michael W. O'Reilly[8], Michaele Peters[12], Andrea Wagenfeld[12], Jan-Peter Ingwersen[12], Jacky L. Snoep[6,13], William R. Scott[1,7], Jan Hilpert[12], Karl-Heinz Storbeck[1,6], Wiebke Arlt[1,7]

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Androgen excess drives metabolic and reproductive complications in polyendocrine metabolic ovarian syndrome (PMOS), affecting 10–15% of women globally. The enzyme AKR1C3 plays a key role in converting inactive classic and 11-oxygenated androgen precursors to the potent androgens Testosterone (T) and 11-ketotestosterone (11KT) in adipose tissue. AKR1C3 is upregulated by insulin, linking androgen excess with insulin resistance. Here, we investigated the contribution of AKR1C3 to systemic and intra-adipose androgen production and its potential as a therapeutic target. Single-nucleus RNA sequencing of adipose tissue demonstrated that AKR1C3 is predominantly expressed in adipocytes, with higher expression in women and individuals with obesity. Notably, the activation of 11-oxygenated androgens was markedly greater than that classic androgens in subcutaneous and visceral adipose tissue explants from women, with up to 10-fold higher 11KT than T production. Pharmacological AKR1C3 inhibition selectively disrupted 11-oxygenated androgen activation, with minimal effects on T generation. Consistent with these findings, 12 weeks of oral AKR1C3 inhibition in premenopausal women selectively reduced 11-oxygenated androgen activation, with minor effects on circulating T. A single dose of a chemically unrelated AKR1C3 inhibitor similarly reduced circulating 11KT in postmenopausal women. Computational modelling based on enzyme kinetics and serum androgen concentrations from women with PMOS and controls predicted a 2.6-fold increase in systemic AKR1C3 activity in PMOS and preferential

suppression of 11KT by AKR1C3 inhibition. Taken together, these findings identify adipose tissue as an important site of 11-oxygenated androgen production and demonstrate that AKR1C3 inhibition preferentially targets 11KT generation systemically and within adipose tissue. AKR1C3 therefore represents a promising therapeutic target for alleviating 11-oxygenated androgen excess in PMOS.

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Bacterial Microbiome Analysis of Vaginal, Cervical and Endometrial Samples in Patients with Adenomyosis During the Window of Implantation

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Adenomyosis is a chronic gynecological condition affecting a substantial portion of women of reproductive age. With symptoms including abnormal uterine bleeding, chronic pelvic pain (CPP), dysmenorrhea and infertility, poor response to symptomatic treatment and unfavorable outcomes of assisted reproductive technologies, adenomyosis remains a significant diagnostic and therapeutic challenge. Emerging evidence suggests that reproductive tract microbiota may interact with local inflammatory, metabolic, and endocrine pathways relevant to disease pathophysiology and endometrial receptivity.

In the present study, we analyzed reproductive tract microbiota in women with adenomyosis (n=33) and healthy controls (n=31). Vaginal, cervical, and endometrial samples were collected using minimally invasive transcervical techniques on day 22 of the menstrual cycle, during the window of implantation. The V3–V4 region of the bacterial 16S rRNA gene was sequenced using next-generation sequencing, followed by bioinformatic and statistical analyses of microbial composition and taxon abundance.

Microbiome profiles were broadly consistent across the three anatomical sites, supporting a reproductive tract microbial continuum. Adenomyosis was positively associated *with Lactobacillus iners* and negatively associated with *Lactobacillus gasseri* and *Gardnerella vaginalis*. *G. vaginalis* more frequently represented a dominant microbiome alternative to lactobacilli in healthy controls, suggesting its context-dependent biological role. Additional low-abundance anaerobes, including *Anaerococcus prevotii*, *Peptoniphilus grossensis*, *and Peptostreptococcus anaerobius*, showed weaker associations with adenomyosis. Differences in taxa abundance were detected in association with adenomyosis clinical symptoms. *L. iners* was associated with dysmenorrhea, heavy menstrual bleeding (HMB) and CPP. *Prevotella disiens, Prevotella timonesis and Dialister micraerophilus* were associated with dysmenorrhea and *Peptoniphilus grossensis* with HMB, respectively. *L. gasseri* and *L. jensenii* appeared to anticorrelate with these symptoms.

These results highlight *L. iners* as a potential indicator of microbiome alterations in adenomyosis and a possible target for microbiome modulation. Vaginal sampling may provide a minimally invasive approach to assessing reproductive tract microbial health, warranting larger functional and metagenomic analyses.

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Transcriptomic and ROS Profiling Reveals Distinct Responses to Medroxyprogesterone Acetate in Ovarian Cancer Cells

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High-grade serous ovarian carcinoma (HGSOC) is the most aggressive ovarian cancer subtype and is characterized by frequent platinum resistance and poor clinical outcomes, emphasizing the need for novel therapeutic strategies. Medroxyprogesterone acetate (MPA), a synthetic progestin with established clinical use in other indications, represents a potential drug repurposing candidate; however, its molecular role and therapeutic potential in HGSOC remain unknown. In our previous study, MPA demonstrated anti-tumor effects in Caov-3 and COV362 in vitro models. To further investigate MPA response mechanisms in HGSOC, Caov-3 and COV362 cells were treated with vehicle or 50 µM MPA for 72 h followed by cytotoxicity assessment and transcriptomic profiling using RNA sequencing (Novogene). Additionally, intracellular reactive oxygen species (ROS) levels were assessed by flow cytometry 24 h after MPA treatment. Baseline transcriptomic comparison revealed major molecular differences between untreated cell lines. Caov-3 cells showed enrichment of extracellular matrix organization, focal adhesion, WNT, and PI3K-AKT signaling pathways, consistent with a more proliferative phenotype. In contrast, genes relatively enriched in COV362 were associated with inflammatory, cytokine-mediated, mesenchymal, and cell adhesion pathways, suggesting a more immune-associated and aggressive transcriptional profile. Following MPA treatment, Caov-3 cells predominantly demonstrated downregulation of pathways associated with cell cycle progression, mitosis, focal adhesion, and extracellular matrix organization. Conversely, the cGMP-PKG signaling pathway was significantly upregulated. In contrast, COV362 cells demonstrated downregulation of inflammatory and interferon-related pathways, including cytokine-cytokine receptor interaction and Toll-like receptor signaling, alongside upregulation of tryptophan metabolism and cytochrome P450-mediated drug metabolism pathways. MPA treatment did not induce significant cytotoxicity despite marked transcriptional alterations, but showed a trend toward reduced ROS levels in both cell lines. These findings indicate that MPA induced distinct transcriptional reprogramming in Caov-3 and COV362 cells, affecting proliferative, inflammatory, and metabolic pathways. Reduced ROS levels in viable cells further suggest modulation of cellular redox homeostasis, warranting further investigation of the underlying mechanisms.

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Lifestyle Intervention Modifies the Endometrial Proteome in Women with Polyendocrine Metabolic Ovarian Syndrome and Obesity

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Polyendocrine metabolic ovarian syndrome (PMOS), previously known as polycystic ovary syndrome (PCOS) is a complex endocrine and metabolic disorder associated with obesity, infertility, and impaired endometrial function. We investigated whether a structured lifestyle intervention modifies the endometrial proteome and clinical characteristics of women with PMOS, obesity, and infertility.

In this prospective case-crossover study, 12 infertile women aged ≤38 years with PMOS phenotype A and body mass index ≥30 kg/m² completed an 8-week lifestyle and weight-loss program comprising supervised exercise and dietary counselling. Endometrial biopsies were obtained during the implantation window before and after the intervention. Paired endometrial samples from six participants were analyzed using antibody microarrays targeting 1,360 proteins. Endocrine-metabolic parameters, body composition, menstrual cycle regularity, and physical performance were assessed at both visits.

Lifestyle modification was associated with significant changes in the endometrial proteome. Protein abundance increased for legumain, insulin-like growth factor-binding protein 7, hepatocyte growth factor receptor, keratin, type II cytoskeletal 7, and cystatin B, whereas B-lymphocyte antigen CD20 abundance decreased after the intervention. Fasting glucose and free testosterone concentrations were significantly reduced. Body weight, body mass index, visceral fat, waist circumference, and several measures of physical performance improved, accompanied by more regular menstrual cycles in a proportion of participants.

A short-term lifestyle intervention in women with PMOS and obesity induced measurable molecular changes in the endometrium together with favourable endocrine-metabolic and anthropometric effects. The differentially abundant proteins may represent candidate biomarkers or mediators linking metabolic health with endometrial receptivity. These exploratory findings support further validation in larger cohorts and investigation of whether lifestyle-induced proteomic changes translate into improved implantation and reproductive outcomes.

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Distinct Temporal Responses to Classic and 11-oxygenated Androgens are Regulated by Differential Metabolism in Prostate Cancer Cells

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Castration resistant prostate cancer is and androgen dependent disease. In the absence of testicular testosterone, the tumour develops the ability to convert adrenal-derived androgen precursors, including 11-oxygenated androgens, to active androgens through the upregulation of key androgen activating enzymes. Intratumoral androgen levels are however also regulated by downstream inactivating enzymes. We previously reported that androgen dependent prostate cancer cell lines, LNCaP and VCaP, inactivate active 11-oxygenated androgens at a slower rate than the classic androgens. Here we show that this reduced rate of inactivation is due to the reduced enzymatic efficiencies of the androgen inactivating enzyme AKR1C2 and the androgen conjugating enzyme UGT2B17. The different rates of classic vs 11-oxygenated androgen inactivation result in temporal differences in the activation of the androgen receptor (AR), including differences in nuclear localisation, receptor dimerization and AR-regulated gene expression in LNCaP cells which express high levels of UGT2B17. These differences are eliminated by UGT2B17 knock out. Moreover, overexpression of UGT2B17 in the 22Rv1 prostate cancer cell line results in rapid, but differential clearance of classic vs 11-oxygenated androgens with concomitant changes in AR-regulated gene expression over time. Taken together, our data demonstrates that 11-oxygenated androgens are resistant to inactivation by AKR1C2 and UGT2B17 with a result that these may be able to accumulate at higher levels in CRPC tumours thereby promoting androgen signalling.

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Thermogenic Adipose Tissue Remodeling During Tirzepatide-Induced Weight Loss: Emerging evidence of Brown Adipose Tissue Recruitment and White Adipose Tissue Beiging

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Tirzepatide induces weight loss, but its effects on thermogenic adipose tissue remain unclear. We investigated whether weight loss is associated with brown adipose tissue (BAT) activation and transcriptional remodeling of subcutaneous white adipose tissue (WAT) toward a beige-adipocyte phenotype.

In TABFAT (NCT06893211), 34 premenopausal women with obesity without diabetes were randomized 1:1 to tirzepatide or placebo for 24 weeks. BAT was assessed by personalized cold-stimulated [^{18}F]FDG PET/CT, thermoneutral supraclavicular MRI, and cold-stimulated infrared thermography. In an imaging-selected tirzepatide subset, paired WAT biopsies underwent exploratory qPCR of beige-adipocyte and thermogenic genes. RNA sequencing and histomorphological analyses are ongoing.

At baseline, PET/CT-detectable BAT was present in 7/17 tirzepatide and 3/17 placebo participants, and at week 24 in 11/17 and 2/17, respectively (between-group difference, 52.9 percentage points; 95% CI, 20.4 to 72.8). Among baseline BAT-negative participants, de novo detection occurred in 4 of 10 versus 0 of 14 (difference, 40.0 percentage points; 95% CI, 8.4 to 68.7). Estimated between-group differences favored tirzepatide for total active BAT volume (+13 mL) and activity (+91.1 SUV·mL), with findings supported by supraclavicular MRI and infrared thermography. Exploratory qPCR in five tirzepatide-treated participants with supraclavicular BAT activation showed increased expression of beige-adipocyte-associated genes in subcutaneous WAT, including *CITED1*, *TMEM26*, and *CD137/TNFRSF9*, while *UCP1* remained unchanged. These findings suggest beiging-related remodeling of subcutaneous adipose tissue. However, results are exploratory and based on a very small sample, precluding formal statistical inference.

Tirzepatide-induced weight loss was accompanied by concordant in vivo BAT recruitment across imaging modalities. Exploratory WAT transcriptional changes suggested beige-adipocyte features. However, analyses are ongoing, and definitive results are awaited before conclusions can be drawn regarding subcutaneous WAT remodeling. These findings provide evidence of tirzepatide-associated BAT activation, whereas coordinated remodeling of thermogenic adipose tissue remains to be determined.

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Association of AKR1C3 with Estrogen and Progesterone Receptor

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Endometriosis is an estrogen-dependent gynecological disease affecting 190 million of women globally. AKR1C3 (aldo-keto reductase family 1 member C3) plays a role in progesterone metabolism and estrogen biosynthesis, but its relationship with estrogen receptor (ER) and progesterone receptor (PR) expression in endometriotic lesions remains poorly characterized. This study aimed to evaluate ER, PR, and AKR1C3 protein expression by immunohistochemistry in different endometriosis lesion types and investigate their correlations with each other and clinical characteristics.

This retrospective study included 45 endometriotic tissue samples from 41 patients with different endometriosis types who underwent laparoscopic surgery at the University Medical Centre Ljubljana. Formalin-fixed, paraffin-embedded tissues were immunohistochemically stained for AKR1C3, ER, and PR. A dedicated pathologist assessed the percentage of positively stained cells (P) for all markers; for AKR1C3, staining intensity (I) was additionally assessed and an immunoreactivity score (Q; P × I) calculated. IHC parameters of protein expression and their associations with patients' clinical, gynecological, and lifestyle characteristics were assessed using Spearman correlation and non-parametric tests in GraphPad Prism 11 and JASP 0.97.

Spearman correlation analysis showed significant positive correlations between ER-positive cells (ER-P) and AKR1C3-positive cells (AKR1C3-P), staining intensity (AKR1C3-I), and immunoreactivity score (AKR1C3-Q), while no significant correlations were observed between PR-positive cells (PR-P) and AKR1C3 parameters or between ER-P and PR-P. AKR1C3-P was positively correlated with bowel endometriotic tissue, while AKR1C3-Q was positively associated with rASRM stage 3. PR-P was positively correlated with rASRM stage 1 and peritoneal endometriosis, and negatively with rASRM stage 3 and ovarian endometriosis. Group comparisons confirmed higher PR-P in peritoneal compared to ovarian endometriosis and in rASRM stage 1 compared with other stages. ER-P was higher in patients in the secretory versus proliferative menstrual phase and in those receiving oral hormonal therapy.

AKR1C3 expression was positively associated with ER expression in endometriotic tissue, supporting a potential link between AKR1C3 and estrogen signaling. Larger, well-characterized cohorts are needed to validate these findings and clarify the relationship between AKR1C3 and ER/PR expression in endometriosis.

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Targeted LC-MS/MS Profiling of Progesterone Metabolism: Simultaneous Quantification of Hydroxylated, 20α-reduced, 5α-reduced, and Neuroactive Progesterone Metabolites

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Progesterone (P4) is a key steroid hormone involved in numerous physiological and pathological processes. P4 undergoes extensive metabolism through hydroxylation, oxidation, and reduction reactions catalyzed by cytochrome P450 enzymes, hydroxysteroid dehydrogenases, aldo-keto reductases, and steroid 5α-reductases, generating biologically active metabolites with diverse physiological functions. To facilitate comprehensive characterization of P4 metabolism, a liquid chromatography-tandem mass spectrometry (LC-MS/MS) method was developed for the simultaneous quantification of pregnenolone, P4, and major hydroxylated, 20α-reduced, 5α-reduced, and neuroactive P4 metabolites.

The analyte panel included pregnenolone; P4 and its hydroxylated metabolites 17α-hydroxyprogesterone (17OHP4), 11β-hydroxyprogesterone (11OHP4), and 11-ketoprogesterone (11KP4); the reduced metabolites 20α-hydroxyprogesterone (20α-OHP4) and 5α-dihydroprogesterone (5α-DHP4); and the pregnanolones allopregnanolone, epiallopregnanolone, and 20α-hydroxy-5α-pregnan-3-one (20α-OH-5α-DHP4). Calibrators and quality-control samples prepared in cell culture medium were fortified with P4-d9 as an internal standard, purified by solid-phase extraction on Strata-X C18 cartridges, and analyzed by LC-MS/MS.

The method demonstrated excellent linearity over the concentration range of 0.1-250 ng/mL for all analytes ($R^2 > 0.99$). Limits of detection (LOD) were 0.01 ng/mL for P4, 17OHP4, 11OHP4, 11KP4, 20α-OHP4, and 20α-OH-5α-DHP4, and 0.05 ng/mL for 5α-DHP4, pregnenolone, and epiallopregnanolone. Lower limits of quantification (LLOQ) were 0.1 ng/mL for P4, 17OHP4, 11OHP4, 11KP4, 20α-OHP4, and 5α-DHP4, and 0.25 ng/mL for pregnenolone, epiallopregnanolone, and 20α-OH-5α-DHP4. Intra- and inter-day precision, accuracy, extraction recovery, and matrix effects are currently being evaluated as part of the ongoing method validation.

The developed LC–MS/MS method enables simultaneous quantification of P4 and structurally diverse metabolites representing the major metabolic pathways of P4. Preliminary validation results demonstrate excellent sensitivity, selectivity, and linearity, supporting its application in studies of progesterone metabolism in cellular models of hormone-dependent diseases. Full method validation is ongoing.

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Mifepristone and Ulipristal Acetate Suppress Growth and Migration in Platinum-Sensitive and Platinum-Resistant High-Grade Serous Ovarian Cancer Despite Low Progesterone Receptor Expression

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High-grade serous ovarian cancer (HGSOC) is the most lethal gynecological malignancy, with platinum resistance representing the greatest clinical challenge. Although progesterone receptor (PR) signaling has been implicated in HGSOC biology, the therapeutic potential of progestins and anti-progestins remains unclear. We investigated the effects of PR agonists (progesterone, medroxyprogesterone acetate (MPA), and levonorgestrel), the PR antagonist mifepristone, and the selective PR modulator (SPRM) ulipristal acetate (UPA) on proliferation and migration in HGSOC models of platinum-sensitive and -resistant disease.

OVSAHO and COV362 cells, previously characterized as platinum-sensitive and -resistant, respectively [Pavlič et al., 2022; Marolt et al., 2024], were assessed for PGR expression by RT-qPCR, while PR-A and PR-B isoforms were evaluated by Western blotting. Cells were treated with progesterone (1 nM-50 µM), MPA, levonorgestrel, mifepristone, or UPA (1-50 µM) for 72 h. Cell viability was measured using AlamarBlue™ and migration by scratch wound-healing assay.

Both cell lines expressed low PGR levels, but PR-A and PR-B isoforms were undetectable. Progesterone did not affect proliferation at nanomolar concentrations but reduced OVSAHO viability and inhibited migration in both cell lines at 50 µM. MPA modestly reduced viability in both models, whereas levonorgestrel had no significant effect. In contrast, mifepristone and UPA reduced viability in both cell lines from 10 µM onward. At 50 µM, mifepristone reduced viability to approximately 25 % in both cell lines, while COV362 cells were less sensitive to UPA than OVSAHO cells. MPA and levonorgestrel did not affect OVSAHO migration, whereas mifepristone and UPA reduced migration at 50 µM. In COV362 cells, all compounds inhibited migration at concentrations ≥20 µM, whereas UPA nearly abolished wound closure already at 1 µM.

These findings show that mifepristone and UPA inhibit HGSOC growth and migration, including in resistant cells. The absence of detectable PR protein suggests PR-independent mechanisms and supports further investigation of these agents as repurposed therapies for chemo-resistant HGSOC.

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Ovarian Stimulation for IVF Alters the Endometrial Proteomic Profile During the Window of Implantation

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Ovarian stimulation induces supraphysiological steroid hormone concentrations that may alter endometrial receptivity. While transcriptomic changes have been described, the effect of stimulation on the endometrial proteome during the window of implantation remains insufficiently characterized. We aimed to identify protein-level alterations associated with ovarian stimulation in women with poor ovarian response.

In this prospective case-crossover clinical trial, 15 women with primary infertility and poor ovarian response underwent endometrial biopsy during the window of implantation in both a spontaneous cycle and a subsequent stimulated cycle. Paired samples were analyzed using antibody-based microarrays targeting 1,466 proteins. Differential protein abundance was assessed using a multifactorial linear model accounting for patient-specific effects. Differential abundance was defined as an absolute log2-fold change >0.5 and a false discovery rate-adjusted p-value <0.05.

A total of 114 antibodies showed differential abundance between spontaneous and stimulated cycles. Prominent changes involved proteins associated with immune and inflammatory responses, including interleukin-8, proteins S100-A8, S100-A9 and cathelicidin antimicrobial peptide, as well as matrix metalloproteinase-9, which is involved in extracellular matrix remodeling. Exploratory pathway mapping indicated alterations in cytokine-cytokine receptor interaction and IL-17 signaling. Unsupervised clustering demonstrated distinct proteomic patterns, with all stimulated-cycle samples showing alterations and 40% exhibiting more pronounced changes.

Ovarian stimulation is associated with measurable alterations in the endometrial proteomic profile during the window of implantation. The identified proteins represent candidate biomarkers of altered endometrial receptivity and may contribute to improved patient stratification and optimization of embryo-transfer strategies. Validation in larger cohorts and correlation with implantation outcomes are required before clinical application.

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Exploring the Vaginal Microbiome and Antimicrobial Resistance Gene Carriage in Women with Dysbiosis and Bacterial Vaginosis

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Bacterial vaginosis (BV) is a common disturbance of the vaginal microbiome in reproductive-age women, characterised by depletion of *Lactobacillus* species and overgrowth of anaerobic bacteria. BV is associated with reduced quality of life and reproductive function. Antimicrobial resistance genes (ARGs) may reduce treatment effectiveness and contribute to recurrence.

To characterise ARGs associated with BV and vaginal dysbiosis, compare their prevalence across clinical groups, and describe vaginal microbiome using 16S rRNA sequencing and additional layers of evidence.

The study included 89 women: controls (n = 15), dysbiosis (n = 35), and BV (n = 39). Healthy and dysbiotic groups were assessed by sequencing: healthy samples were *Lactobacillus*-dominated, dysbiotic samples showed heterogeneous profiles without clinical BV symptoms. BV samples were hospital-collected and diagnosed by whiff test. Vaginal swabs were collected, and Nugent scores were determined from smears. DNA was extracted using the QIAampPathogen Mini Kit. The *V1–V9* region of the *16S rRNA* gene was sequenced to evaluate microbial composition. ARGs selected from metagenomic analysis were evaluated by real-time PCR, and group ARG differences were analysed using Fisher's exact test.

The microbiome analysis showed highly heterogeneous patterns in the dysbiosis and BV groups. Higher Nugent scores were associated with lower *Lactobacillus* abundance and a greater proportion of BV-associated anaerobic bacteria. The *ermA* and *tetQ* genes were more frequent in dysbiosis and BV than in controls ($p < 0.01$). Genes *ermA*, *tetQ*, and *cfxA* differed significantly between controls and BV ($p < 0.01$). The BV group had the highest ARG burden and often carried multiple resistance genes.

Vaginal dysbiosis and BV were associated with a higher prevalence of ARGs, which may impair treatment response and promote recurrence. Nugent scores aligned with *16S rRNA* sequencing results, supporting sequencing as a complementary method for evaluating vaginal microbiome status and dysbiosis.

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AKR1C1 and AKR1C2 Expression and Their Potential Role in Carboplatin Response in High-Grade Serous Ovarian Cancer

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Ovarian cancer is one of the most lethal gynecological malignancies, largely due to late diagnosis and the frequent development of resistance to platinum-based chemotherapy. Aldo-keto reductases, particularly AKR1C1 and AKR1C2, have been associated with cancer progression and chemoresistance through their involvement in steroid metabolism, detoxification processes, and protection against chemotherapy-induced oxidative stress in different cancers. Given the limited information regarding their role in carboplatin sensitivity in high-grade serous ovarian cancer (HGSOC), the aim of this study was to investigate the expression of *AKR1C1* and *AKR1C2* in the ovarian cancer cell lines Caov-3 and OVCAR-3 exposed chronically to carboplatin vs baseline, and to evaluate whether inhibition of these enzymes effects cell viability and response to carboplatin.

Expression of AKR1C1 and AKR1C2 genes and proteins were assessed by qPCR and Western blotting, while the effects of carboplatin alone and in combination with the AKR1C inhibitors mefenamic acid (MEF) and flufenamic acid (FLU) were evaluated using *in vitro* cell viability assays. Chronic carboplatin exposure did not significantly affect *AKR1C1* expression in either cell line, although a decreasing trend was observed in Caov-3 cells. Similarly, *AKR1C2* expression remained unchanged in OVCAR-3 cells, whereas a significant decrease in *AKR1C2* expression was observed in chronically exposed Caov-3 cells. Cell viability results showed 250 µM MEF and/or 50 µM carboplatin reduced cell viability significantly compared to vehicle. In contrast, FLU alone (10 to 250 µM) had no significant effect on cell viability. When combined with 50 µM carboplatin, a significant reduction in cell viability was observed only with 50 and 100 µM FLU.

Overall, these findings support the potential involvement of AKR1C enzymes in the response of ovarian cancer cells to platinum-based chemotherapy.

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Directed C–H Activation of 13α-estrone Derivatives Leads to Novel AKR1C2-selective Inhibitors

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Aldo-keto reductase family 1C (AKR1C) enzymes regulate local steroid hormone availability by catalyzing the interconversion of active and inactive steroid ligands. Dysregulated AKR1C1–3 activity contributes to the progression of hormone-dependent cancers and has been associated with resistance to multiple chemotherapeutic agents, highlighting these enzymes as attractive therapeutic targets. Building on our previous identification of potent A-ring halogenated 13α-estrone-based AKR1C inhibitors, we explored further structural diversification of this scaffold through directed C–H activation chemistry.

Following the introduction of suitable directing groups, selective C-2 hydroxylation and acetoxylation reactions were performed on 13α-estrone derivatives. The synthesized compounds were evaluated for their inhibitory activity against recombinant human AKR1C1, AKR1C2 and AKR1C3 enzymes. Several compounds displayed measurable inhibition, with the 3-*O*-(*N*,*N*-dimethylcarbamoyl) and the 3-*O*-(2-pyridyl) derivatives emerging as the most promising candidates. Both exhibited low micromolar inhibitory potency and notable selectivity toward AKR1C2 over the closely related AKR1C1 and AKR1C3 isoenzymes. To gain insight into the molecular basis of their activity, *in silico* docking studies were conducted using representative active compounds, including the 3-*O*-(2-pyridyl), the 3-*O*-(4,6-dimethoxy-1,3,5-triazin-2-yl), and the 3-*O*-(*N*,*N*-dimethylcarbamoyl) derivatives. Docking results suggested favorable accommodation of these ligands within the AKR1C2 active site, where they establish key hydrophobic interactions with residues Trp86, Val128, Ile129 and Trp227. These interactions are proposed to contribute to both binding affinity and isoform selectivity.

The identified AKR1C2-selective inhibitors represent promising starting points for the development of novel anticancer agents aimed at limiting metastatic progression in aggressive tumor types. Given the overlapping substrate specificities of AKR1C isoenzymes, future optimization may focus not only on enhancing selectivity but also on developing broader-spectrum AKR1C inhibitors capable of overcoming compensatory enzymatic mechanisms in cancer cells.

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Diagnosis and Prognosis of Hormone Dependent Diseases

Unlocking the Circulating Proteome from a Single Drop of Blood

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The discovery and implementation of molecular biomarkers are central to advancing translational research, enabling earlier diagnosis, patient stratification, treatment monitoring, and a deeper understanding of disease mechanisms. However, the identification and validation of clinically useful biomarkers are often constrained by limited access to longitudinal biospecimens and the logistical challenges of repeated blood sampling. Dried blood samples (DBS) offer a minimally invasive, decentralized alternative with the potential to transform molecular phenotyping across infectious, endocrine and metabolic diseases.

Here, we establish scalable proteomics workflows for microsampled DBS and present a systematic characterization of the dried blood proteome across population cohorts and longitudinal studies. Standardized DBS sampling, protein extraction, and analytical workflows were developed for compatibility with both affinity-based and mass spectrometry proteomics platforms. Multiplexed assays were used to quantify thousands of proteins, including circulating plasma proteins, cellular blood proteins, pathogen-specific antibodies, and autoantibodies. The workflows were applied across large cohort collections and longitudinal studies relevant to endocrine and metabolic health.

Home-sampled blood enabled sensitive and reproducible quantification of hundreds to thousands of proteins from samples collected in decentralized settings. Longitudinal analyses revealed highly stable individual proteomic signatures while capturing dynamic molecular changes associated with health and disease. The approach enabled repeated assessment of proteins involved in immune response, endocrine signaling, metabolism, inflammation, and tissue remodeling, supporting applications in longitudinal monitoring and biomarker discovery. Furthermore, systematic profiling of more than 4,000 proteins, we generated a comprehensive and open-access map of the dried blood proteome.

The presentation will discuss our studies using plasma and DBS for high-dimensional proteomics in translational research. By enabling comprehensive molecular profiling from a single drop of blood, microsampling supports decentralized sampling, longitudinal monitoring, and population-scale biomarker studies. These advances provide a foundation for patient-centric biomarker discovery, including precision endocrinology.

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Liquid Biopsy in Endometrial Cancer

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Endometrial cancer is the most common gynaecological cancer in developed countries, and its management is increasingly moving towards molecular characterisation of the disease and individualisation of treatment. Liquid biopsy enables the minimally invasive acquisition of information on tumour and host characteristics from body fluids and represents a potential complement to conventional histopathological diagnostics.

In endometrial cancer, the main analytes under investigation are circulating cell-free DNA (cfDNA), circulating tumour DNA (ctDNA), microRNA (miRNA), DNA methylation patterns, circulating tumour cells, and extracellular vesicles. Our research focuses primarily on cfDNA and miRNA in peripheral blood and on their association with clinicopathological characteristics and the contemporary molecular classification of endometrial cancer. The results indicate that cfDNA concentration and characteristics, as well as profiles of selected miRNAs, may reflect the biological heterogeneity of the disease; however, a single biomarker is unlikely to be sufficient for reliable clinical decision-making.

The greatest potential of liquid biopsy lies in combining multiple types of molecular information. Integration of cfDNA, miRNA, and epigenetic markers could improve preoperative risk assessment, enable monitoring of minimal residual disease, and facilitate earlier detection of disease recurrence. Longitudinal sampling also provides an opportunity to monitor dynamic changes in tumour biology during and after treatment. Particularly important is the possibility of obtaining molecular information in cases where tissue samples are limited or repeated biopsies are not feasible.

Despite the rapid development of the field, key challenges remain, including standardisation of pre-analytical and analytical procedures, sensitivity of methods in early-stage disease, and prospective clinical validation. Future approaches will likely be based on multimodal models integrating liquid biopsy with histopathological, molecular, and clinical data. Liquid biopsy therefore does not currently replace tissue-based diagnostics, but it may substantially complement molecular stratification and personalised monitoring of patients with endometrial cancer.

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Steroid Hormone Profiling Reveals a Distinct Adrenal Androgen Signature that Could Support Non-invasive Diagnosis of Endometriosis

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Endometriosis is a chronic, hormone-dependent condition affecting an estimated 190 million women worldwide. Although the role of estrogens is well established, research on androgens in endometriosis is limited and the contribution of adrenal-derived 11-oxygenated androgens remains largely unknown.

We collected blood from healthy controls (n=57) and women with laparoscopically confirmed endometriosis (n=159). Written informed consent was obtained prior to study participation. Serum samples were analyzed using LC–MS/MS to comprehensively profile classic androgens; DHEA, A4, T, and DHT, as well as 11-oxygenated androgens; 11β-hydroxyandrostenedione (11OHA4), 11β-hydroxytestosterone (11OHT), 11-ketoandrostenedione (11KA4), and 11-ketotestosterone (11KT).

We found that women with endometriosis had a distinct hormone signature characterized by systemic differences in both classic and 11-oxygenated androgens. Concentrations of DHEA, A4, T, 11OHT and 11KT were significantly greater in those with endometriosis compared to healthy controls ($p<0.001$). 11KA4 was significantly lower in those with endometriosis ($p<0.001$). Substrate to product ratios were altered in endometriosis consistent with an altered adrenal androgen profile.

Using androgen hormone profiling data, we generated statistical models that showed robust discrimination between healthy controls and women with endometriosis (AUC = 0.99; positive predictive power = 96.84%, negative predictive power = 92.86%) consistent with an endometriosis-specific hormone signature. To explore diagnostic utility, data were partitioned into train and validation groups and a refined model identified >95% of endometriosis patients in a blinded sample set.

Collectively, these data reframe endometriosis as an androgen-dependent disorder and highlight 11-oxygenated androgens as potential diagnostic biomarkers and future therapeutic targets.

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Preoperative Prediction of MMR Deficiency and Lymphovascular Space Invasion in Endometrial Cancer using Machine Learning Models Integrating Soluble Immune Checkpoints

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Mismatch repair (MMR) deficiency and lymphovascular space invasion (LVSI) are key determinants of risk group assignment and adjuvant treatment in endometrial cancer (EC), but both are usually established only after surgical staging. Soluble immune checkpoints (sICs) are circulating forms of membrane-bound immune molecules that have been proposed as non-invasive prognostic and predictive biomarkers. The aim of this analysis was to determine whether machine learning models combining sICs with routinely available clinical, imaging and preoperative histology data can predict MMR deficiency and LVSI before surgery.

Plasma levels of 16 sICs were measured prior to surgical staging in 50 patients with histologically confirmed EC using a fluorescence-based multiplex immunoassay. Machine learning models were constructed with MMR deficiency and LVSI as outcomes, using sIC concentrations alone and in combination with preoperative clinical parameters, imaging findings and preoperative histology. Performance was assessed by cross-validated discrimination metrics with variable importance analysis and compared with models based on routine preoperative variables alone.

The cohort included 66% of patients with a non-aggressive histological type; 33% of tumours were MMR deficient and 16% exhibited substantial LVSI. Most tumours were confined to the uterus, with 16% of patients having stage IIIA or higher disease. In univariate analyses, sPD-1, sPD-L1, sLAG-3, sICOS, sGITR and sCD86 were significantly higher in MMR-deficient tumours, while sTIM-3, sCD27, sHVEM and sCD40 were higher in tumours with LVSI. Multimodal machine learning models integrating sICs with clinical, imaging and preoperative histology data showed encouraging discrimination for both MMR deficiency and LVSI, with the most informative checkpoint molecules mirroring the univariate associations, and outperformed models restricted to routine preoperative variables.

Circulating immune checkpoint proteins may carry information about MMR status and LVSI that is complementary to routinely available preoperative data, and that their integration in multimodal models may support preoperative risk stratification, extent of surgical staging and identification of candidates for immune checkpoint inhibition. Given the limited sample size and the exploratory nature of the modelling, validation in larger, prospective and externally independent cohorts is required before clinical implementation.

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Multimodal Biomarker Integration Enhances Non-invasive Detection of Endometrial Cancer

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Blood-based biomarkers for endometrial cancer (EC) diagnosis have shown promising results, but none have yet been adopted in clinical practice. Moreover, the extent to which different biomarker classes provide complementary diagnostic information remains unclear. We investigated whether integrating metabolomic, protein, steroidomic, and clinical biomarkers could improve EC detection.

This single-center case-control study included 112 women undergoing surgical treatment, comprising 50 patients with histologically confirmed EC and 62 controls with benign uterine conditions. Two previously published diagnostic models were evaluated: a protein-based model incorporating CA-125, HE4, and BMI, and a metabolomic model based on a three-metabolite signature (C16/PCae C40:1, Pro/Tyr, and PCaa C42:0/PCae C44:5). Given its superior discrimination, the metabolomic model was selected as the baseline model for incremental biomarker integration. Clinical variables, steroid biomarkers, and protein biomarkers were then added incrementally. Logistic regression, support vector machines, and artificial neural networks were assessed using bootstrap validation with 1,000 resamples.

The metabolomic signature achieved an AUC of 0.808 ± 0.06. Adding clinical variables resulted in modest improvement (AUC up to 0.829 ± 0.06), while steroid biomarkers provided little additional discriminatory value (AUC up to 0.818 ± 0.06). In contrast, protein biomarkers substantially improved performance. Addition of CA-125 increased the AUC to 0.844 ± 0.05, whereas HE4 increased it to 0.861 ± 0.05. Combining both protein biomarkers achieved an AUC of 0.864 ± 0.05. The best-performing model combined the metabolomic signature, BMI, and HE4, yielding an AUC of 0.868 ± 0.05. Logistic regression performed comparably to more complex machine-learning approaches.

Integrating multiple biomarker classes improved diagnostic discrimination compared with the metabolomic signature alone. Among the evaluated markers, HE4 provided the greatest incremental diagnostic value, whereas steroid biomarkers contributed minimal additional information despite being associated with disease status. These findings support the development of multimodal, minimally invasive diagnostic approaches for EC, warranting further validation.

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Prognostic Potential of Plasma AKR1B1 and AKR1B10 in Endometrial Cancer: A Pilot Study

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Endometrial cancer (EC) is the most common gynecological malignancy in industrialized countries, highlighting the need for non-invasive biomarkers for preoperative risk stratification and prognostic assessment. We previously found lower AKR1B1 and AKR1B10 expression in EC tissue compared to adjacent normal endometrium, while above-median expression of both markers was associated with longer overall and disease-free survival[1]. Based on these findings, we aimed to investigate circulating AKR1B1 and AKR1B10 as potential prognostic biomarkers and their ability to predict lymphovascular invasion (LVI) preoperatively.

Preoperative plasma samples from 78 postmenopausal women with histologically confirmed EC who underwent hysterectomy at the University Medical Centre Ljubljana were analyzed. AKR1B1 and AKR1B10 levels were measured by ELISA, and their associations with patients´ clinicopathological characteristics were evaluated. Logistic regression models incorporating clinical variables and both biomarkers were developed to predict LVI. Survival was assessed using Kaplan–Meier and Cox proportional hazards analyses.

AKR1B10 plasma levels correlated positively with age in patients with LVI ($r=0.40$, $p<0.05$). In addition, AKR1B10 levels were significantly higher in Grade 3 than Grade 1–2 EC (AUC= 0.86, 95% CI 0.76–0.97). However, these findings should be interpreted as hypothesis-generating given the small number of patients in the Grade 3 subgroup (n=10). The best-performing LVI prediction model, combining AKR1B1, AKR1B10, and clinical variables (BMI, age, smoking, parity, hormone replacement therapy, previous use of contraceptives) achieved an AUC of 0.764 in the training set, but only 0.651 in the test set, indicating limited predictive clinical utility. Neither biomarker alone was significantly associated with overall or recurrence-free survival. However, patients with both AKR1B1 and AKR1B10 levels below the median showed significantly longer overall survival ($p=0.04$; HR=0.33, 95% CI 0.10–1.01) and recurrence-free survival ($p=0.005$; HR=0.09, 95% CI 0.02–0.49).

Larger multicenter studies are needed to validate these findings and assess their value in multimarker prognostic models.

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Literature:

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Studies of Selected Proteins as Possible Diagnostic Markers of Endometriosis

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Endometriosis is a chronic inflammatory disease affecting ~10% of women of reproductive age, causing pain and infertility. Due to the delayed (4–11 years) and potentially unnecessary use of laparoscopic diagnostics, the development of non-invasive biomarkers, particularly for the peritoneal form of the disease, is of critical importance. In our previous proteomic study using antibody microarrays, we identified 16 differentially expressed proteins in peritoneal fluid, including S100A8/A9, IGFBP4, and TIMP1 as potential diagnostic candidates.

The aim of this study was to measure the concentrations of S100A8/A9, TIMP1 and IGFBP4 in the peritoneal fluid of patients with endometriosis and controls, and to evaluate their diagnostic potential in a larger cohort of participants.

A validation study was conducted on 64 women with primary infertility – 40 with ovarian, peritoneal, deep or a combination of different types of endometriosis in stages I–IV and 24 in a control group with unexplained infertility. Peritoneal fluid samples collected during surgery were analyzed by quantitative sandwich ELISA using specific monoclonal antibodies. S100A8/A9 protein concentrations in the peritoneal fluid of patients were statistically significantly elevated compared with the control group ($p < 0.0001$). ROC analysis for S100A8/A9 demonstrated good diagnostic potential (AUC = 0.8384, 61.1% sensitivity, 100% specificity). Statistically significant differences according to individual factors (endometriosis type, stage, etc.) were observed only for S100A8/A9. For IGFBP4 and TIMP1, no statistically significant differences in concentrations were identified, indicating that they have no diagnostic value in this cohort.

The study confirms that S100A8/A9 represents a promising biomarker candidate for the detection of endometriosis in peritoneal fluid, justifying further research in blood samples. While IGFBP4 and TIMP1 show no diagnostic potential, the results for S100A8/A9 may contribute to the development of non-invasive diagnostic tools needed to shorten diagnostic delay.

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Transcriptomic and Proteomic Validation of BTLA, CAMP, and K2C8 in Endometriosis Associated Infertility

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Endometriosis is one of the most common benign gynaecological disorders, affecting 10% of all women and 35-50% of women with conception problems. Endometriosis-associated infertility is a complex condition involving inflammatory, endocrine, epithelial, immune, and endometrial abnormalities. In our recent study, we identified B- and T-lymphocyte attenuator (BTLA), Keratin type II cytoskeletal 8 (K2C8) and Cathelicidin antimicrobial peptide (CAMP) as differentially abundant in uterine cavity flushings of endometriosis patients versus controls using protein antibody microarrays. We aimed to validate our previous findings in a larger cohort in patients' uterine fluid, peritoneal fluid, and plasma samples, and to examine expression of the corresponding genes in eutopic and ectopic tissue using the Turku Endometriosis Database.

Patient samples (uterine and peritoneal fluid, and plasma) were collected under standard operating procedures (SOPs) at UMC Ljubljana and analyzed using commercially available ELISA kits. The cohort included a discovery group (n=11, matching the microarray study) and an independent validation cohort of new patients (n=54). For gene expression analysis, data for ectopic endometriotic tissue (n=190) and paired eutopic endometrium (n= 144) were retrieved and analyzed from EndometDB, a repository of microarray gene expression profile data for normal endometrium and endometriosis lesions from 115 patients and 53 controls.

All three proteins were undetectable by ELISA in uterine and peritoneal fluid across endometriosis patients and controls reflecting their low abundance. Plasma K2C8 levels were significantly higher in controls than cases within the discovery cohort (n=11), but this statistical significance was lost in the validation cohort (n=54). Plasma CAMP and BTLA levels showed no significant differences between the groups. Gene expression analysis revealed that the expression of KRT8 gene (encoding K2C8) was decreased in ectopic lesions compared to paired eutopic endometrium, while CAMP and BTLA expression did not differ significantly between the two tissue types.

Although K2C8, BTLA, and CAMP exhibit concentrations below the limit of assay detection in uterine and peritoneal fluid, our results in plasma correlate with gene expression analysis. The analyzed genes are connected to altered epithelial differentiation, tubal-factor impairment, and immune activation, which confirms their relevance to endometriosis pathophysiology, though further studies are required to establish their direct diagnostic value for endometriosis-associated infertility.

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Using REDCap to consolidate clinical and lifestyle data for endometriosis research

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Patients' clinical and lifestyle data are essential for biomarker discovery and other medical research; however, these data are often not adequately organised. At the Laboratory for Translational Molecular Endocrinology at the Institute of Biochemistry and Molecular Genetics, Faculty of Medicine, University of Ljubljana in collaboration with Daily Center for Endometriosis at University Medical Centre Ljubljana, we aimed to transfer data from tabular files with identified weaknesses into an information system that allows standardisation of the collected data.

We collected anonymised data on patients for biomarker discovery in the field of endometriosis. More than 100 variables were recorded, including general information about the participants (14 variables), data on their diet and lifestyle (22), pain and stress (13), and clinical and gynaecological data (67). As the primary tool for consolidating data, we used REDCap (REsearch Data Capture), a secure web application for building and managing online surveys and databases, developed by a multi-institutional consortium initiated at Vanderbilt University and maintained by our faculty's IT Department.

The REDCap endometriosis project reduced or eliminated the need for individual spreadsheets stored on different data carriers. User-rights management allows control over what users can do in a given project, while audit trails provide functionality for tracking every view, edit, and export made by any user for compliance and accountability. The REDCap information system and data are stored in the Faculty of Medicine's servers. REDCap databases can be backed up according to a defined schedule. The data backups are kept in a secure environment and are recoverable. Data can be exported in various formats to work with popular statistical packages such as SPSS, Stata, SAS, R, or office applications like Excel or LibreOffice Calc. Data are also accessible via an application programming interface (API). REDCap is available free of charge to non-profit, academic, and government consortium partners. Data organised in this way will contribute to further studies of biomarker discovery using omics and multi-omics approaches.

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Research on Hormone Dependent Diseases – Patients' Perspectives

The Daily Endometriosis Centre in Ljubljana: Integrating Comprehensive Clinical Care and Research

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Endometriosis is a chronic, complex disease that affects multiple dimensions of a woman's life, including fertility, pain, sexual health, intimate relationships, psychological well-being, fatigue, and work capacity. The Daily Endometriosis Centre at the University Medical Centre Ljubljana has provided specialised care since 2013. More than 4,000 women have entered regular care to date, with long-term follow-up tailored to their symptoms, reproductive stage, current priorities, and reproductive wishes. The Centre offers a comprehensive and individualised pathway encompassing medical and surgical treatment, fertility assessment, assisted reproductive technologies, including in vitro fertilisation, and oocyte cryopreservation when indicated. Between 350 and 400 women with endometriosis undergo surgery at the Centre each year. Operating within a tertiary university medical centre provides direct access to specialists from other disciplines, supports multidisciplinary decision-making, and facilitates the introduction and evaluation of new diagnostic and treatment approaches. Recognising that optimal care extends beyond disease control and fertility outcomes, the Centre also provides patient meetings and psychological support.

The Centre serves as a hub connecting longitudinal clinical care with academic and laboratory research through close collaboration with the Faculty of Medicine and its research institutes. Its large, well-characterised patient population, continuity of follow-up, substantial surgical activity, and access to biological samples provide a strong foundation for translational research. Equally important is close collaboration with laboratory scientists and experts in translational medicine, whose methodological expertise and advanced laboratory facilities enable rigorous, high-quality, clinically relevant research. This integrated model allows clinical observations and unmet patient needs to generate research questions, while laboratory discoveries and research findings can be translated back into improved diagnostics, innovative treatment strategies, and long-term care. Previous successful projects and publications demonstrate the scientific value of combining multidisciplinary clinical expertise, prospective follow-up, biological samples, and specialised laboratory knowledge within a dedicated endometriosis centre.

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Beyond Survival: Early Menopause and Unmet Needs in Gynaecological Cancer Care

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Scientific advances have improved outcomes for women with gynecological cancers. However, clinical and research outcomes do not always reflect how women live during and after treatment. Effects on health, sexuality, relationships, family life and work may remain insufficiently recognized.

Premature or early menopause is one such challenge. It may result from systemic treatment, pelvic radiotherapy, surgery or risk-reducing procedures in women with hereditary predisposition to gynecological cancers. Consequences extend beyond vasomotor symptoms and may include cognitive changes ("brain fog"), fatigue, sexual and genitourinary symptoms, urinary incontinence, pelvic floor dysfunction and psychological distress, as well as long-term effects on bone and cardiovascular health. Management can be particularly complex when menopausal hormone therapy is contraindicated or requires individualized assessment.

Europa Donna Slovenia is a national patient organization with more than 3.700 members and one of the 47 national member organizations of EUROPA DONNA – The European Breast Cancer Coalition. In response to needs expressed by women with gynecological cancers, Europa Donna Slovenia established Section for Women with Gynecological Cancers in 2018. The organization provides information, peer-to-peer and professional psychosocial support to patients and their families, promotes physical activity, financial support and education on treatment and survivorship, and supports women in returning to work. Local groups make support and programmes accessible across Slovenia, while advocacy ensures that patients' needs are heard by healthcare professionals and decision-makers.

Daily contact with women affected by gynecological cancers that are going through the treatment now and ones who went through treatment years ago enable patient organizations to identify unmet needs that may remain invisible in care and research. Europa Donna Slovenia brings lived experience into clinical research and clinical practice. Future involvement in gynecological cancer research can help ensure that priorities and outcomes reflect what matters to patients. Meaningful patient involvement can translate scientific progress not only into longer survival, but also into better lives.

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