

Cytoreductive Surgery
for Advanced Tubo-ovarian Cancer

Tubercular Serpiginous
Choroiditis

Superficial
and Medium-Depth
Chemical Peels

Imaging
of Endometriosis

POISONS ADVICE TO DOCTORS

 1774

UNITED FOR LONG-LASTING[†] LDL-C CONTROL¹

LEQVIO is administered every 6 months* and provides effective LDL-C control, supported by 6+ years of data^{1,2}

*Two doses a year after the two initial doses. Single subcutaneous injection at the start of treatment, again at 3 months, and thereafter every 6 months.¹
[†]LDL-C reduction was maintained during each 6-month dosing interval after 2 initial doses of inclisiran.

 **LEQVIO**[®]
inclisiran

▼ LEQVIO[®]

PRESENTATION: Leqvio 284 mg solution for injection in pre-filled syringe. Each pre-filled syringe contains inclisiran sodium equivalent to 284 mg inclisiran in 1.5 ml solution. Each ml contains inclisiran sodium equivalent to 189 mg inclisiran.

INDICATION: Leqvio is indicated in adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet; in combination with a statin or statin with other lipid-lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin, or alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated.

DOSAGE: The recommended dose is 284 mg inclisiran administered as a single subcutaneous injection: initially, again at 3 months, followed by every 6 months. • **Missed doses:** If a planned dose is missed by less than 3 months, inclisiran should be administered and dosing continued according to the patient's original schedule. If a planned dose is missed by more than 3 months, a new dosing schedule should be started – inclisiran should be administered initially, again at 3 months, followed by every 6 months. • **Treatment transition from monoclonal antibody PCSK9 inhibitors:** Inclisiran can be administered immediately after the last dose of a monoclonal antibody PCSK9 inhibitor. To maintain LDL-C lowering it is recommended that inclisiran is administered within 2 weeks after the last dose of a monoclonal antibody PCSK9 inhibitor. • **Elderly, hepatic impairment, renal impairment:** no dose adjustment is necessary. Inclisiran should be used with caution in patients

with hepatic and renal impairment. • **Paediatric population:** The safety and efficacy of inclisiran in children aged less than 18 years have not yet been established. • **Method of administration:** Inclisiran is intended for administration by a healthcare professional via subcutaneous route. Each pre-filled syringe is for single use only.

CONTRAINDICATIONS: Hypersensitivity to the active substance or to any of the excipients listed in the SmPC.

WARNINGS/ PRECAUTIONS: • **Haemodialysis:** The effect of haemodialysis on inclisiran pharmacokinetics has not been studied. Considering that inclisiran is eliminated renally, haemodialysis should not be performed for at least 72 hours after inclisiran dosing. • **Sodium content:** This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially "sodium-free".

INTERACTIONS: Inclisiran is not an inhibitor or inducer of cytochrome P450 enzymes or common drug transporters. Therefore, inclisiran is not expected to have clinically significant interactions with other medicinal products. Based on the limited data available, clinically meaningful interactions with atorvastatin, rosuvastatin or other statins are not expected.

PREGNANCY, LACTATION AND FERTILITY: • There are no or limited amount of data from the use of inclisiran in pregnant women. As a precautionary measure, it is preferable to avoid the use of inclisiran during pregnancy. • It is unknown whether

inclisiran is excreted in human milk. A risk to newborns/ infants cannot be excluded. A decision must be made whether to discontinue breastfeeding or to discontinue/abstain from inclisiran therapy, taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman. • No data on the effect of inclisiran on human fertility are available.

ADVERSE REACTIONS: *Common:* Adverse reactions at the injection site.

LEGAL CATEGORY: POM

PACK SIZES: Pre-filled syringe: x1 pre-filled syringe. Pre-filled syringe with needle guard: x1 pre-filled syringe with needle guard.

MARKETING AUTHORISATION HOLDER: Novartis Europharm Limited, Vista Building, Elm Park, Merrion Road, Dublin 4, Ireland.

MARKETING AUTHORISATION NUMBER: EU/1/20/1494/001-2

Please refer to Summary of Product Characteristics (SmPC) before prescribing. Full prescribing information is available on request from Novartis Pharma Services Inc, Representative Office Malta, P.O. Box 4, Marsa MRS 1000 Malta. Tel +356 21222872.

2022-MT-LEQ-24-MAR-2022

References: 1. Leqvio Summary of product characteristics. Novartis. August 2022. 2. RS Wright, FJ Raal, W Koenig, U Landmesser, LA Leiter, GG Schwartz, A Lesogor, P Maheux, Z Tallocczy, S Vikarunnessa, X Zang, KK Ray. ORION-8: Long-term efficacy and safety of twice-yearly inclisiran in high cardiovascular risk patients. Data presented at the ESC Congress on August 28, 2023.

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The day you choose **JAKAVI**[®] (ruxolitinib) is the day you could change their life¹⁻⁵

RESPONSE

CONTROL

SURVIVAL



JAKAVI is indicated for the treatment of adult patients with myelofibrosis (MF), including primary myelofibrosis, post-polycythemia vera myelofibrosis or post-essential thrombocythemia myelofibrosis.¹

JAKAVI[®]
ruxolitinib

PRESENTATION: Each tablet contains 5mg, 10mg, 15mg or 20mg Ruxolitinib. **INDICATIONS:** Jakavi is indicated for the treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis (also known as chronic idiopathic myelofibrosis), post polycythemia vera myelofibrosis or post essential thrombocythemia myelofibrosis. Jakavi is indicated for the treatment of adult patients with polycythemia vera who are resistant to or intolerant to hydroxyurea. Jakavi is indicated for the treatment of graft host versus host disease or chronic graft versus host disease in patients over the age of 12 who have inadequate response to corticosteroids or other systemic therapies. **DOSAGE:** Jakavi treatment should only be initiated by a physician experienced in the administration of anti cancer medicinal products. A complete blood cell count, including a white blood cell count differential, must be performed before initiating therapy with Jakavi. The recommended starting dose in MF is of 5mg ruxolitinib twice daily for patients with platelet count between 50,000/mm³ and 75,000/mm³, 10mg twice daily for patients with platelet count from 75,000/mm³ to 100,000/mm³, 15 mg ruxolitinib twice daily for patients with a platelet count between 100,000/mm³ and 200,000/mm³ and 20 mg twice daily for patients with a platelet count of >200,000/mm³. Treatment may be continued as long as the benefit-risk remains positive. However the treatment should be discontinued after 6 months if there has been no reduction in spleen size or improvement in symptoms since initiation of therapy. Jakavi is to be taken orally, with or without food. If a dose is missed, the patient should not take an additional dose, but should take the next usual prescribed dose. The recommended dose for PV is 10mg given orally twice daily. Treatment should also be interrupted when haemoglobin is below 8g/dl. After recovery of blood counts above these levels, dosing may be restarted at 5mg twice daily and gradually increased based on careful monitoring of complete blood count. Dose reduction should also be considered if haemoglobin decreases below 12g/dl and is recommended if it decreases below 10g/dl. If efficacy is considered insufficient and blood counts are adequate, doses may be increased by a maximum of 5mg twice daily, up to a maximum dose of 25 mg twice daily. The recommended dose in GvHD is 10mg given orally twice daily. It can be added to continued corticosteroid use and/or calcineurin inhibitors (CNIs). Dose reductions and temporary interruptions of treatment may be needed in GvHD-patients with thrombocytopenia, neutropenia, or elevated total bilirubin after standard supportive therapy including growth-factors, anti-infective therapies and transfusions. In GvHD, tapering of Jakavi may be considered in patients with a response and after having discontinued corticosteroids. A 50% dose reduction of Jakavi every two months is recommended. **CONTRAINDICATIONS:** Hypersensitivity to the active substance or to any of the excipients. Pregnancy and lactation. **WARNINGS/PRECAUTIONS:** Treatment with Jakavi can cause haematological adverse drug reactions, including thrombocytopenia, anaemia and neutropenia. A complete blood count, including a white blood cell count differential, must be performed before initiating therapy with Jakavi. Patients should be assessed for the risk of developing serious bacterial, mycobacterial, fungal and viral infections. Tuberculosis has been reported in patients receiving Jakavi. Before starting treatment, patients should be evaluated for active and inactive ("latent") tuberculosis, as per local recommendations. Hepatitis B viral load increases have been reported in patients with chronic HBV infections taking Jakavi. Therefore such patients should be treated and monitored according to clinical guidelines. It is recommended to screen for HBV prior to commencing treatment with Jakavi. Physicians should educate patients about early signs and symptoms of herpes zoster, advising that treatment should be sought as early as possible. Progressive multifocal leukoencephalopathy (PML) has been reported with Jakavi treatment for myelofibrosis. Non-melanoma skin cancers have been reported in patients treated with ruxolitinib. Periodic skin examination is recommended for patients who are at risk for skin cancer. Treatment with Jakavi has been associated with increased lipid parameters and therefore lipid monitoring and treatment of dyslipidaemia according to clinical guidelines is recommended. The starting dose of Jakavi should be reduced in patients with severe renal impairment. For patients with end-stage renal disease on haemodialysis the starting dose should be based on platelet counts. The starting dose of Jakavi should be reduced by approximately 50% in patients with hepatic impairment. Following interruption or discontinuation of Jakavi, symptoms of myelofibrosis may return over a period of approximately one week. There have been cases of patients discontinuing Jakavi who sustained more severe events, particularly in the presence of acute

intercurrent illness. Jakavi contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product. **INTERACTIONS:** Interaction studies have only been performed in adults. When administering Jakavi with strong CYP3A4 inhibitors the unit dose of Jakavi should be reduced by approximately 50%, to be administered twice daily. Patients should be closely monitored (e.g. twice weekly) for cytopenias and dose titrated based on safety and efficacy. Patients should be closely monitored and the dose titrated based on safety and efficacy. In healthy subjects given ruxolitinib (50 mg single dose) following the potent CYP3A4 inducer rifampicin (600 mg daily dose for 10 days), ruxolitinib AUC was 70% lower than after administration of Jakavi alone. No dose adjustment is recommended when ruxolitinib is co-administered with mild or moderate CYP3A4 inhibitors (e.g. erythromycin). There is no interaction study with oral contraceptives. It cannot be excluded that ruxolitinib inhibits CYP3A4 in the intestine. Ruxolitinib may inhibit P-glycoprotein and breast cancer resistance protein (BCRP) in the intestine. This may result in increased systemic exposure of substrates of these transporters, such as dabigatran etexilate, ciclosporin, rosuvastatin and potentially digoxin. The concurrent use of haematopoietic growth factors and Jakavi has not been studied. The concomitant use of cytoreductive therapies and Jakavi has not been studied. The safety and efficacy of this co-administration is not known. **ADVERSE REACTIONS: MF patients – Very common:** Urinary tract infections, Herpes zoster, Pneumonia, Anaemia, Thrombocytopenia (any CTCAE grade and CTCAE grade 3), Neutropenia (any CTCAE grade), Bleeding (any bleeding including intracranial bleeding, gastrointestinal bleeding other bleeding), Bruising, Gastrointestinal bleeding, Other bleeding (including epistaxis, post-procedural haemorrhage and haematuria), Hypercholesterolaemia (any CTCAE grade), Hypertriglyceridaemia (any CTCAE grade), Weight gain, Dizziness, Headache, Elevated lipase (any CTCAE grade), Constipation, Raised alanine aminotransferase (any CTCAE grade), Raised aspartate aminotransferase (any CTCAE grade), Hypertension. **Common:** Sepsis, Thrombocytopenia (CTCAE grade 4), Neutropenia (CTCAE grades 3&4), pancytopenia, Intracranial bleeding, Flatulence, Raised alanine aminotransferase (CTCAE grade 3), PV patients – Very common: Urinary tract infections, Herpes zoster, Anaemia (any CTCAE grade), Thrombocytopenia (any CTCAE grade), Bleeding (any bleeding including intracranial, and gastrointestinal bleeding, bruising and other bleeding), Bruising, Other bleeding (including epistaxis, post-procedural haemorrhage and haematuria), Hypercholesterolaemia (any CTCAE grade), Hypertriglyceridaemia (any CTCAE grade), Weight gain, Dizziness, Headache, Elevated lipase (any CTCAE grade), Constipation, Raised alanine aminotransferase (any CTCAE grade), Raised aspartate aminotransferase (any CTCAE grade), Hypertension; **Common:** Pneumonia, Anaemia (CTCAE grade 3), Thrombocytopenia (CTCAE grade 3), Neutropenia (any CTCAE grade), pancytopenia, Gastrointestinal bleeding, Flatulence. For a full list of adverse reaction please refer to the Summary of Product Characteristics. **LEGAL CATEGORY: POM PACK SIZE: 56 Tablets MARKETING AUTHORISATION HOLDER:** Novartis Europharm Limited, Vista Building, Elm Park, Merriem Road, Dublin 4, Ireland. **MARKETING AUTHORISATION NUMBER:** EU/1/12/773/005, 008, 011, 015.

Please refer to Summary of Product Characteristics (SmPC) before prescribing. Full prescribing information is available on request from Novartis Pharma Services Inc., Representative Office Malta, P.O. Box 4, Marsa, MRS 1000, Malta. Tel: +356 21222872.2022-MT-JAK-29-APRIL-2022. To report adverse events electronically please use the following link: www.novartis.com/report or by e-mail at drug_safety_malta@novartis.com.

References: 1. JAKAVI[®] (ruxolitinib) Summary of Product Characteristics, April 2022. 2. Verstovsek S, et al. N Engl J Med. 2012;366:799-807. 3. Harrison C, et al. N Engl J Med. 2012;366:787-798. 4. Verstovsek S et al. J Hematol Oncol. 2017; 10(1): 55. 5. Verstovsek S et al. J Hematol Oncol. 2017; 10(1): 156.



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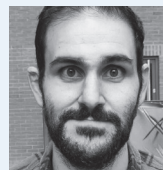
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Dr Mark Brincat MD, MSc, MRCOG, EFOG is a gynaecologist who pursued post-CCT ESGO subspecialisation training in Surgical Gynaec-Oncology at the Royal London Hospital. His special interests include ultraradical cytoreductive surgery for advanced gynaecological malignancies and fertility-preserving surgery for early-stage cancers.



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PUBLISHED SINCE OCTOBER 1996

Malta National Poisons Centre



Robert Louis Stevenson, the Scottish novelist - best known for books which we treasured in our childhood like *Treasure Island* - was a remarkable man, despite being seriously sick for most of his life, most probably with bronchiectasis; he was a prolific writer and traveller till the very end, dying in Samoa aged 44.

His masterpiece the *Strange Case of Dr. Jekyll and Mr. Hyde* explores the interplay between a kind respected doctor Dr Henry Jekyll and his alter ego the murderous Mr Edward Hyde. One of the most prominent interpretations of this novel remains the examination of the duality of humanity, expressed as an inner struggle between good and evil.

Similarly, a clinical toxicologist bridges the science of substances which can heal us, but can also lead to our death. Pharmacology and toxicology are intertwined. What can kill can possibly cure, and what can cure, can most definitely also kill. This Jekyll-Hyde duality has been recognized since antiquity ... a serpent coiled around a rough-hewn branch symbolizes Asclepius, the Greek god of medicine and healing.

Paracelsus, a 16th-century Swiss physician whom we refer to as the father of toxicology, probably summed it best: *"All things are poison, and nothing is without poison; the dosage alone makes it so a thing is not a poison"*.

Arsenic, the king of poisons, is a case in point. Arsenic trioxide (As_2O_3) was the poison of choice of the Borgias, also referred to as *poudre de succession*, helping ambitious princes secure thrones. Long before that, the Greek physicians Hippocrates and Galen recommended the naturally occurring arsenic disulfide (As_2S_3) for treating ulcers. Fowler's solution (1% potassium arsenate, K_3AsO_4) created in 1786 was used for more than 150 years to treat everything from asthma to cancer. In 1907 an arsenic compound arsphenamine, became the first effective remedy for syphilis. Arsanilic acid (Atoxyl[®]) developed by Paul Ehrlich, a German physician, and Kiyoshi Shiga, a Japanese physician, was also the first effective treatment for African trypanosomiasis, but blindness was a serious side effect. In 1890 the Canadian physician William Osier founder of modern medical education, pronounced arsenic the best drug for leukaemia, and today, as we speak, the same arsenic trioxide used by the Borgias as a poison is an effective chemotherapy agent which we use for cases of acute promyelocytic leukaemia.

However, arsenic is there again the epitome of the poison paradox as described by John Timbrell, Professor of Biochemical Toxicology at King's College in London.

Going full circle, arsenic poisoning in contaminated groundwater in Bangladesh is a case in point, ongoing and affecting millions, and described as the worst mass poisoning of a population in history¹.

What should we make of all this and what relevance does it have to our everyday lives wherever we live in Malta and beyond? Clinical toxicology is relevant not just in the treatment of the poisoned or overdosed patient but in all clinical specialties without fail.

We live in a chemical world. The number and volume of industrial and agricultural chemicals, recreational drugs, consumer products and pharmaceuticals are increasing every year.

Toxicities, irrespective of whether intentional or accidental, recreational, or occupational, are a matter of public health concern. Human exposure to chemical agents is increasing, and additional preventive action is required. That is where poison centres come into play².

A poison centre is a specialized unit advising on and assisting in the prevention, diagnosis and management of acute and chronic poisoning. Poison centres contribute to reducing the burden of diseases related to poisonings and exposure to hazardous chemical agents in emergencies and in everyday life. Another aim is to achieve progress in the implementation of global and regional chemical safety-related strategies, adding meaningful value to healthcare systems, actively saving lives and reducing the costs of healthcare related to poisonings³.

The Malta National Poisons Centre was officially inaugurated by the Hon. Minister Jo-Etienne Abela on 9 May 2024.

Monday – Sunday 8:00am - 8:00pm

After-hours support is available exclusively for healthcare professionals through clinical toxicologists on-call. The contact number for after-hours assistance can be found on Kura.



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2. Jackson G, Zammit ML. Poison centres as essential unit for poisoning prevention and sound chemicals management. Technical summary. Copenhagen: WHO Regional Office for Europe. 2023. Licence: CC BY-NC-SA 3.0 IGO.
3. Jackson G, Zammit ML. At least one poison centre in each country: summary for decision makers. Copenhagen: WHO Regional Office for Europe. 2023. Licence: CC BY-NC-SA 3.0 IGO.

Cytoreductive Surgery for Advanced Tubo-ovarian Cancer – A Paradigm Shift

ABSTRACT

Complete macroscopic cytoreduction is the best prognostic variable a patient could experience during treatment for advanced ovarian cancer. Malta needs to make great strides to satisfy European-standard quality indicators for surgical management of advanced gynaecological cancer, and to progress toward 5-year survival rates of neighbouring countries. Surgical cytoreductive management requires a dedicated centralised team that can provide subspecialised multidisciplinary care. This article provides an overview of the role of cytoreductive surgery along the disease trajectory of advanced tubo-ovarian cancer.

KEYWORDS

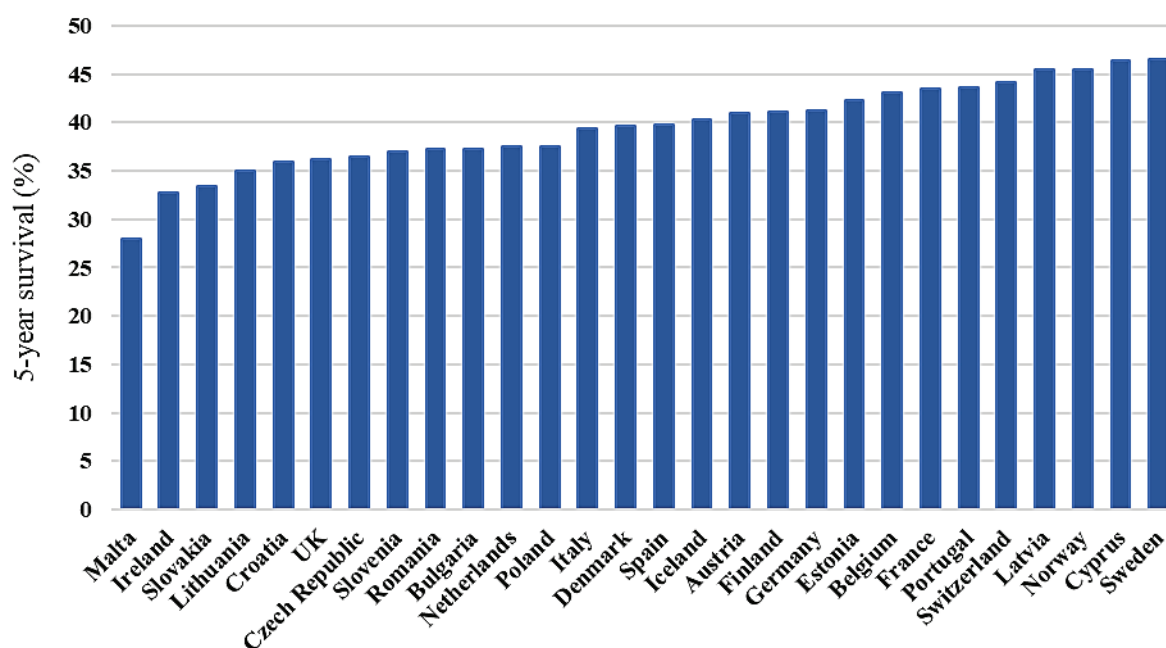
cytoreductive surgery, ovarian cancer, gynaecological oncology

BACKGROUND

Tubo-ovarian cancer represents the second most common gynaecological malignancy in Malta, with a local 5-year prevalence of 57 cases per 100,000, following uterine cancer with a 5-year prevalence of 138 cases per 100,000.¹ More than 75% of patients with tubo-ovarian carcinoma are diagnosed at an advanced stage of the disease, which is associated with poorer overall survival. Symptoms at presentation are vague and non-specific, contributing to late diagnosis. Meanwhile, only 20% of women with uterine cancer present with advanced disease. This is in part secondary to recognisable symptoms such as postmenopausal bleeding.

The CONCORD 3 collaborative project covering the period 2010-2014, showed that Maltese ovarian cancer patients had the lowest five-year age-standardised net survival (28%) of

Figure 1. Ovarian cancer 5-year age-standardised survival, Europe.²



THE CONCORD 3 COLLABORATIVE PROJECT COVERING THE PERIOD 2010-2014, SHOWED THAT MALTESE OVARIAN CANCER PATIENTS HAD THE LOWEST FIVE-YEAR AGE-STANDARDISED NET SURVIVAL (28%) OF ALL 31 COUNTRIES PARTICIPATING IN STUDY. THE TEMPORAL SURVIVAL TREND IS LESS THAN PROMISING; 5-YEAR SURVIVAL IN MALTESE OVARIAN CANCER PATIENTS WAS 34.2% IN 1995-1999, 39.6% IN 2000-2004 AND 27.5% IN 2005-2009

all 31 countries participating in study.² (Figure 1) The temporal survival trend is less than promising; 5-year survival in Maltese ovarian cancer patients was 34.2% in 1995-1999, 39.6% in 2000-2004 and 27.5% in 2005-2009.

Treatment for advanced gynaecological malignancies, particularly advanced ovarian cancer (AOC), consists of a combination of cytoreductive surgery and adjuvant treatment (such as chemotherapy), with maintenance treatment as appropriate (including agents such as Bevacizumab, Olaparib and Niraparib). Surgical cytoreduction, with the aim of achieving a state of no gross residual macroscopic disease, is the best prognostic variable a patient could experience throughout the disease trajectory. Each additional 10% cytoreduction of disease yields a 5.5% increase in median survival.³

Malignant epithelial ovarian tumours characteristically spread onto peritoneal surfaces via the transcoelomic route. Disease is expansile and characteristically respects peritoneal planes, enabling resection through a retroperitoneal approach. Localisation of peritoneal metastases is not random but is influenced by gravity, peritoneal fluid flow, peristalsis and peritoneal cavity recesses and ligaments. Spread typically occurs along the visceral and parietal peritoneal surfaces of the lower abdominal cavity, omental tissue, as well as diaphragmatic surfaces. Peritoneal fluid physiologically flows from the deep pelvis via the right paracolic gutter, cranially to Morison's pouch and right subdiaphragmatic space, and back down to the pelvis. For this reason, right-sided upper abdominal surfaces are more frequently involved in the disease process.⁴

A MULTIVISCERAL, MULTICOMPARTMENTAL APPROACH

Several classifications enable the quantification of residual disease at cytoreduction. The most common

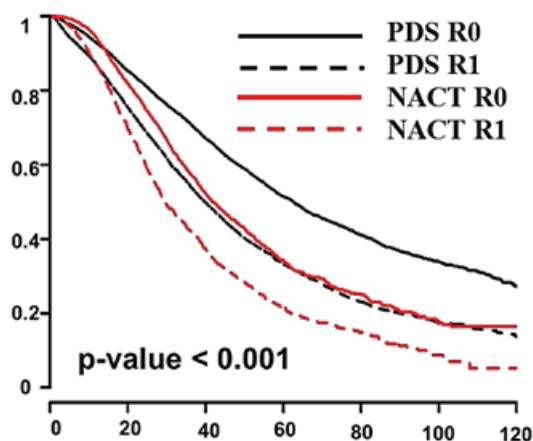
terminology includes complete gross resection (CGR/R0 no residual macroscopic disease), optimal cytoreduction (R1<1cm residual disease) and suboptimal cytoreduction (R2 ≥1cm residual disease). The surgical objective for advanced gynaecological malignancy is that of achieving a CGR/R0 resection, as this is associated with the greatest progression-free survival (PFS) and overall survival (OS) benefit. In specific circumstances, an R1 resection may also confer a PFS and OS benefit. An R2 resection confers no PFS or OS benefit, but may provide palliation of symptoms from a specific disease site.

Achieving this target often requires a multivisceral, multicompartmental approach. Close to half the patients with advanced tubo-ovarian malignancy require a bowel resection (± enterostomy) to achieve CGR.⁵ 39.5% of patients with advanced-stage disease require an upper abdominal resection - this includes right diaphragmatic stripping or full-thickness resection (29.3%), splenectomy (7.5%), lesser sac disease resection (5.4%) and porta-hepatis disease resection (5.4%).⁶ Cases may also include the resection of enlarged pelvic, aortocaval, inguinal and/or cardiophrenic nodes. Routine resection of macroscopically normal lymph nodes in AOC is no longer recommended following the findings of the LION trial which showed this confers no PFS/OS benefit and is associated with a higher incidence of postoperative complications.⁵

SURGICAL TIMING

Several investigators have studied the impact of surgical timing on AOC patient outcomes. Surgery can be upfront (PDS, Primary debulking surgery), or may be undertaken halfway through chemotherapy (IDS, Interval debulking surgery). Delayed debulking surgery (DDS) is cytoreductive surgery after more than 5 cycles of chemotherapy. IDS and DDS need to be carefully timed to avoid surgery during the chemotherapy-induced nadir and associated

Figure 2. Impact of surgical timing on median survival (months) in AOC patients.¹²



Treatment sequence	Residual disease after surgery	Median survival	95% CI
PDS	R0	62.6	60.5, 64.5
	R1	39.8	38.6, 41.1
NACT	R0	41.8	40.2, 44.2
	R1	29.5	28.4, 31.9

complications such as anaemia, neutropenia and thrombocytopenia.

Major trials addressing surgical timing (EORTC⁷, CHORUS⁸ trials) showed that survival data for IDS are non-inferior to upfront surgery and this approach was associated with less surgical morbidity. A major criticism of these trials is that the maximal cytoreductive effort in their cohorts appears to be suboptimal, with a median operating time of less than three hours and CGR achieved in less than 20% of patients. The European Society of Gynaecological Oncology (ESGO) quality indicator for ovarian cancer cytoreductive surgery recommends a minimum CGR rate of 50% with an optimal target of >65%.⁹ Malta's CGR rate between 2008-2016 was 9.5%.¹⁰

Evidence in the context of advanced uterine cancer, or AOC at DDS setting, has only shown an OS advantage with complete macroscopic resection. This means no statistically significant survival advantage is conferred with any residual disease at cytoreduction. Several proponents suggest that a maximal cytoreductive effort should be undertaken as early as possible if the patient is fit and the disease is deemed resectable on clinico-radiological assessment. At a physiological level, this means subsequent adjuvant chemotherapy would be targeting microscopic disease as opposed to gross tumour tissue. Surgery also eliminates cell subpopulations within the heterogeneous tumour environment, that could potentially become a chemo-resistant clone. Resection of ovarian tumour may also improve host immunity by removing from the host certain cells such as T-regulatory cells, which have known immunosuppressive properties.¹¹

In a seminal paper titled 'Interval debulking surgery is not worth the wait' Lyons et al presented data from a cohort of 36,602 AOC patients, and showed that an R0 resection at PDS confers the best OS benefit, while an R1 resection at PDS is equivalent to an R0 resection at IDS (with prior neoadjuvant chemotherapy (NACT))¹² (Figure 2). ESGO quality indicators for AOC recommend >50% of cytoreductions should be at the PDS stage.⁹

The ongoing SUNNY¹³ and TRUST¹⁴ trials aim to re-investigate surgical timing and their protocols have emphasised standardised surgical quality and radicality for the participating teams.

The most common tubo-ovarian carcinoma subtype is high-grade serous adenocarcinoma which is associated with good chemotherapeutic response rate of over 70%. Upfront radical surgery is particularly important in chemo-resistant tumour subtypes such as low-grade serous adenocarcinoma, clear cell carcinoma and mucinous carcinoma.¹⁵

WHAT ARE THE LIMITS OF RESECTABILITY?

Specific disease sites are technically termed 'critical lesions' that should prompt a neoadjuvant chemotherapy approach (Figure 3). Preoperative radiological CT assessment is essential to identify patients at risk of a 'futile' (open-close) laparotomy or at a higher risk of residual disease following cytoreduction. However, a futile laparotomy at primary surgery does not mean a patient is ineligible to have an IDS/DDS attempt following treatment response to chemotherapy.

Figure 3. Critical lesions that preclude a primary cytoreductive approach in AOC patients.⁹

- ▶ Diffuse deep infiltration of the root of small bowel mesentery
- ▶ Diffuse carcinomatosis of the small bowel involving such large parts that resection would lead to a short bowel syndrome (remaining bowel <1.5 metres)
- ▶ Diffuse involvement/deep infiltration of:
 - stomach/duodenum
 - head or middle part of pancreas
- ▶ Involvement of coeliac trunk, hepatic arteries, left gastric artery
- ▶ Central or multisegmental parenchymal liver metastases
- ▶ Multiple parenchymal lung metastases (preferably histologically proven)
- ▶ Non-resectable lymph nodes

Quantifying the extent of bowel serosal and mesenteric deposits on CT is technically difficult to perform and report. One of the limitations of CT is its inability to demonstrate small volume 'miliary' (<5mm) deposits on the bowel serosa and mesentery, which are perhaps the most common rate-limiting steps precluding CGR. Evaluation may thus sometimes necessitate laparoscopic assessment to further assess disease distribution and resectability. Despite these limitations, with good imaging acquisition and interpretation, CT remains excellent with reported accuracies of 70-90% for detection of disease at all stages.¹⁶ During gynae-oncological multidisciplinary meetings, a systematic CT reporting approach is essential to identify and communicate important sites of disease, which may alter treatment approach by the multidisciplinary team.¹⁷ If a patient is not offered upfront surgery, a 'rate-limiting step' should be clearly documented in the multidisciplinary meeting outcome – this guides radiologists interpreting follow-up imaging when the case is being considered for IDS or DDS.

Following a systematic laparoscopy or exploratory laparotomy, the surgical team may in specific circumstances conclude that the risks of morbidity or quality of life impact of proceeding with maximal effort cytoreduction outweigh the benefits, based on the patient's clinical condition, frailty and the radicality required to achieve CGR. One may for example choose to abandon a primary cytoreduction attempt if achieving CGR would require a total colectomy and end ileostomy in a chemo-naïve patient, but may *not* reach the same conclusion if the patient has had neoadjuvant chemotherapy and is at IDS or DDS stage.

SECONDARY CYTOREDUCTIVE SURGERY

Following completion of primary AOC treatment, that is, a combination of surgical cytoreduction (PDS, IDS or DDS) and six chemotherapy cycles (generally Carboplatin + Paclitaxel ± Bevacizumab), the patient would then go onto maintenance treatment. This may include Bevacizumab (a VEGF inhibitor) or a PARP inhibitor such as Olaparib.

A majority of patients experience disease recurrence, at which point surgery also plays an important role. Surgery at this stage is termed secondary cytoreduction surgery (SCS). The landmark DESKTOP 3 trial showed a survival advantage in patients successfully undergoing SCS when compared to chemotherapy alone.¹⁸ Among patients in the surgery arm who had complete tumour resection, the median overall survival was 61.9 months (95% CI 55.3-78.9), as compared with 27.7 months (95% CI 23.5-38.7) among patients who did not have complete resection, and 14 months (95% CI 12.7-15.4) in patients ineligible for SCS.

Not all patients with recurrent disease are eligible for SCS. DESKTOP 3 used the AGO criteria to assess patient eligibility: ECOG Performance status of 0, no residual disease at the initial cytoreductive surgery and ascites of <500ml on current imaging. Eligibility also requires relapsed disease to be at least 6 months after the last course of initial platinum-based chemotherapy e.g. carboplatin, cisplatin (i.e. platinum-sensitive disease). These criteria led to CGR in 76% of patients.¹⁸ The most common recurrence sites at SCS are the pelvic peritoneum (34.4%), rectosigmoid serosa (31.3%), small bowel mesentery (25.0%) and small bowel serosa (20.3%). The proportion of women having bowel resection during SCS for recurrent epithelial ovarian cancer is quoted to be 29.7%.¹⁹

CONCLUSION

Tubo-ovarian cancer incidence is projected to increase by 5% over the next decade with an accompanying 15% decrease in mortality rate, reflecting population ageing and improved treatment strategies.^{20,21}

A surgical team is as effective as the system that supports them. A multidisciplinary approach by appropriately trained professionals is necessary to improve outcomes for patients with advanced gynaecological malignancies such as AOC. This starts from preassessment, counselling and prehabilitation by dietetic teams, exercise physiologists, clinical nurse specialists and anaesthetic teams. It continues with appropriate support from non-gynaecological surgical specialities, as well as early postoperative monitoring within a high-dependency unit setting with input from physiotherapists, occupational therapists and other health care professionals.

In April 2023 NICE published its guidance supporting maximal cytoreductive surgery for AOC.²² Several units have reported improved CGR rates and better AOC survival with homogenisation of care and centralised patient management by dedicated surgical gynaec-oncology teams.²³ We need to tackle geographic disparities that exist in patient access to specialised gynaecological cancer care. Malta needs a paradigm shift in its surgical management of advanced gynaecological malignancies. Even when disease appears to be limited to the pelvis, surgery for suspected or confirmed ovarian cancer should only be undertaken with surgical preparedness to proceed with appropriate colorectal or upper abdominal procedures necessary to achieve CGR.

No conflicts of interest to declare.

EVEN WHEN DISEASE APPEARS TO BE LIMITED TO THE PELVIS, SURGERY FOR SUSPECTED OR CONFIRMED OVARIAN CANCER SHOULD ONLY BE UNDERTAKEN WITH SURGICAL PREPAREDNESS TO PROCEED WITH APPROPRIATE COLORECTAL OR UPPER ABDOMINAL PROCEDURES NECESSARY TO ACHIEVE COMPLETE GROSS RESECTION

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Continued from Issue 1

An Overview of Superficial and Medium - Depth Chemical Peels – Part II

B. MEDIUM-DEPTH PEELS

Medium-depth and deep peels are the techniques of choice for deeper wrinkles and photodamaged skin.¹¹

Medium-depth peels use:

1. Trichloroacetic acid (TCA) 35-50%, which may lead to scarring and dyspigmentation.
2. Combination Peels
 - Monheit Peel - Jessner's solution (14% salicylic acid, 14% lactic acid, and 14% resorcinol in 95% ethanol) in combination with 35% TCA.
 - Brody's Peel - Solid CO₂ (dry ice) plus 35% TCA.
 - Coleman Peel - Glycolic acid at 70% plus 35% TCA.
3. 88% phenol, however, it carries the risk of hypopigmentation and cardiotoxicity.¹

MECHANISM OF ACTION

Medium-depth peels reach the papillary and upper reticular dermis. Precipitation of proteins and coagulative necrosis of the epidermal cells occur in 5-7 days. Collagen necrosis in the papillary and upper reticular dermis also occurs. The process causes dermal oedema.¹² Re-epithelialization becomes evident at the radicular shaft of the follicles several days after the necrotic layers have sloughed. This epidermal reepithelization usually occurs at day 7.

1. TRICHLOROACETIC ACID 35-50%

TCA is highly water soluble. The depth of penetration correlates directly to the concentration. TCA penetrates slowly, so one must wait for 5 minutes before assessing the frosting endpoint to avoid overcoating.

The degree of the frosting correlates with the depth of solution penetration.

Level I frosting is speckled white frosting with mild erythema and corresponds to superficial penetration.

Level II is characterized by an even white-coated frost with background erythema. This degree of frosting is usually desirable for medium-depth peels.

Level III is solid white opaque frost with little or no background erythema, usually characterizing deep peels and not desirable in TCA procedures.

The frosting seen with TCA corresponds to epidermal and dermal protein denaturation.

INDICATIONS

Treatment of photoaging and rhytides, actinic keratoses, lentigines, and other pigmentary dyschromias are the principal indications for the TCA chemical peel.

It is also occasionally used, but is variably effective, for superficial acne scars, PIH, melasma, dilated pores, vitiligo, rosacea, seborrheic dermatitis, and other conditions. It compares favorably with 5-fluorouracil (5-FU) cream for the treatment of actinic keratoses, and the duration of benefit may be longer. It has a definite role in improving the fine crosshatched facial rhytides and even moderately deep perioral wrinkles but is not indicated for deeper rhytides caused by muscles of facial expression or lax skin.

As with other chemical peel agents, it generally renders to skin a more pleasant, smooth, and less dry or irritated appearance and feel.¹¹⁻¹³

PREPARATION

Preparation is similar to that for superficial peels. No other cosmetic treatments with bleaching, depilation or exfoliation should be used for one week before the treatment. Shaving must also be avoided 24 hours before a peel. Signing a consent form before the procedure is recommended.

The face should be wiped with a cleansing and degreasing agent. Vaseline is applied to sensitive areas like what was described for the superficial peels.



APPLICATION METHOD

The TCA is applied using a cotton-tipped applicator, saturated gauze pad or a brush. Smooth strokes are used. Once the peel is applied, 'frosting' appears as a white colour, and this is a consequence of epidermal and dermal protein coagulation.

The endpoint for 35-40% TCA peels is the presence of a uniform white frost that clears in 10-15 mins. This means that there is epidermal and papillary dermal injury. The endpoint of a 50% TCA peel is a white, dense, uniform frost that clarifies in 40-50 mins. If there is the presence of a yellow-grey frost, this means that the mid-to-deep reticular dermis was reached and injured and it takes more than 40 mins to disappear.¹² Cool compresses are applied after the peel, to ameliorate the burning sensation in the area. A small fan can also be used.

SIDE EFFECTS

TCA peels are easy to use and predictable at low concentrations of 10-30%, with a low incidence of complications. However, they become unpredictable and erratic at higher concentrations of over 35%. TCA peels at 50% concentrations may result in textural changes and hypopigmentation. It may also produce hypertrophic scarring or full-thickness tissue loss followed by contractile scars.

Other more common complications are pigmentary disturbances, like hypo or hyperpigmentation. Hyperpigmentation is usually post-inflammatory and temporary and can be treated with tretinoin, bleaching creams and sun protection creams. Bacterial infections are uncommon, and when they occur are often thought to be the result of inadequate postoperative wound care.¹²

2. COMBINATION PEELS

The trend is to combine lower concentration TCAs with less potent superficial peeling agents due to the risks involved with higher concentration TCA peels.

A. MONHEIT PEEL – JESSNER'S SOLUTION PLUS 35% TCA

This peel uses Jessner's solution (JS) as a keratolytic agent to further TCA penetration.¹⁴ It is performed by first degreasing the face using a degreasing agent followed by the application of JS. The endpoint is reticulate frost.³

JS is a superficial peeling agent that has been used for over 100 years. This superficial peeling agent was formulated by Dr Max Jessner, a German dermatologist, and constitutes a mixture of 14g each of salicylic

acid, resorcinol, and 85% lactic acid in 95% ethanol to make 100ml of the effective peeling agent.¹⁵ After pre-treatment with the JS, 35% TCA can be applied to extend injury into the dermis. The combination of JS and 35% TCA peel is rarely associated with scarring complications.¹⁶

INDICATIONS

The Monheit peel is useful for moderate actinic damage, pigmentary dyschromias, and minor wrinkles.¹²

B. BRODY PEEL - SOLID CO2 (DRY ICE) PLUS TCA 35%

This approach of combining solid CO2 and TCA creates a controlled medium-depth peel. Dry ice is easily available and can be found at local supermarkets or pharmaceutical companies.

After degreasing, a hand-sized block of dry ice dipped in a 3:1 acetone solution is initially applied on the face to cause epidermal injury. This allows for the superficial-to-deep penetration of the TCA. The application time of solid CO2 ranges from 3 to 15 seconds. The endpoint is transient white frost with residual erythema. This step is followed by the application of 35% TCA. This extends the injury into the dermis. The endpoint of the TCA application is an even light white or solid white frost.^{3,12} Histological studies show that this type of peel results in damage through the papillary dermis.¹⁷

INDICATIONS

The indication of this peel is moderate actinic damage, superficial hyperpigmentation and minor wrinkles. This type of peel can also be used for the improvement of the contours of pitted scars.

C. COLEMAN PEEL: GLYCOLIC ACID 70% PLUS TCA 35% COMBINATION PEEL^{3,12}

70% glycolic acid superficial peel is used followed by 35% TCA to extend injury to the dermis. The technique of application is slightly different. Before the procedure, patients are asked to wash their faces with soap.

The glycolic acid is applied for approximately 2 minutes until an endpoint of erythema is reached. It then needs to be neutralised with water or an alkaline neutralising agent, like 10% sodium bicarbonate, ammonium salts or sodium hydroxide prior to the application of the TCA.

INDICATIONS

It is useful for moderate actinic damage, pigmentary dyschromias, and minor wrinkles. A medium-depth peel should not be used elsewhere other than on the face or the scalp because of the risk of scarring.

3. PHENOL PEEL

Unoccluded 88% phenol is a medium-depth peel. It is rarely used for full-face peeling because of the risks of cardiotoxicity including cardiac arrhythmias (phenol has dual hydrophilic and lipophilic properties and is readily absorbed through the skin and distributes widely through the body within minutes) and hypopigmentation.¹⁸ Coagulation of epidermal and superficial dermal proteins occurs immediately after phenol application. Histologically there is an increase in collagen and elastic fibers. A new way of applying 88% phenol was described by de Mendoca et al.¹⁹ This was the punctuated pattern technique for individual rhytids. The advantage is that it decreases phenol exposure.

CONCLUSION

A chemical peel can be a simple office procedure. Superficial and medium-depth peels can treat a variety of conditions, like pigmentation, photoaging and superficial scarring. Careful patient and peel selection will ensure procedural success with excellent results. Chemical peels are not a one-time procedure and should be repeated with maintenance peels to achieve maximum improvement and prevent recurrence. With the advent of lasers and newer techniques, the use of chemical peels has slightly declined, however, its simplicity as an office procedure, minimal morbidity, easy availability and cost-effectiveness ensure that it still holds an important place as a tool to treat dyschromias and photoaging.

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Imaging of Endometriosis



BACKGROUND

Endometriosis is a common chronic gynaecological condition, characterised by the presence of endometrial tissue outside the uterus, which can cause pelvic pain and infertility.¹⁻³ The aetiology of endometriosis is not fully understood, but genetic, hormonal and immunological factors are thought to play a role.⁴

Endometriosis is thought to affect approximately 10% of women in their reproductive years.¹ It is found in 20-50% of women suffering from infertility and in a majority of women who suffer from chronic pelvic pain.^{1,5} There is an increased risk for endometriosis if a first-degree relative/s suffers from the condition.^{1,6}

SYMPTOMS

The two most common symptoms of endometriosis are pelvic pain and infertility. Other symptoms of endometriosis are dependent on the affected locations in the pelvis (or outside of the pelvis) and include dysmenorrhea (painful menstruation), dyspareunia (pain during or after intercourse), dysuria (pain and/or burning sensation associated with urination), dyschezia (painful defaecation), haematochezia (passage of fresh blood through the anus) and cyclical pain and swelling of the Caesarean section scar. There is, however, a poor correlation between the severity/extent of the disease and symptoms.⁷ In addition to the described symptoms,

women affected by this condition often experience diminished quality of life, adverse effects on intimate relationships, limitations in their daily activities, loss of productivity and significant healthcare costs.⁷

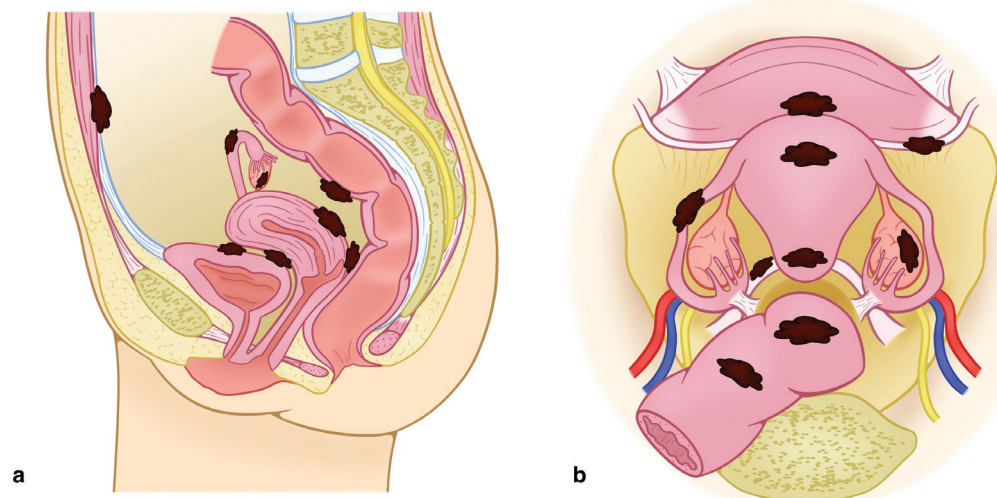
The mean delay between onset of symptoms to diagnosis of endometriosis has been estimated to range between 4 and 11 years.⁷ This delay contributes to the morbidity and psychological burden experienced by affected women.

DIAGNOSIS OF ENDOMETRIOSIS

Endometriosis may be divided into three types – ovarian endometriomas, superficial peritoneal endometriosis and deep infiltrative endometriosis (DIE).⁸ Ovarian endometriomas, also referred to as “chocolate cysts” or endometriotic cysts are a localized form of endometriosis within the ovary. Superficial peritoneal endometriotic deposits are non-invasive implants which are often recognized at laparoscopy.

Deep infiltrative endometriosis is defined by invasion of the endometrial glands and stroma at least 5 mm beneath the peritoneal surface.³ The latter form is associated with fibrosis and disruption of normal anatomy and is the one which is thought to contribute most frequently to pelvic pain and infertility, which are the two main manifestations of this condition.³ Figures 1 a and b depict the most common locations of endometriotic lesions detected on MRI.

Figure 1.
Drawings of the female pelvis in the sagittal (a) and axial (b) planes showing the most frequently encountered locations of endometriotic lesions on MRI.



CLINICAL EXAMINATION

While a pelvic (vaginal) examination is often an important part of the initial assessment, its diagnostic accuracy for the detection of endometriosis is low.⁴ Therefore, a normal physical exam does not exclude the diagnosis.

IMAGING OF ENDOMETRIOSIS

For many years, visualization of endometriotic deposits at laparoscopy with subsequent histological confirmation was the gold standard for diagnosis.⁹ Over the last years, there has been a paradigm shift towards an initial assessment with non-invasive imaging techniques in cases of suspected endometriosis.

Transvaginal ultrasound (TVUS) is often performed as a first-line investigation. It has a number of advantages, namely its ease of use, availability, minimal invasiveness, dynamicity and cost-effectiveness.⁹ For adnexal endometriosis, the equivalence in diagnostic performance of TVUS, MRI and laparoscopy has been demonstrated.¹⁰ TVUS performed systematically by gynaecologists specifically trained in the detection of endometriosis, may provide useful information with regard to organ mobility (e.g. ovarian mobility), assessment of the pelvic compartments (for non-bowel DIE) and of the anterior wall of the rectum (for bowel DIE).¹¹ It has however a number of limitations in assessing for deep pelvic endometriosis as a number of affected structures are beyond its reach and while it shows high specificity, it may lack sensitivity.¹⁰

MRI

MRI is often performed following an initial TVUS when deep pelvic endometriosis is detected or suspected. It is the imaging modality showing the highest accuracy for assessing the burden of DIE and shows high sensitivity for endometriotic deposits in view of its excellent soft-tissue resolution.⁹ MRI is considered the gold standard imaging examination for DIE and provides exquisitely detailed multiplanar anatomical images of the pelvis without the inherent operator-dependency of US. It also provides a roadmap which is essential in preoperative planning.⁸

Patient Preparation for MRI

Patients undergoing MRI for endometriosis should fast from food for at least four hours prior to the start of the examination and avoid large meals before this period. A moderately filled bladder is recommended. Just before commencing the scan, an antispasmodic agent (IV hyoscine butylbromide) is administered (unless contraindicated) to reduce bowel peristalsis and prevent associated artefacts.

MRI Protocol

MRI examinations for endometriosis are mainly based on the acquisition of multiplanar T2-weighted images (T2w) and T1-weighted (T1w) images. The examination is performed without injection of IV contrast and further sequences are not usually required unless unexpected pathology (e.g. malignancy) is detected. Scan time is usually not longer than about 30 minutes.

MR Imaging Features and Staging of Endometriosis

Endometriosis is a condition that can involve multiple pelvic organs and structures, and can also occur in areas outside the pelvis.^{1,9} A standardized compartment-based reading and reporting approach, such as that proposed by the ENDOVALIRM group⁸ may be used for MRIs performed for DIE. This provides a degree of standardization and facilitates communication between radiologists and surgeons.

DIE is seen more frequently in the posterior pelvic compartments, including the torus, rectovaginal septum, USLs, Douglas pouch and anterior rectal wall. It is seen less frequently in the anterior pelvic compartments including the vesicouterine pouch and the bladder.⁹

DIE often manifests in the pelvis as nodules, or plaque-like lesions and adhesions with a low signal intensity on T2w images and intermediate signal intensity on T1w images.^{1,3,9}

Ovarian endometriomas may be seen as single or multiple thick-walled cysts with a high signal intensity on T1w fat-saturated images (corresponding to haemorrhagic content) and may sometimes demonstrate T2w shading on MRI.^{1,3,9}

MRI is also excellent at detecting adenomyosis, which in 30% of cases is associated with deep infiltrating endometriosis.⁹ This usually manifests as either thickening of the junctional zone >12 mm or as nodules with hyperintense foci within the uterine wall on T1w and T2w.⁹

Bowel involvement commonly manifests as nodular or plaque-like T2w hypointense deposits along its wall with loss of the fat planes between the bowel loops and uterus or other organs, with the most frequently affected sites being the rectum and sigmoid colon.⁹ Bowel involvement may result in cyclical symptoms of dyschezia, bloating and bowel cramping which are relieved after passage of air or faeces.¹

Urinary tract endometriosis presents in around 20% of cases with the bladder being the most frequently involved organ.¹ Symptomatic women may experience dysuria, urgency and gross haematuria during menstruation. Endometriotic bladder lesions may result in infiltration of the bladder wall muscle and appear as a mass within the bladder wall which projects into the bladder lumen.¹

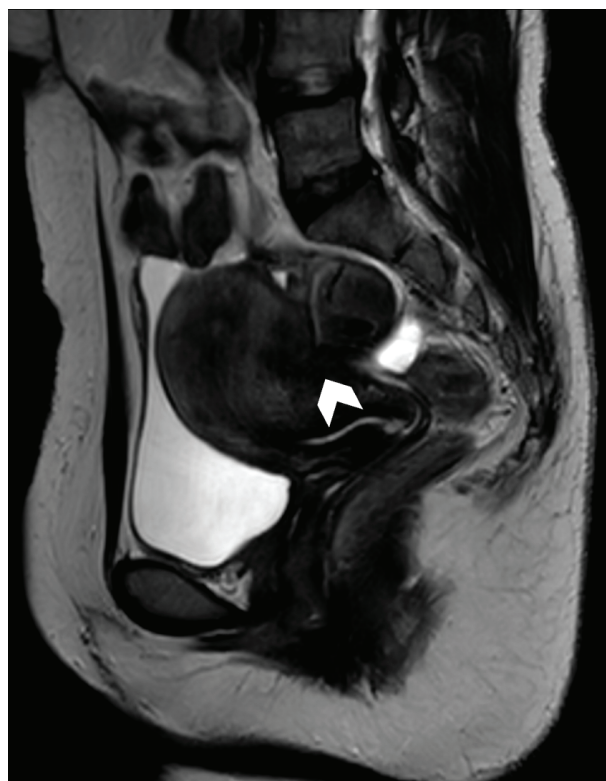
Figures 2 a-d show various endometriotic manifestations in the pelvis.

Extrapelvic involvement may be detected by MRI or by US depending on the affected location. Abdominal wall nodules (including nodules within the Caesarean section scar) may be assessed with US or MRI (Figure 3). Involvement of the sigmoid colon, caecum-ileum-appendix or ureters is initially best assessed with MRI.

MR imaging has gained wide acceptance as the best imaging modality for the diagnosis and staging of deep pelvic endometriosis. The accuracy of MRI is dependent upon the reporting radiologist; therefore, it is recommended that such examinations are performed using a standardized MRI protocol and are reported by radiologists with appropriate training and experience in gynaecological MR imaging.

Although MRI is the most sensitive imaging modality for DIE, the use of physical examination and TVUS may increase specificity. Roditis et al. showed that a combined analysis by means of physical examination, TVUS and MRI with ≥ 2 positive tests appears to be the most valid model for diagnosing DIE, with an accuracy of 91.4% in a retrospective cohort study.¹²

Figure 2a. Sagittal T2w MR image of a patient with clinically suspected endometriosis, showing a deep infiltrating endometriotic deposit at the torus uterinus with infiltration of the posterior uterine wall (arrowhead). An ovarian endometrioma adherent to the posterior uterine wall is also seen at the same level.



LAPAROSCOPY

While a high sensitivity and specificity in the detection of endometriosis may be achieved by the combined use of TVUS and MRI, negative imaging does not rule out endometriosis. In cases of discordance between the intensity of symptoms, despite treatment, and negative imaging results, laparoscopic surgery may be indicated.¹⁰ Laparoscopy may also detect small superficial endometriotic deposits which may not be visible on TVUS or MRI.

MANAGEMENT OF ENDOMETRIOSIS

Patients with endometriosis are managed by gynaecologists with medical treatment (pain relief and/or hormone treatment) and surgery as appropriate.¹³ Cases of deep infiltrating endometriosis are optimally discussed in a multidisciplinary setting with collaboration between gynaecologists, radiologists and colorectal surgeons (in case of bowel involvement), in order to achieve an optimal tailor-made management for each patient.

CONCLUSION

Endometriosis is a common and important condition which may greatly influence the quality of life of affected women. The combined use of non-invasive imaging modalities such as TVUS and MRI provides high sensitivity and specificity in diagnosing and characterizing this disease, which can guide treatment in order to ensure the best possible patient outcomes.

ACKNOWLEDGEMENT

The author would like to thank Ms Emma Tabone for creating and providing the drawings shown in Figure 1.

Figure 2b. Axial T2w MR image of the same patient showing the 'kissing ovary sign' with the ovaries (arrows) adherent to each other and to the posterior uterine wall.

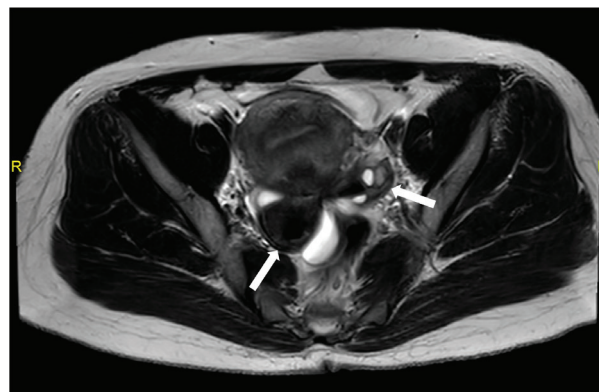


Figure 2c. Axial T1w fat-saturated MR image shows bilateral ovarian endometriomas (arrows), larger on the right, with a typical hyperintense signal on this sequence.

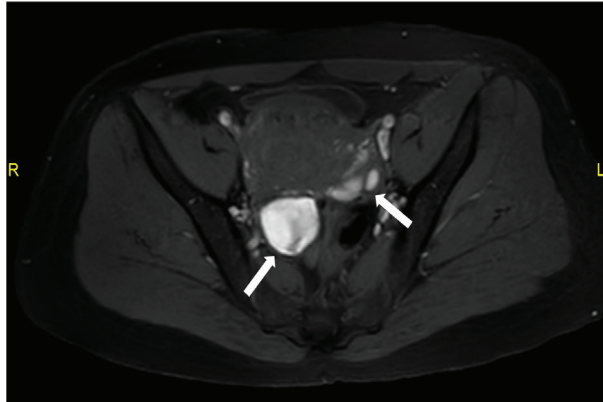
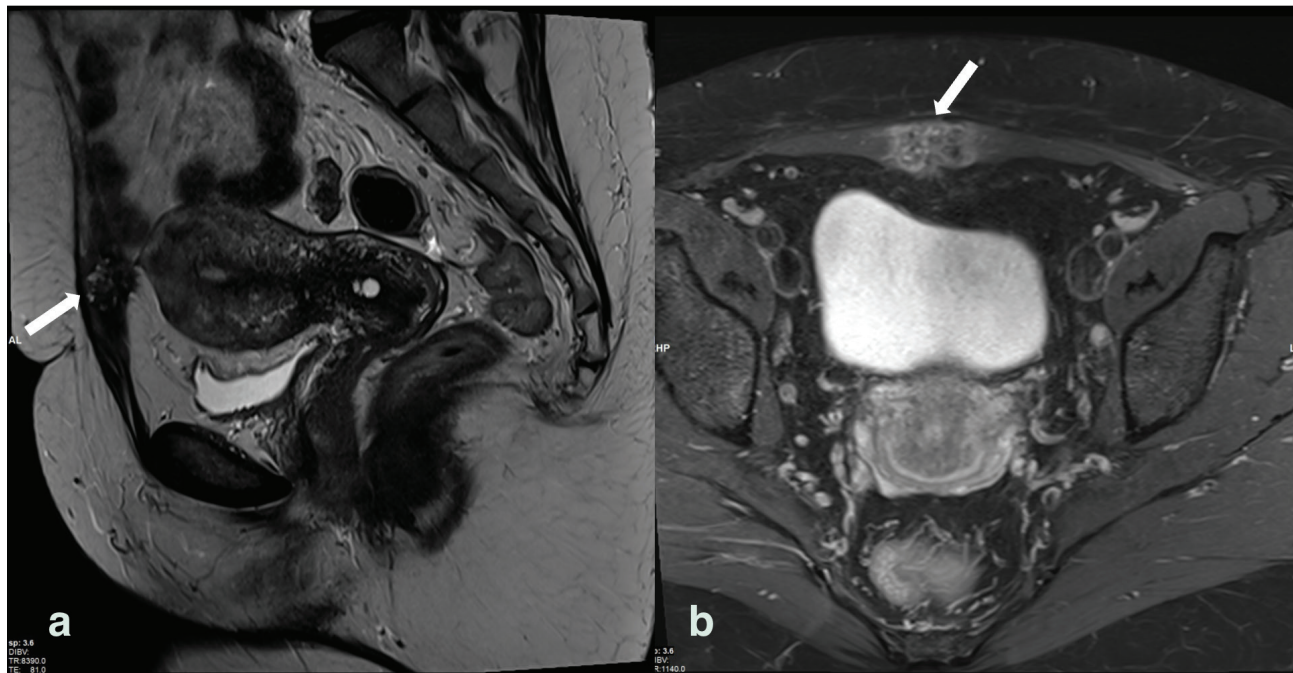


Figure 2d. Axial T2w MR image shows endometriotic deposits at the posterior uterine wall (arrow) with tethering to multiple points along the anterior rectal wall. Thickening of the right uterosacral ligament is also seen (arrowhead).



Figure 3. (a) Sagittal T2w MR image showing an abdominal wall endometrioma (arrow) within the rectus muscle at the site of the C-section scar. (b) axial T1 fat-saturated post-contrast image showing enhancement of the endometrioma (arrow) within the rectus muscle at the site of the C-section scar.



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Tubercular Serpiginous Choroiditis

ABSTRACT

A 40-year-old Indian male presented to the emergency department three days following ocular trauma caused by an airborne insect. Initial complaints included a central scotoma and diminished visual acuity. The patient had no significant medical or surgical history. Following a thorough ocular examination, imaging tests, and laboratory investigations, the diagnosis of Serpiginous-Like Choroiditis (SLC) secondary to tuberculosis (TB) infection was established. Subsequent initiation of anti-tuberculous and immunosuppressive therapy led to a progressive amelioration of symptoms. This case highlights the significance of prompt diagnosis and comprehensive management in optimizing outcomes for individuals afflicted with SLC.

CASE PRESENTATION

A 40-year-old male of Indian origin, who resided for a long time in Dubai prior to relocating to Malta, presented to the emergency department three days after sustaining trauma to the left eye by an airborne insect while driving his motorcycle. Although the patient didn't suffer from any immediate discomfort, he subsequently reported the development of a relative central scotoma. The patient did not have any past ophthalmic history of note and denied suffering from similar symptoms in the past. The patient had no significant medical or surgical history.

Figure 1. Fundal photo of the left eye demonstrating the serpiginous-like lesion involving the macula on presentation to the ophthalmic casualty department.



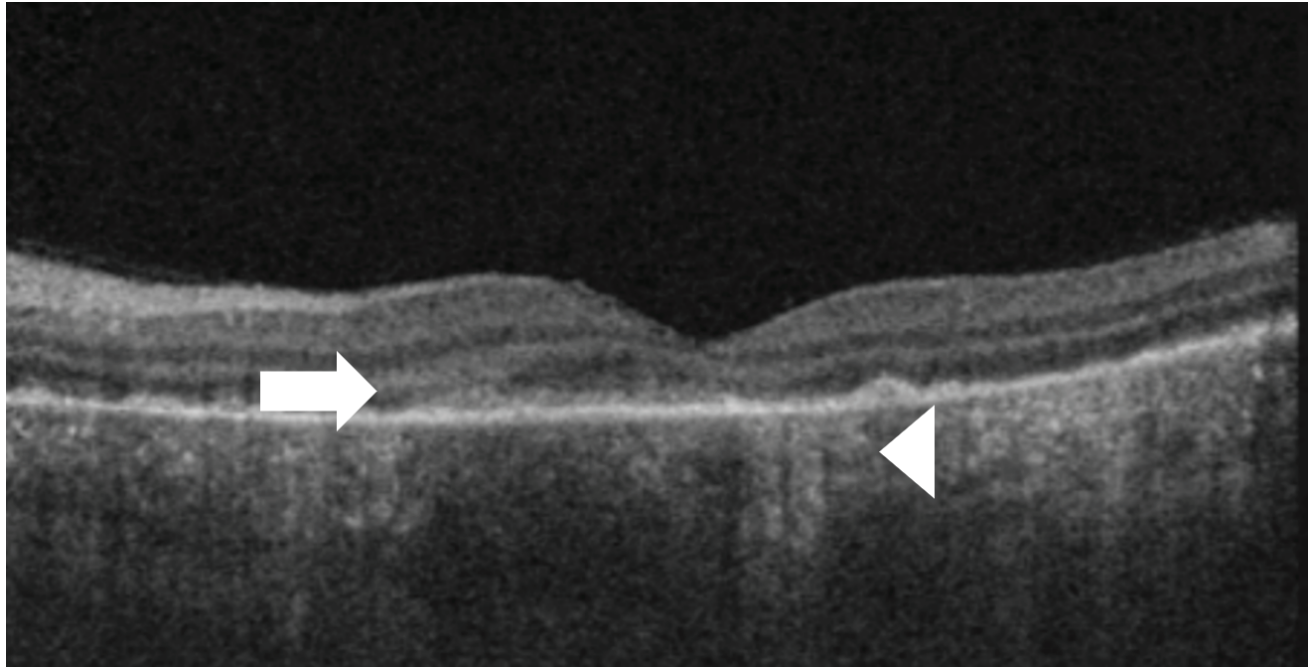
Initial examination at the ophthalmic casualty room revealed a visual acuity (VA) of 6/6-1 (Snellen) in the right eye and 6/60+1 in the left eye. Ishihara testing yielded scores of 13/13 for the right eye and 10/13 for the left eye. No relative afferent pupillary defect was observed. Anterior segment examination of both eyes was unremarkable with no evidence of cells or flare in the anterior chamber. Posterior segment evaluation revealed normal findings in the right eye, while the left eye exhibited 1+ cells (by Standardisation of Uveitis Nomenclature criteria) in the vitreous. No vitreous condensations were seen, however multifocal irregular placoid chorioretinitis (contiguous to disc) was visualised (Figure 1).

Following a comprehensive systemic inquiry, the patient indicated an absence of gastrointestinal, musculoskeletal, respiratory, dermatological, or neurological symptoms. Additionally, the patient was uncertain regarding his history of TB vaccination or contact with other individuals who suffered from the illness in the past. After the initial evaluation, the primary impression leaned towards SLC, with potential differentials including Acute Posterior Multifocal Placoid Pigment Epitheliopathy, toxoplasmosis chorioretinitis, or Syphilitic placoid chorioretinitis. Blood samples were obtained to rule out the aforementioned conditions.

These blood tests revealed a normal white cell count and CRP level. Serum Angiotensin-Converting Enzyme, used to help diagnose sarcoidosis was also normal. Additionally, the patient tested positive for TB-Quantiferon. Furthermore, serological testing for various viral entities indicated positive results for Herpes IgG and Varicella Zoster IgG. HIV, Syphilis and Toxoplasma IgG all resulted to be negative. The chest X-ray was unremarkable.

In view of the positive TB-Quantiferon test the patient was referred to the Infectious Disease Unit (IDU). Upon assessment at the IDU, the patient reported no history of cough, sputum production, fevers, chills, rigors, or weight loss. While uncertain about past exposure, the patient denied prior active treatment for tuberculosis (TB). The plan from an infectious disease standpoint included further investigations to exclude other possible infectious aetiologies, including Toxocariasis and viral infection, prior to committing to starting tuberculostatic treatment. The investigations did not show any evidence of active parasitic or viral infection.

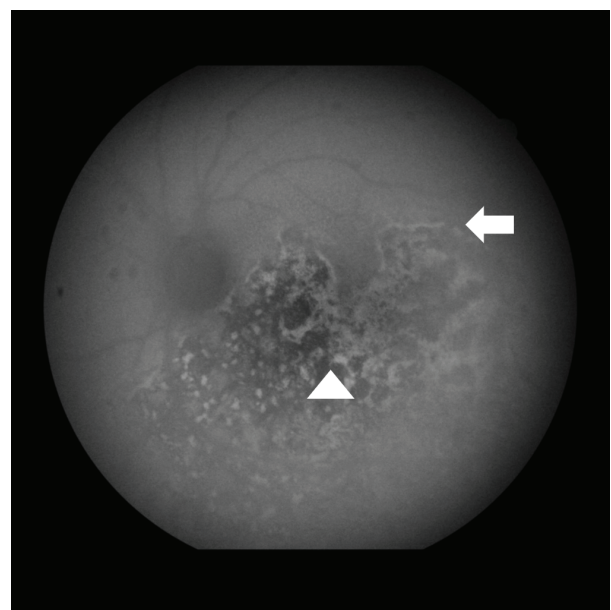
Figure 2. OCT B-Scan (foveal cut) of the left eye demonstrating hyper-reflectivity within the outer plexiform layer and outer nuclear layers (arrow) indicating active inflammation as well as hyper-transmission through the affected retinal pigment epithelium (arrowhead).



The patient was subsequently given an appointment to return to the ophthalmology outpatients in order to perform a baseline optical coherence tomography (OCT) and fundus auto-fluorescence (FAF). OCT showed loss of cone outer segment tips and an interrupted ellipsoid layer over the affected area. The fovea was also involved in the disease process. OCT also showed early choriocapillaris sclerosis (Figure 2). FAF showed hyper-autofluorescence at the lesion border suggesting advancing disease, with a mixed autofluorescence pattern within the serpiginous lesion suggestive retinal pigment epithelial loss within the affected area (Figure 3). Following the completion of the two aforementioned investigations, the diagnosis of SLC was conclusively established.

Without delay, the patient was commenced on anti-Tuberculosis therapy as instructed by IDU, specifically the standardized regimen known as RIPE therapy, comprising rifampin 300mg BD, isoniazid 150mg BD, pyrazinamide 2g daily, and ethambutol 1200mg daily. Following the initiation of RIPE therapy, the patient was promptly directed to initiate adjunctive corticosteroid therapy namely prednisolone at a dosage of 70mg daily, alongside vitamin D/Calcium supplementation BD and Omeprazole 20mg BD for gastro-protection.

Figure 3. Fundal Auto-Fluorescence Imaging of the left eye at presentation. Leading edge (arrow) demonstrates hyper-autofluorescence whereas the healing lesion core (arrowhead) demonstrates mixed pattern hyper/hypo-autofluorescence.



Subsequently, the patient underwent regular monitoring, during which significant improvements were observed. Within a span of 10 days, the visual acuity (VA) in the left eye notably improved from 6/60+1 to 6/24, while the right eye maintained a VA of 6/6. Over subsequent visits, a progressive reduction in the central scotoma was documented alongside improving results on OCT and FAF, both of which were systematically repeated. Following a month-long course of RIPE therapy, a point of remission of SLC was attained. At this juncture, the central scotoma had completely resolved, and the patient exhibited a VA of 6/6 in the right eye and 6/9 in the left eye.

Following two months of RIPE therapy, the patient underwent a thorough assessment by the infectious disease specialists, who decided to transition the treatment regimen to dual therapy, namely rifampin and isoniazid for an additional four months. Concurrently, the dosage of prednisolone was systematically tapered until reaching a maintenance dose of 10mg daily. At this juncture, the patient's treatment plan was augmented with the introduction of mycophenolate mofetil (MMF) to ensure quiescence whilst avoiding the need for higher corticosteroid doses. The initiation phase of MMF therapy commenced with a dosage of 500mg BD during the initial week, which was subsequently escalated to 1.5g BD. Throughout this period, bloods were taken on a weekly basis to monitor for potential MMF-induced toxicity. Notably, the patient's blood results remained consistently within normal ranges since the initiation of MMF therapy.

During the follow-up visits, novel extensions of the disease were identified upon fundoscopic evaluation. Consequently, the steroid dosage was escalated to 35mg daily, and a regimen for gradual tapering was reinitiated. Subsequent monitoring revealed a favourable response of the newly identified lesions to the adjustment in steroid dosage.

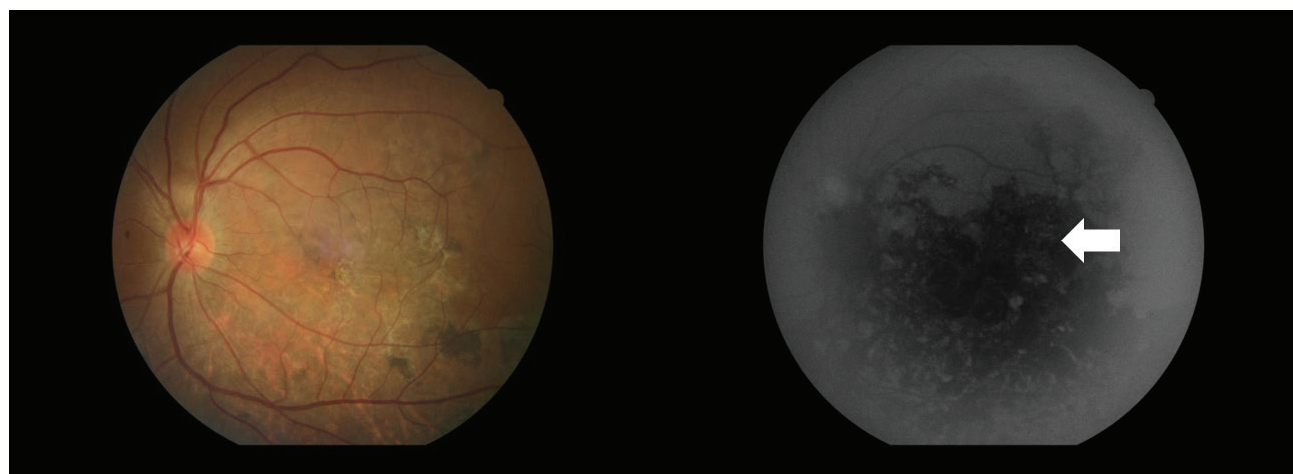
The patient managed to taper down the prednisolone dose to 5mg daily without any evidence of lesion extension noted over the last 4 months (Figure 4).

DISCUSSION

TB is a contagious bacterial infection primarily caused by *Mycobacterium tuberculosis*. It commonly affects the lungs but can also target other parts of the body including neural and ocular tissue. TB is spread via droplet transmission when an infected person coughs or sneezes, making it highly contagious. Despite being treatable and preventable, TB remains a significant global health concern, particularly in regions with limited access to healthcare resources.¹

TB remains a significant public health challenge in developing countries like India, with much higher rates of incidence when compared to developed nations. In India, TB exhibits an incidence rate of 193 cases per 100,000 population. This high prevalence of TB in developing countries is attributed to factors such as constrained resources, deficient healthcare infrastructure, and socioeconomic inequalities, all of which present considerable obstacles to effective TB control measures.²

Figure 4. Fundal photo and fundal auto-fluorescence imaging of the left eye 4 months after initiating steroid-sparing treatment. Generalized hypo-autofluorescence (arrow) can be seen within the lesion core with no evidence of inflammatory activity at the border.



WHILE TB INCIDENCE RATES MAY BE RELATIVELY LOW IN DEVELOPED COUNTRIES LIKE MALTA, THE SIGNIFICANT BURDEN IN DEVELOPING COUNTRIES AS WELL AS THE INCREASING SCALE OF MIGRATION FLOWS FROM THE LATTER COUNTRIES HIGHLIGHTS THE ONGOING NEED FOR ENHANCED TB CONTROL MEASURES AND ADDRESSING ITS SOCIOECONOMIC DETERMINANTS

Between 15-20% of TB patients present with or are sequentially affected by extra-pulmonary TB.³ Approximately 20% of patients with serological evidence of TB suffer from ocular manifestations namely TB Uveitis (TBU)³ with reported prevalence of 2.7% in non-endemic countries.⁴

Ocular TB reaches the eye and its adnexal tissue via haematogenous spread from the lungs or extra-pulmonary tissue which explains why the uveal layer and epiretinal vasculature are more commonly affected in TBU with involvement of both the anterior and posterior segment of the globe.⁵

The main issue when dealing with TBU is primarily reaching a diagnosis owing to its multiple modes of presentation and its ability to mimic other uveitic entities. Based on the extensive research performed by the Collaborative Ocular Tuberculosis Study Group, TBU can be mainly categorized into 3 groups namely: (i) TB-associated retinal vasculitis (ii) TB Choroiditis (including SLC and Tuberculomas) and (iii) TB Panuveitis.⁶ Other entities which may stem from TB include solitary optic nerve head granulomas, neuroretinitis and panophthalmitis and these have all been described in the literature.⁷

SLC usually initiates centrally and spreads in a helicoid manner and is associated with the evolution of surrounding satellite lesions. Contrary to this presentation, the lesions are usually non-contiguous to the optic nerve head.^{7,8} The presence of multifocal lesions and mild-to-moderate vitritis, lack of peripapillary involvement and evidence of TB infection distinguish SLC from Serpiginous Choroiditis which is thought to be an exclusively autoimmune choriocapillaropathy.⁸ The main pathophysiological mechanism of SLC is thought to be related to Mycobacterial aggregation within the retinal pigment epithelial layer which in turn triggers inflammation in the overlying neuro-sensory retina and underlying choriocapillaris thus highlighting the importance of treating this condition with both tuberculostatic and immunosuppressive therapy.⁹

CONCLUSION

This case report emphasizes the challenges in diagnosing and managing TBU, focusing on SLC. Timely recognition of ocular manifestations, coupled with a comprehensive evaluation, facilitated the diagnosis of this rare condition. Initiation of anti-tuberculous therapy and adjunctive corticosteroids led to favorable treatment response, evidenced by progressive improvement in visual acuity and resolution of central scotoma. The successful transition to a tailored treatment regimen guided by the infectious disease specialists underscores the importance of multidisciplinary collaboration in optimizing clinical outcomes.

While TB incidence rates may be relatively low in developed countries like Malta, the significant burden in developing countries as well as the increasing scale of migration flows from the latter countries highlights the ongoing need for enhanced TB control measures and addressing its socioeconomic determinants. Let us not forget that migrants are a hard-to-reach group and this translates into a challenge for TB control in higher-income countries. This case underscores the importance of clinical vigilance and comprehensive management strategies when addressing ocular TB sequelae, with the ultimate aims being improving patient quality of life, mitigating TB resistance, and minimizing transmission.

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Revitalize Your Day

magnetrex™



Composition / Σύνθεση	Per 1 Tablet / Ανά 1 Δισκίο	% RDA* / % ΣΠ*
Magnesium Bisglycinate / Διογλυκινικό μαγνήσιο Magnesium / Μαγνήσιο	441 mg 75 mg	20 %
Taurine / Ταυρίνη	100 mg	
Vitamin B6 / Βιταμίνη B6	1.96 mg	140 %
Citrus Sinensis Extract / Εκχύλισμα Citrus Sinensis	250 mg	

Effects of Magnetrex®

– Magnesium, Taurine, Citrus sinensis and Vitamin B6 – on Muscle Cramps and Anxiety in an Adult Population: A Retrospective Chart Review

ABSTRACT

INTRODUCTION

The development of effective interventions, including pharmacotherapy and dietary supplements, to alleviate symptoms of stress, anxiety, and related physiological discomfort such as cramps has gained considerable interest in recent years. In this context, several components like magnesium, taurine, Citrus sinensis, and vitamin B6 have individually shown promising effects on stress reduction, anxiety management and associated cramp reduction.

OBJECTIVES

To evaluate the potential effects of supplementation with Magnetrex® (Surveil Pharma), a combination of magnesium, taurine, Citrus sinensis, and vitamin B6, on signs and symptoms of stress and anxiety in adults as well as muscle cramps.

METHODS

A retrospective chart review design was employed among adults in Malta initiated on Magnetrex®. Data were extracted from medical records and Perceived Stress Scale (PSS) and Hamilton Anxiety Rating Scale (HAM-A) scales which were used to assess stress and anxiety symptoms,

respectively, at baseline and at four-month follow-up. Changes in stress symptoms, anxiety, and muscle cramps were analyzed, and linear mixed models adjusted for relevant covariates were performed to test changes in PSS and HAM-A scales from baseline to follow-up.

RESULTS

This study included 57 subjects who initiated Magnetrex® supplementation. Our results showed significant improvements in various stress symptoms and a significant decrease in the PSS and HAM-A scales, indicating lower levels of stress and less severity of anxiety symptoms after four months of Magnetrex® supplementation. Improvement in muscle cramps was also reported.

CONCLUSIONS

The results of this study suggest that supplementation with Magnetrex® may be effective in improving mental conditions such as stress and anxiety, and in reducing muscle cramps.

KEYWORDS

Magnesium, Vitamin B6, Taurine, Citrus sinensis, Stress Management, Muscle Cramps.

INTRODUCTION

In 2019, mental disorders affected around 970 million individuals, with a global prevalence representing approximately one out of every eight people, with anxiety and depression ranking as the most prevalent conditions.¹ Significant prevention and management efforts have been investigated to reduce the burden of these mental health problems². In keeping with this, the last decade has seen an expansion of novel therapeutic options, including several mineral agents and herbal compounds, for the treatment of stress and anxiety-related symptoms³.

Notable new evidence highlights the potential benefits of vitamin B6 in managing stress and anxiety, including a large cross-sectional study that found higher vitamin B6 intake in anxious and depressed people was associated with a lower risk of depression and anxiety⁴. Another compound that has received a lot of attention is magnesium. Although the evidence remains inconclusive, a systematic review suggested that magnesium may be beneficial in the management of mild anxiety symptoms⁵. In more severely stressed individuals, the beneficial synergistic effect of magnesium and vitamin B6 supplementation on anxiety⁵

and stress^{6,7} has been demonstrated. Concerning muscle cramps, the efficacy of magnesium is controversial. Studies have shown that supplementation with specific magnesium salts was not effective in reducing cramps^{8–10}, while others have found a significant reduction in cramps in pregnant women^{11,12}.

Within the context of the limited clinical studies available, Citrus sinensis and taurine have emerged as compounds with potential roles in stress and anxiety management and in improving energy levels. Taurine, with its antioxidant and anti-inflammatory effects in the central nervous system, plays a role there. It acts as a cytoprotectant against stress-induced neuronal damage and is well known for its energizing anti-fatigue properties¹³. However, only animal studies have demonstrated the efficacy of Citrus sinensis in alleviating depression-like symptoms^{14,15}.

The aim of this study is to evaluate the response to Magnetrex®, a combination of magnesium, taurine, Citrus sinensis and vitamin B6, in improving symptoms of daily fatigue, apathy and lack of energy, muscle cramps including nocturnal ones, and anxiety in adults. By evaluating the response to Magnetrex®, we aim to add to the growing body of evidence supporting the potential benefits of its components in stress and anxiety management.

METHODS

DESIGN AND SETTINGS

We conducted a retrospective chart review of patients attending a sample of general practitioners in Malta, who were initiated on Magnetrex® tablets, a combination of magnesium bisglycinate (441 mg), taurine (100 mg), Citrus sinensis (250 mg), and vitamin B6 (1.96 mg) per tablet, for the relief of stress symptoms and anxiety, between August 2020 and December 2022. A 30-month period was needed due to the fact that patient visits to general practitioners during COVID-19 decreased considerably. Data were extracted from patients' medical records at a baseline time point corresponding to the initial visit and at a follow-up time point four months after baseline.

DATA COLLECTION

Data collection was sourced from medical records of patients 18 years of age or older who had reported symptoms of daily stress such as fatigue, apathy, lack of energy, and generalized anxiety disorder, and pregnant women in the 2nd or 3rd trimester with sleeping difficulties, stress, anxiety, and muscle cramps. The data which was collected excluded patients who were taking other similar supplements, those receiving lithium for neurological treatment, and those in the first trimester of pregnancy.

DATA COLLECTION AND OUTCOME MEASURES

A convenience sample of 17 general practitioners practicing in Malta, whose practice utilized a system of patient medical records, was selected for this study. The physicians were informed of the purpose and the conduct of the study. Data from both the baseline and follow-up visits were extracted from patients' medical records and the data was used to compile electronic case report forms (e-CRF). e-CRFs were either compiled by the physicians in an anonymous manner or by a medical representative since some physicians opted to fill the CRF as a hard copy and give this to a medical representative in order for the data to be transferred to a soft copy. The hard copies filled by the physicians and handed to the medical representative were totally anonymous.

The baseline characteristics which were extracted from patients' medical records included age, sex, weight, height, occupation, tobacco smoking, alcohol consumption, current medication, and food supplement use including nutraceuticals, although not all medical records contained the required information. Patient medical history was also collected, such as pregnancy status, presence of cardiovascular disease, hypertension, diabetes, chronic kidney disease, cancer, if known, psychiatric disorder (general anxiety disorder or depression), and family history of psychiatric illness. The presence of stress signs and symptoms, including headache, tense muscle cramps, presence of muscle cramps including nocturnal ones, fatigue, anxiety/worry/phobias, difficulty falling asleep, irritability, outbursts of anger/hostility, boredom/depression, eating a lot or not enough, gastrointestinal symptoms (flatulence, cramps, diarrhoea, constipation), and any restlessness/tics/itching were collected at baseline and follow-up visits. Not every medical record contained the required information. Data from the use of two scales were collected at baseline and after four months of Magnetrex® supplementation: Perceived Stress Scale (PSS) and Hamilton Anxiety Rating Scale (HAM-A).

The PSS consists of 10 items and is used to measure participants' perceptions of stress. Each question has 5 response options depending on how often patients feel a certain way, ranging from "never" to "very often". The total score was calculated according to the official scoring system by summing across all items, which range from 0 to 40. Higher scores indicate higher levels of stress. The HAM-A scale was used to assess the severity of anxiety symptoms. It consists of 14 items scored on a scale from 0 "not present" to 4 "severe". The scores were summed to produce a total score ranging from 0 to 56, with higher scores representing more severe anxiety symptoms.

ETHICAL CONSIDERATIONS

The study was an observational analysis of pre-existing medical records and did not involve direct contact with participants. The participating physicians provided the anonymized patients' records from which data was extracted for the study. As a result, data collection did not require the study researchers to meet the patients in person.

STATISTICAL ANALYSIS

Baseline characteristics of patients were summarized using descriptive statistics, i.e., means and standard deviations (SD) for quantitative continuous variables and frequencies and percentages for categorical variables. Changes in the presence of stress signs and symptoms and the presence of muscle cramps at 4 months from baseline were assessed using the McNemar chi-square test. Two-tailed paired sample t-tests were used to compare changes from baseline for the PSS and HAM-A scales. Baseline to follow-up changes in PSS and HAM-A scores were assessed using linear mixed models adjusted for sex, concomitant medication, smoking, alcohol use, presence of other psychiatric illness (depression, anxiety), diabetes, and hypertension. A p-value less than 0.05 was considered statistically significant. All statistical analyses were performed with Stata v17.0 software.

RESULTS

PATIENT CHARACTERISTICS

A total of 57 subjects were reviewed, of which 32 (56.1%) were female. Table 1 shows the characteristics of the patients at baseline. The mean age was 50.4 (standard deviation [SD]=14.3) years, and the mean weight was 70.1 (SD=14.4) kg. Medication and dietary supplement use were reported by 38.6% and 24.6% of participants, respectively.

Five of the participants (8.8%) had cardiovascular disease, 16 (28.1%) had hypertension, and 4 (7%) had diabetes. While a large proportion of subjects (24.6%) had a psychiatric disorder including anxiety or depression, none had cancer or kidney disease (Table 2).

CHANGE IN STUDY OUTCOMES BETWEEN BASELINE AND FOLLOW-UP

Table 2 shows the changes in stress signs and symptoms, muscle cramps including nocturnal ones from the PSS and HAM-A scale results between the baseline visit and follow-up visit four months after initiation of Magnetrex® supplementation. There was a statistically significant improvement in all stress signs and symptoms compared to baseline, along with a statistically significant decrease in PSS from 17.7 ± 7.5 to 14.0 ± 6.3 and HAM-A from 12.0 ± 8.4 to 6.1 ± 16.0 scales, indicating lower levels

Table 1. Sociodemographic and lifestyle characteristics of patients (n=57).

	Mean	Standard deviation
Age (years)	50.4	14.3
Weight (kg)	70.1	14.4
Height (cm)	163.7	7.9
	Frequency	Percentage
Sex		
Women	32	56.1
Men	25	43.9
Pregnancy	1	1.8
Chronic medication use	22	38.6
Supplements use	14	24.6
Tobacco use	7	12.3
Alcohol consumption	7	12.3
Medical conditions		
History of coronary artery disease	5	8.8
Hypertension	16	28.1
Diabetes	4	7
Kidney Disease	0	0
Cancer	0	0
Psychiatric Disorders	14	24.6
Family history of psychiatric illness	0	0
Summary statistics are expressed as mean and standard deviation for continuous variables and as frequency and percentage for categorical variables.		

of stress and less severe anxiety symptoms, respectively, between baseline and follow-up.

After adjustment for sex, concomitant medication, smoking, alcohol use, presence of other psychiatric illness, diabetes, and hypertension, the linear mixed models showed a statistically significant decrease in mean PSS scale (coefficient = -3.7, $p < 0.001$, 95% CI: -5.2 to -2.2) and mean HAM-A scale (coefficient = -5.9, $p < 0.001$, 95% CI: -7.6 to -4.2) between baseline and follow-up (Table 3).

DISCUSSION

In this study, stress- and anxiety-related symptoms assessed by the PSS scale, and severity of anxiety symptoms assessed by HAM-A scale significantly improved after four months of Magnetrex® administration.

This is consistent with the results of several studies on the individual components of Magnetrex®. The observed reduction in stress and anxiety symptoms is consistent

Table 2. Signs and symptoms appearing at least once a day for patients initiated on Magnetrex[®] at baseline and 4-month follow-up.

	Baseline	Follow-up	P-value
	n (%)	n (%)	
Headache	11 (19)	4 (7)	<0.001
Fatigue	28 (49)	9 (16)	0.001
Anxiety and phobia	25 (44)	10 (18)	<0.001
Sleeping difficulties	13 (23)	4 (7)	<0.001
Irritability	13 (23)	7 (12)	<0.001
Anger and hostility	4 (7)	0 (0)	<0.001
Depression or boredom	3 (5)	2 (4)	<0.001
Irregular eating habits	6 (11)	5 (9)	<0.001
Gastrointestinal symptoms	4 (7)	2 (4)	<0.001
Restlessness, tics or itching	11 (19)	1 (2)	<0.001
Tense Muscles or cramps	26 (46)	3 (5)	<0.001
Presence of muscle cramps	22 (39)	11 (19)	<0.001
Night cramps (n=22)	11 (50.0)	1 (4.5)	<0.001
Intensity of cramps evaluated using NRS or FRS	3	0	
	Mean ± SD	Mean ± SD	
PSS Score ± SD	17.7 ± 7.5	14.0 ± 6.3	<0.001
HAM-A Score ± SD	12.0 ± 8.4	6.1 ± 16.0	<0.001

PSS: Perceived Stress Level; HAM-A: Hamilton Anxiety Rating Scale; NRS: Numerical Rating Scale; FRS: Faces Rating Scale; SD: Standard deviation.

with previous research suggesting the potential benefits of magnesium in the treatment of anxiety⁵, depression¹⁶, and stress⁶. Another study also showed that a reduction in HAM-A score in depressed patients was associated with higher levels of magnesium¹⁷, highlighting, along with our results, the impact of magnesium on stress and anxiety management.

A number of studies have found positive effects on measures of stress and anxiety following vitamin B6 supplementation, which actively relieves symptoms

Table 3. Linear mixed models for the change in PSS and HAM-A scores between baseline and after four months of Magnetrex[®] use.

	Coefficient	95% CI	P-value
PSS Score	-3.7	-5.2 to -2.2	<0.001*
HAM-A Score	-5.9	-7.6 to -4.2	0.010*

*models adjusted for sex, concomitant medications, smoking, alcohol, presence of other psychiatric illnesses, diabetes, and hypertension

associated with depression and anxiety^{4,18}. Our findings are consistent with these results and suggest that vitamin B6 was one of the main drivers of our results and provides a partial explanation for the effects that we found.

In this regard, several studies have previously demonstrated the synergistic effect of magnesium and vitamin B6 in reducing stress in a highly stressed population^{6,7}. While our results are consistent with this trend, measuring the exact magnitude of this synergistic effect remains challenging. In addition, this finding is consistent with the results of a study of subjects with chronic psychological stress and fatigue, which showed that supplementation with a combination of minerals and vitamins, including magnesium, taurine, vitamin B6, and other ingredients, resulted in significant improvements in subjectively perceived stress¹⁹.

While there is evidence that taurine and Citrus sinensis are effective in treating depression and anxiety-like symptoms in animals^{14,15,20-23}, to our knowledge, no studies have examined their effects on stress and anxiety in humans. Therefore, it is important to acknowledge that the effects observed in our study may be due to the interaction of the components of Magnetrex[®] rather than their individual efficacy. While the inclusion of taurine and Citrus sinensis in the formulation of Magnetrex[®] added unique insights to our study and to the evolving strategies and interventions for stress and anxiety management, the exact contribution of these compounds in the context of stress and anxiety relief warrants future investigation.

As discussed above, data on the role of magnesium in reducing cramps have shown inconsistencies. Our results support previous findings demonstrating the potential of magnesium in the treatment of muscle cramps. This discrepancy may be due to the different forms of magnesium used, the differential effect of magnesium in different populations, baseline magnesium levels, and potential interactions with other agents. The form of magnesium used in Magnetrex[®],

magnesium bisglycinate, offers several advantages in the administration of magnesium over other salts. Studies have demonstrated the high bioavailability and safety of magnesium bisglycinate and efficacy at lower doses, outperforming inorganic magnesium salts such as magnesium carbonate, oxide and sulphate, and some organic salts such as magnesium citrate or lactate in certain preparations. Magnesium absorption from magnesium bisglycinate was 2.3 times greater than from magnesium carbonate, 3.6 times greater than from magnesium sulfate, and 8.8 times greater than from magnesium oxide^{24,25}. This appears promising for the reduction of muscle cramps and increases the possibility of synergistic effects of magnesium, taurine, hesperidin, and vitamin B6 contributing to the observed improvements and physiological benefits of Magnetrex®.

LIMITATIONS

The main limitation of our study was the convenience sampling nature of physician recruitment which may have resulted in a non-representative sample of patients, limiting the generalizability of the results to the broader Maltese population. In addition, the lack of a control group and the lack of adjustment for other variables that were not collected in the study and that may be important to adjust for in the analysis, prevented us from distinguishing between the true effects of Magnetrex® and other potential factors that could affect stress, anxiety and muscle-related outcomes, such as diet and lifestyle changes, life events, and the presence of nutrient deficiencies or concomitant interventions given to patients at the same time as Magnetrex®. Another limitation of the study is the relatively short follow-up period of 4 months, which did not allow for seasonality to be taken into account when assessing changes in outcomes. Furthermore, considering that the study was retrospective, some data may not have been collected in its entirety, including baseline characteristics of patients, patient medical history and presenting ailments. Given these limitations, our findings are considered exploratory and require confirmation in appropriately designed randomized controlled trials.

CONCLUSION

In conclusion, the novelty of this study is the demonstration that a combination of chelated magnesium bisglycinate, taurine, Citrus sinensis, and vitamin B6 can have a positive synergistic effect in improving stress and anxiety-related symptoms and reducing cramps in adults. Therefore, this study suggests that Magnetrex® may be a suitable nutraceutical for improving mental wellbeing in selected patients suffering from anxiety and cramps.

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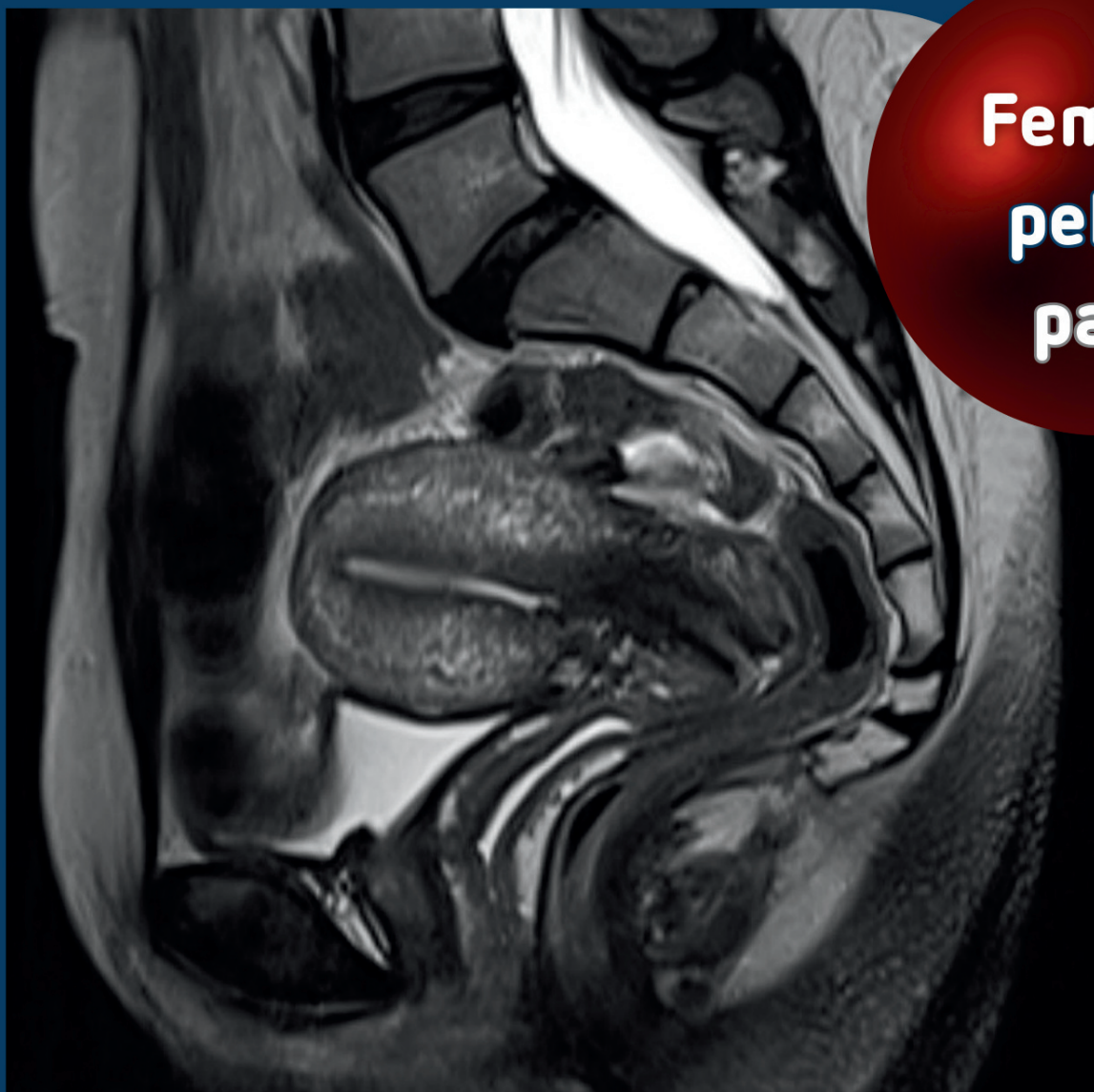
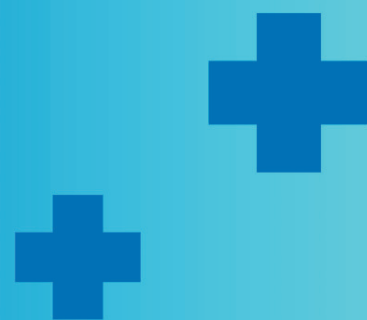
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