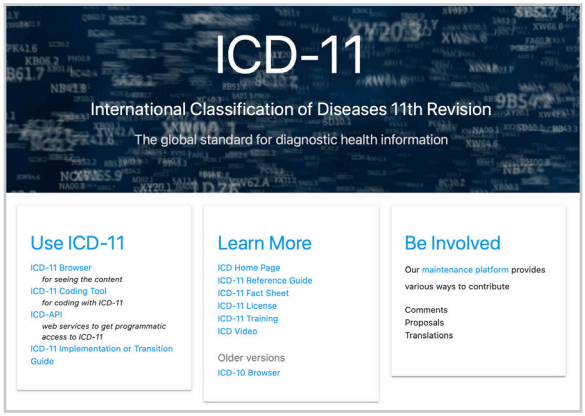
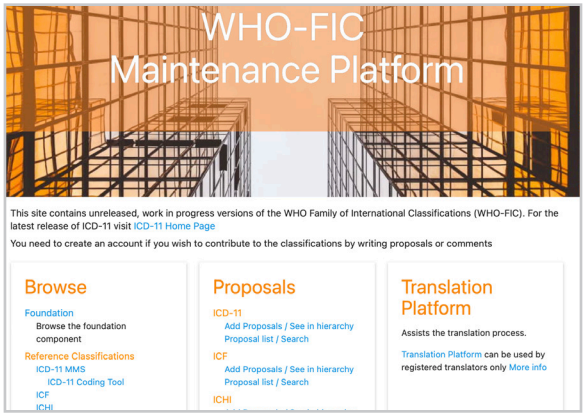
ICD-11
Endometriosis
& Associated Cancer ICD-O

Clinical Guidelines
International Classification of Disease

2023

endometriosisalliance.org





ICD11 online

icd.who.int

Implementation Map

www.who.int/standards/classifications/classification-of-diseases

ICD-11 provides best-practice guidance drawn from international standards and concepts for patient medical records. The guide uses strategic planning and operations for the improvement and maintenance of an ICD system. The efforts described in this guide will help to strengthen the quality and completeness of diagnostic factors. To allow for accurate analysis, interpretation and use, data collected on international medical records should be coded according to the standard of the ICD. For each task the reader can find references to published key resources for further learning and application.

ICD-11 is used by:

- Governments to allocate resources
- Researchers to collaborate across borders
- Doctors to document their cases
- Health providers in algorithms for decision support
- Hospitals to count the frequency of health problems
- Laboratories to exchange investigative data
- Insurance companies for billing purposes
- International organizations to assess trends in public health

The Endometriosis ICD-11 guide visualizes the systemic design that impacts the healthcare model.

The guide is dedicated to:

- Patients who endure this illness which impacts their quality of life in hope to create a better life course approach
- Doctors who put in countless hours to learn imperative techniques and knowledge to maintain expert care.
- Professors and scientists who pursue research to gain more insight and clarity
- Advocates who volunteer their support to the patient, policy and medical community
- Policymakers who added Endometriosis to the NCD Advocacy Agenda with the UN

Well wishes, Julie Prilling
Data Scientist | Systemic Designer | Health Policy Advocate
Endometriosis Alliance
@EndoStats

An international classification of diseases for the twenty-first century

Understanding diseases in ways that enable prevention, treatment, and the allocation of resources requires measurement. To be useful, measurement must be reliable, allow valid comparisons to be made between places and over time, and enable coherent summarization of large volumes of data. A classification of diseases and related things is essential for such measurement. Changes in design and structure reflect the arrival of the networked digital era, for which ICD-11 has been prepared. Uses of the ICD are diverse and widespread, extending directly to much of the world and indirectly to all populated places. Much of what is known about the extent, causes and consequences of human disease world-wide rests on use of data classified according to the ICD. Clinical modifications of ICD are the main basis for statistics on disease, particularly cases treated by hospitals. These statistics underlie crucial functions such as payment systems, service planning, administration of quality and safety and health services research. ICD-11 is a different and more powerful health information system, based on formal ontology, designed to be implemented in modern information technology infrastructures, and flexible enough for future modification and use with other classifications and terminologies. It is better able to capture clinically relevant characteristics of cases and to permit summarization of information for various purposes, has flexibility allowing use in more and less elaborate modes, and has integrated support for multiple languages. The information framework for ICD-11 has three integrated parts: a database referred to as the Foundation, classifications derived from the Foundation, and a common biomedical ontology linked to the Foundation. The more adequately the ontology underlying ICD-11 represents the relevant domain of knowledge the more straightforward it should be to incorporate new entities.

Harrison, J.E., Weber, S., Jakob, R. et al. ICD-11: an international classification of diseases for the twenty-first century. BMC Med Inform Decis Mak 21, 206 (2021). https://doi.org/10.1186/s12911-021-01534-6

ICD-11

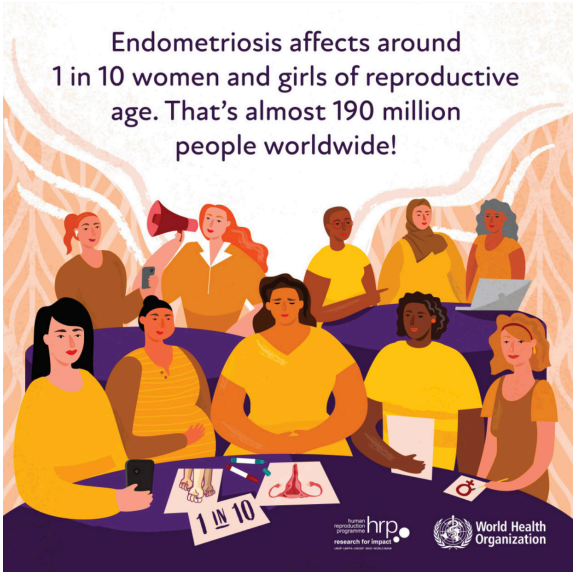
Table of Contents

ICD11 is the clinical classification standard. The codes are legally mandated for use by Health Care Providers and consist of codes, plus definitions and business rules for their use.

Decision making at the patient level

Common standards for a connected world

The World Health Organization (WHO) recognizes the importance of endometriosis and its impact on people's sexual and reproductive health, quality of life, and overall well-being. WHO aims to stimulate and support the adoption of effective policies and interventions to address endometriosis globally, especially in low and middle-income countries.WHO recognises the importance of advocating for increased awareness, policies and services for endometriosis, and collaborates with civil society and endometriosis patient support groups in this regard. WHO is also collaborating with relevant stakeholders to facilitate and support the collection and analysis of country- and region-specific endometriosis prevalence data for decision making.



Health, social and economic benefits of addressing Endometriosis

Endometriosis has significant social, public health and economic implications. It can decrease quality of life due to severe pain, fatigue, anxiety and infertility. Some individuals with endometriosis experience debilitating associated pain that prevents them from going to work or school. In these situations, addressing endometriosis can reduce absence from school or increase an individual's ability to contribute to the labour force. Addressing endometriosis will empower those affected by it, by supporting their human right to the highest standard of sexual and reproductive health, quality of life, and overall well-being. In addition to fertility problems and reduced quality of life, this enigmatic disease also has serious economic consequences. Direct healthcare costs for women with endometriosis are more than twice as high as women without the disease. This amount also includes additional costs beyond hospitalization of the disease e.g. lost days at work, layoffs, having to change jobs, sick leave, and time off for having surgery.

Addressing current challenges and priorities

In many countries, the general public and most front-line healthcare providers are not aware that distressing and life- altering pelvic pain is not normal, leading to a normalization and stigmatization of symptoms and significant diagnostic delay. Patients who could benefit from medical symptomatic management are not always provided with treatments due to limited awareness of Endometriosis among primary healthcare providers. Due to limited capacity of health systems in many countries, access to speciali3zed surgery for those who need it is sub-optimal. In addition, and especially in low and middle- income countries, there is a lack of multi-disciplinary teams with the wide range of skills and equipment needed for the early diagnosis and effective treatment of endometriosis.
In addition, many knowledge gaps exist, and there is need for non-invasive diagnostic methods as well as medical treatments that do not prevent pregnancy.

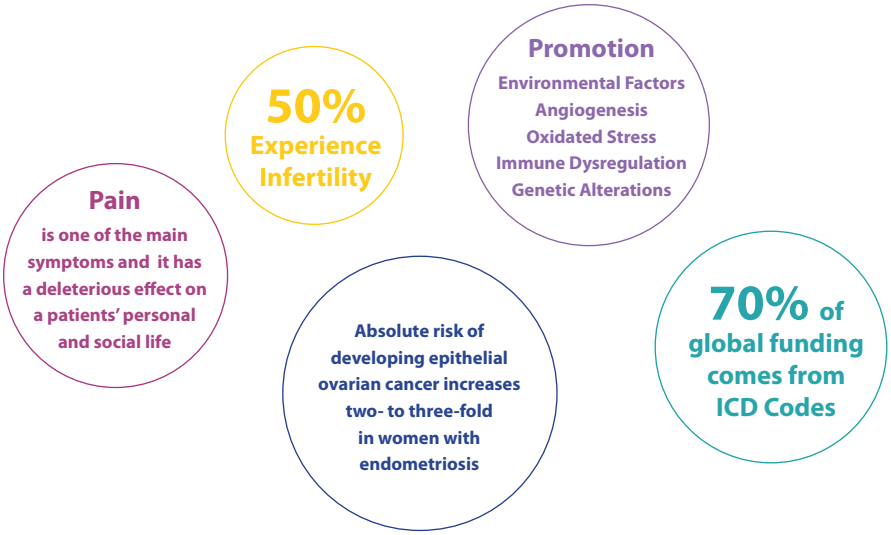
WHO: Knowledge Action Portal Women and Global Health Policy Key Messages

- NCDs, including mental health, are the leading causes of mortality and morbidity for women globally
- To address the shift, we need to adopt a life-course approach, in which early, health-related measures can be indicators for health outcomes later in life
- Health data must be routinely collected and analyzed separately for women and men to support targeted interventions
- Integrating NCD services into maternal and reproductive health care offers an opportunity to meet the growing need for prevention and care within the existing health infrastructure
- Women and girls disproportionately take on care-giving roles to support family and community members with NCDs – and health systems must recognize and remunerate these positions

www.knowledge-action-portal.com

Gender minorities

ICD-11 provides standardized data and vocabulary to help diagnose and monitor health around the world. The new codes will impact provisions of care and health financing, with new changes to reflect modern understandings of sexual health and gender identity. Gender minorities comprise an estimated 0.3–0.5% (25 million) of the global population.



Priorities related to endometriosis include

- Raising awareness about endometriosis among health care providers and wider communities. Local, national and international information campaigns to educate the public and healthcare providers about normal and abnormal menstrual health and symptoms are needed.
- Training all healthcare providers to improve their competency and skills to screen, diagnose, manage, or refer patients with endometriosis. This can range from basic training of primary healthcare providers to recognize endometriosis, to the advanced training of specialist surgeons and multidisciplinary teams.
- Ensuring that primary health care plays a role in screening, identifying and providing basic pain management of endometriosis, in situations where gynecologist or advanced multidisciplinary specialists are unavailable.
- Setting up referral systems and care pathways consisting of well-linked primary healthcare centres and secondary and tertiary centres with advanced imaging, pharmacologic, surgical, fertility and multi-disciplinary interventions.
- Strengthening capacity of health systems to achieve early diagnosis and management of endometriosis by enhancing availability of equipment (e.g. ultrasound or magnetic resonance imaging) and pharmaceutical).
- Accelerating collaborative global action to improve access to reproductive health care for women globally, including in low- and middle-income countries.
- There is a need for more research and awareness raising around the world to ensure effective prevention, early diagnosis, and improved management of the disease.

Social Determinants of Health

Factors influencing health status or contact with health services

Problems associated with finances
QD50 Poverty
QD51 Low income

Problems associated with drinking water or nutrition
QD60 Problems associated with inadequate drinking-water
QD61 Inadequate food

Problems associated with the environment
QD70 Problems associated with the natural environment or human-made changes to the environment
QD71 Problems associated with housing

Problems associated with employment or unemployment
QD80 Problem associated with unemployment
QD81 Problem associated with change of job
QD82 Problem associated with threat of job loss
QD83 Problem with employment conditions
QD83.1 Problem associated with stressful work schedule
QD85 Burnout

Problems associated with education
QD90 Problem associated with illiteracy or low-level literacy
QD91 Problem associated with education unavailable or unattainable

Endometriosis

ICD-11

Medical Informatics and Decision Making

International Classification of Diseases – 11th revision: from design to implementation.

Digital Health

ICD-11 emerges in the context of a reality never experienced by societies. Before, it was almost impossible to integrate the whole world, but nowadays, considering the advent of computerized communication systems and the possibility of access, almost in real time, to relevant information, it is possible. ICD-11 was developed to reduce notification errors, to increase practicality and provide more scope to the information cataloged.

Some relevant points have guided this update. The wide range of professionals from different realities enabled a necessary heterogeneity to reflect regional particularities. Clinicians, statisticians, coders, information and technology specialists have integrated this update, a type of global participation unprecedented in the history of ICD. The new version is completely digital, aiming at practicality in registering and appointments, reducing notification errors and easing the dissemination and consolidation of this new version. ICD-11 brings changes to content and presentation format as well as new tools.

With these guidelines, ICD-11 presents great improvements compared with the previous version, among them:

- Updated medical knowledge. Scientific development is represented by the wide range of nosographic entities.
- Contemporary concepts of primary care, with greater attention to the field in which most diagnoses are made.
- Revision and update of the section that deals with patient safety.
- Supplemental section for functional evaluation of the patient before and after the medical intervention.
- Incorporation of all rare diseases. Important gain in the field of scientific research.

It is essential to understand that the main challenges lies in the establishment of measures that change the understanding of ICD users. A consistent and complex classification system cannot be interpreted as a purely descriptor and bureaucratic document of morbidity and mortality conditions. The classification must be definitively consolidated in health practice as a strategic action capable of defining directions for the entire care and preventive system.

ICD purpose and uses

As a classification and terminology ICD-11:

- Allows the systematic recording, analysis, interpretation and comparison of mortality and morbidity data collected in different countries or regions and at different times;
- Ensures semantic interoperability and re-usability of recorded data for the different use cases beyond mere health statistics, including decision support, resource allocation, reimbursement, guidelines and more.

Overview

- The global standard for health data, clinical documentation and statistical aggregation.
- Multiple uses, including primary care
- Thoroughly and scientifically updated, and designed for -use in a digital world.
- State-of-the-art technology reduces the costs of training and implementation.
- Multilingual design facilitates global use while the proposal platform allows stakeholder participation in keeping ICD–11 up-to-date.
- Countries have already commenced preparing for implementation of ICD–11, Arabic, Chinese, English, French & Spanish. Russian and 20 more languages are underway.

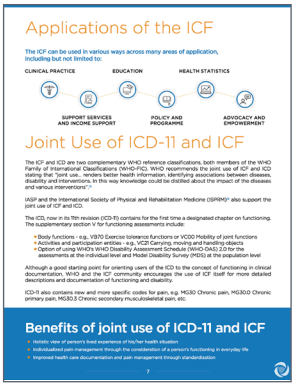
ICD11 is the result of a collaboration with clinicians, statisticians, epidemiologists, coders, classification and IT experts from around the world. ICD11 is a scientifically rigorous product which accurately reflects contemporary health and medical practice.

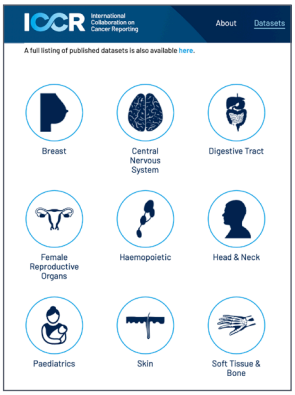
- **Multilingual**
- **Digital**
- **Interoperable**
- **Local configuration**
- **Optional real time big data**

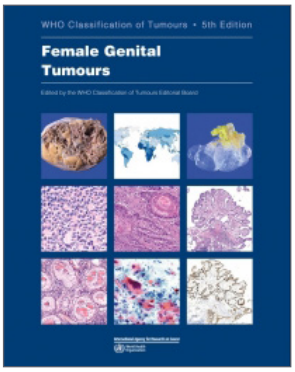
Created by:

- 15,000 proposals
- 99 countries
- 300 institutions
- Hundreds of scientists

International Classification of Diseases – 11th revision: from design to implementation. Almeida, M. S. C., Sousa Filho, L. F. de, Rabello, P. M., & Santiago, B. M. (2020). Revista De Saúde Pública, 54, 104. https://doi.org/10.11606/s1518- 8787.2020054002120







ICD-11 Hospital Software

WHO Family of International Classifications Network

The ICD11 incorporates or links with the following classifications and terminologies through the Foundation and Linearization:

Primary Care

New primary care concepts for application in settings where simple diagnoses are made.

Functioning, Disability and Health – ICF

New supplementary section for Functioning Assessment. This section allows monitoring of functional status through the recording before and after the intervention, and permits the calculation of a summary functioning score. This describes functional health status and social impact (bio-psycho-social model)

Health Interventions - ICHI

ICHI provides a common tool for reporting and analyzing health interventions for statistical purposes. Interventions for treatment, prevention and diagnostics: medical, nursing, rehabilitation, laboratory, imaging, ultrasound, public health.

Disease for Oncology – ICD-O

There is an urgent need to integrate these facets of diagnosis into classification internationally. The understanding of tumors at a molecular level has now reached the point that this information must be included in diagnoses.

External Causes of Injury – ICECI

Documentation of patient safety events has been fully overhauled and systematically tested. It allows for all necessary detail and complies with the WHO patient safety framework and reporting.

OrphaNet

In collaboration with several partners, including OrphaNet, ICD11 has incorporated all rare diseases to allow registries and researchers access to detailed epidemiological data on conditions of interest.

SNOMED-CT Terminology

SNOMED is a global clinical terminology, created for use in health records for recording relevant clinical information to support patient care, sharing and analysis of information.

Traditional Medicine

A new Supplementary Chapter for Traditional Medicine provides standardized descriptions for data capture and allows for country-level monitoring through dual documentation alongside mainstream practice, as well as international comparison.

Spotlight on ICD-11: New Features and New Opportunities

BMC Medical Informatics and Decision Making

- ICD-11 extension codes support detailed clinical abstraction and comprehensive classification
- The three-part model for coding causes and mechanisms of healthcare-related adverse events
- Overview of ICD-11 architecture and structure
- Postcoordination of codes in ICD-11
- Decision algorithm for when to use the ICD-11 3-part model for healthcare harms
- Incorporation of complementary and traditional medicine in ICD-11
- Coding mechanisms for diagnosis timing in the ICD11

Harrison, J.E., Weber, S., Jakob, R. et al. ICD-11: an international classification of diseases for the twenty-first century. BMC Med Inform Decis Mak 21, 206 (2021). https://doi.org/10.1186/s12911-021-01534-6

What's New in ICD11

Diseases of the immune system
Sleep-wake disorders
Sexual Health
Symptoms signs or clinical findings
Injury and Patient Safety
Factors influencing health status
Functional Assessment
Traditional Medicine

Print

https://icd.who.int/dev11/l-m/en/Printables

Print Versions for the ICD-11 ICD-11 for Mortality and Morbidity Statistic

You may download individual chapters or the full linearization using the *all ch*

Title	Print Version
Top level category list	
All Chapters	
01 Certain infectious or parasitic diseases	
02 Neoplasms	
03 Diseases of the blood or blood-forming organs	
04 Diseases of the immune system	
05 Endocrine, nutritional or metabolic diseases	
06 Mental, behavioural or neurodevelopmental disorders	
07 Sleep-wake disorders	
08 Diseases of the nervous system	
09 Diseases of the visual system	
10 Diseases of the ear or mastoid process	
11 Diseases of the circulatory system	
12 Diseases of the respiratory system	
13 Diseases of the digestive system	
14 Diseases of the skin	
15 Diseases of the musculoskeletal system or connective tissue	
16 Diseases of the genitourinary system	
17 Conditions related to sexual health	
18 Pregnancy, childbirth or the puerperium	
19 Certain conditions originating in the perinatal period	
20 Developmental anomalies	
21 Symptoms, signs or clinical findings, not elsewhere classified	
22 Injury, poisoning or certain other consequences of external causes	
23 External causes of morbidity or mortality	
24 Factors influencing health status or contact with health services	
25 Codes for special purposes	
26 Supplementary Chapter Traditional Medicine Conditions - Module I	
V Supplementary section for functioning assessment	
X Extension Codes	
Alphabetical Index	
Alphabetical Index For the Traditional Medicine Chapter	

Chapter 16: Diseases of the genitourinary system

Chapter 16 has been reordered to distinguish diseases of the female genital system, the male genital system, breast disorders and the urinary system. The changes to Chapter 16 are aimed at increasing the clinical utility of the classification by providing a more user-friendly hierarchical structure, increased international comparability and standardisation of genitourinary conditions. There is more specificity within the section on the female genital system reflecting current scientific understanding. The female genital system hierarchy is now divided into non-inflammatory disorders and inflammatory disorders, which are further divided by anatomical groupings. These groupings are in order followed by gynaecological and obstetric examinations (ie from external to internal genitalia). These groupings have further subdivisions for congenital and acquired abnormalities, as appropriate.

All diseases relating to the kidney are now classified under the main category for 'Diseases of the urinary system'. The kidney failure section of the classification has been revised to incorporate the current evidence-based definitions and staging classification of acute kidney failure and chronic kidney disease as proposed by Kidney Disease Improving Global Outcomes (KDIGO). These concepts have been pre-coordinated.

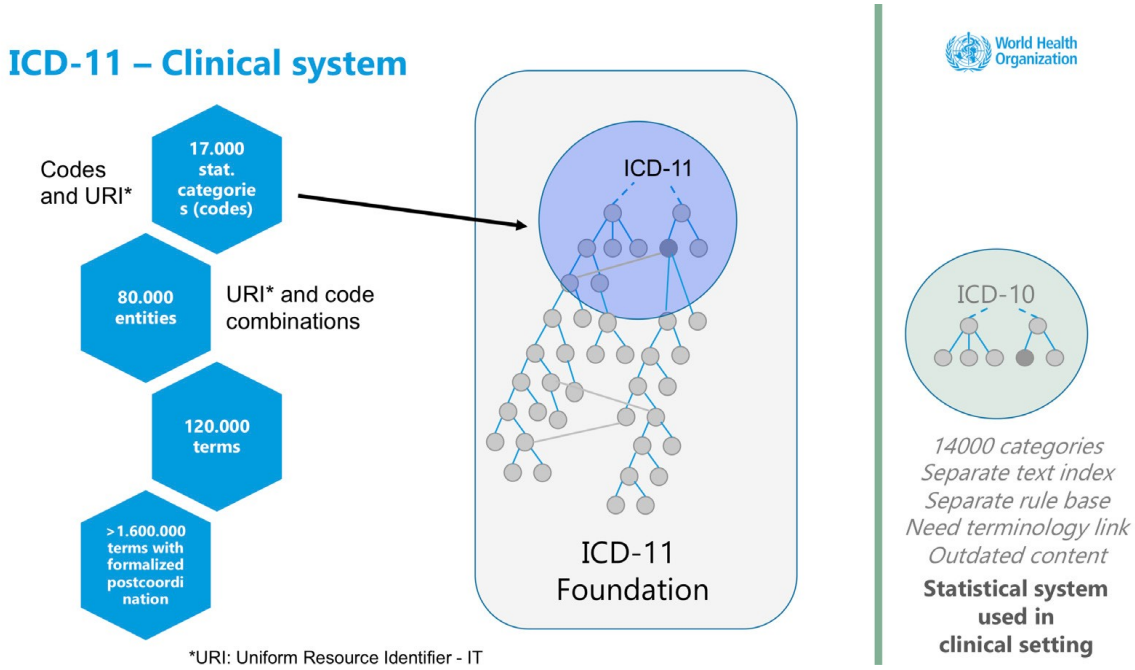
Additional detail has been included for the following areas:

Amenorrhoea
Ovarian dysfunction
Female pelvic pain
Endometriosis
Adenomyosis
Female infertility
Male infertility
Recurrent pregnancy loss

What Is New on Ovarian Carcinoma:

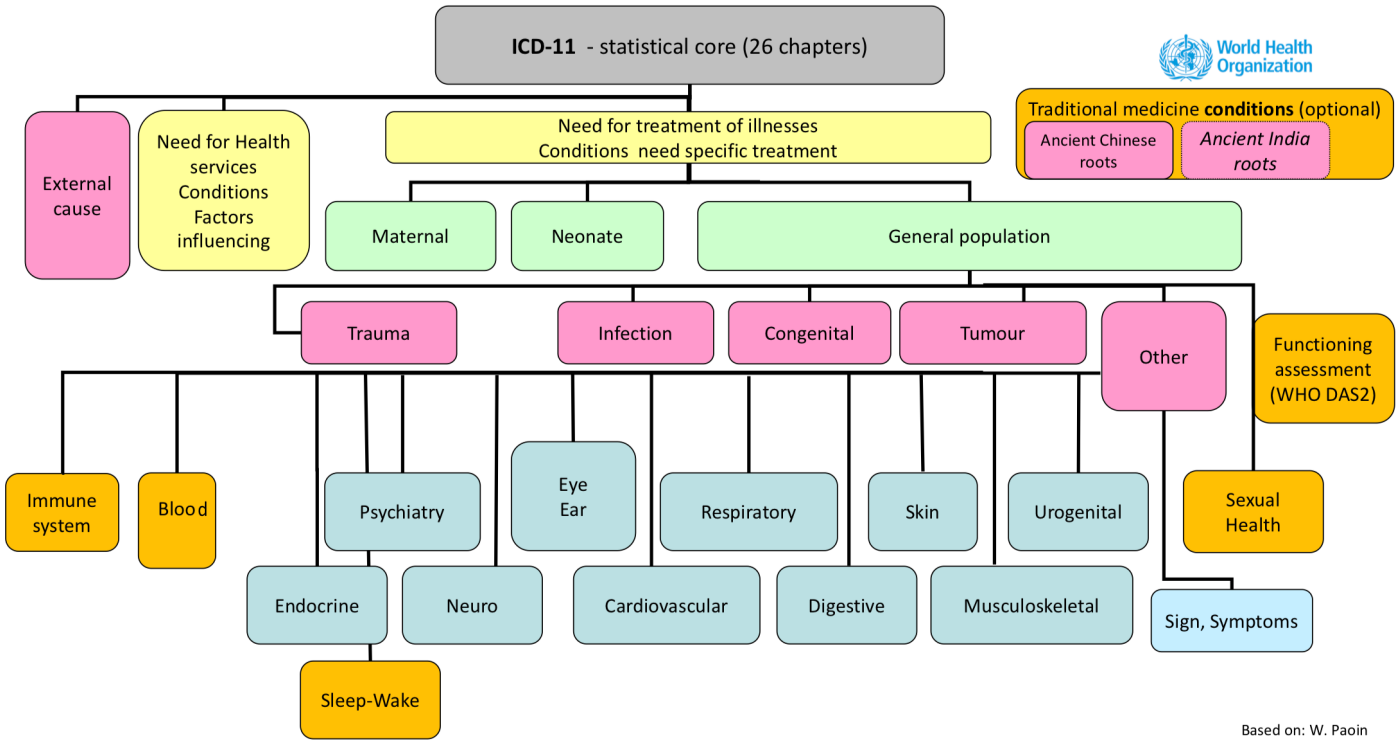
Integrated Morphologic and Molecular Analysis Following the 2020 World Health Organization Classification of Female Genital Tumors

Update in Details



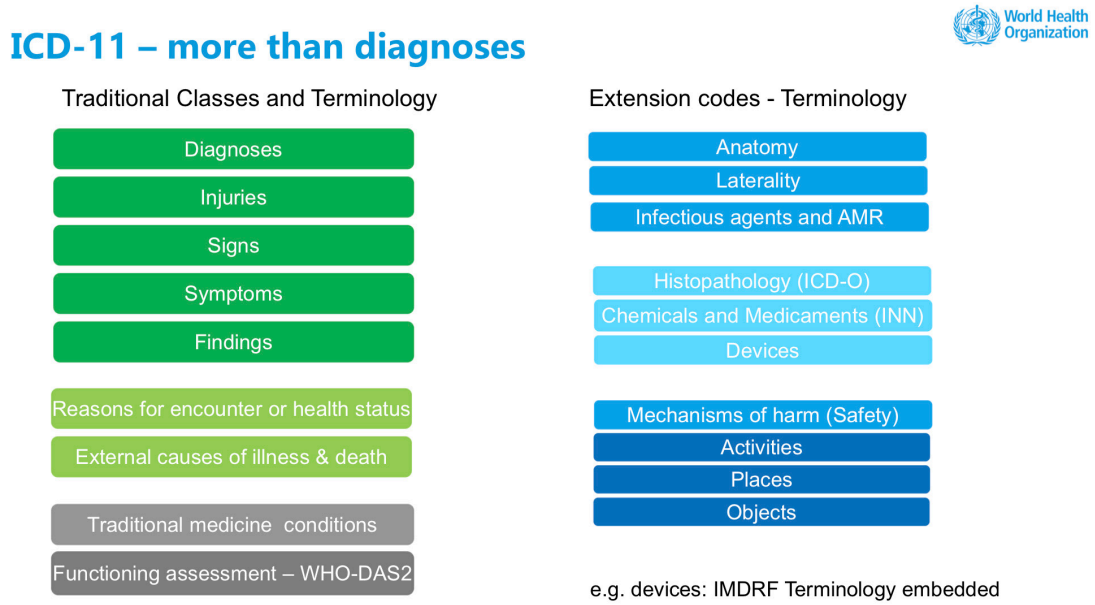
https://www.slideshare.net/citiustech/icd-11-impact-on-payer-market-174066618

Overview of ICD-11 Chapters



Structure

ICD11 features updates to terms of scientific content, technology, usability, utility, medicaments and histopathology and connects with ICD-O: Classification of Tumors.

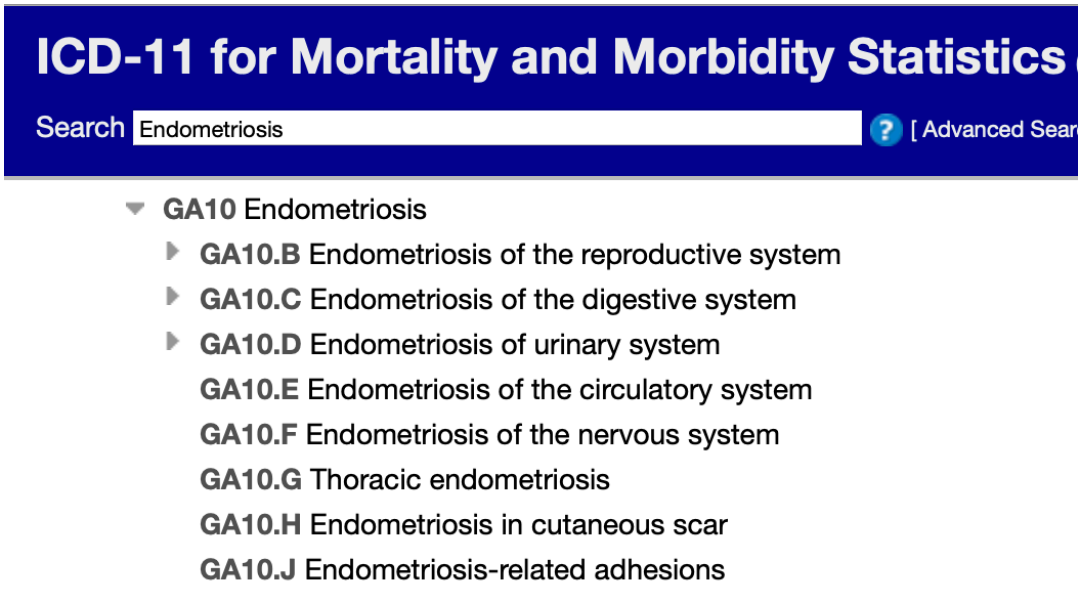


Coding Rules

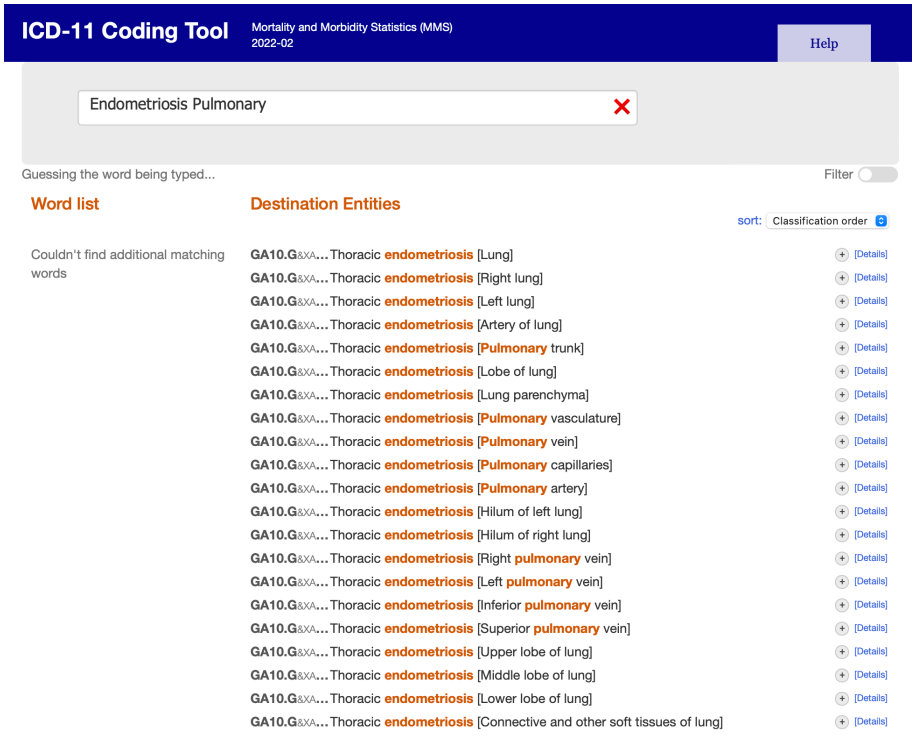
ICD-11 Term	Explanation
Foundation component	Underlying database content that holds all necessary information to generate print versions of the tabular list and the alphabetical index, as well as additional information that is needed to generate specialty linearizations of ICD-11 and country specific modifications.
Stem code	Stem codes are codes that can be used alone. They are found in the tabular list of ICD-11 for Mortality and Morbidity Statistics. Stem codes may be entities or groupings of high relevance, or clinical conditions that should always be described as one single category. The design of stem codes makes sure that in use cases that require only one code per case, a meaningful minimum of information is collected.
Extension code	Extension codes are designed to standardise the way additional information is added to a stem code when users and settings are interested in reporting more detail than is included in a stem code. Extension codes can never be used without a stem code and can never appear in the first position in a cluster.
Precoordination	Stem codes may contain all pertinent information about a clinical concept in a pre-combined fashion. This is referred to as 'precoordination'.
Postcoordination	Postcoordination refers to linking (through cluster coding) multiple codes (i.e. stem codes and/or extension codes) together, to fully describe a documented clinical concept.
Cluster coding	Cluster coding refers to a convention used (either forward slash (/) or ampersand (&)) to show more than one code used together (e.g. stem code/stem code(s)&extension code(s)) to describe a documented clinical concept.
Primary and secondary parents concepts	The hierarchy of ICD-11 is defined the same as it was in previous versions of ICD. The possibility to connect specific diseases and within the classification to another parent code was introduced to enable specific extracts of the Tabular list for medical specialties or for specific use cases.

Browser

Should be GA10.A



Coding Tool



Multilingual

GA10.G Endometriosis torácica

Entidad padre

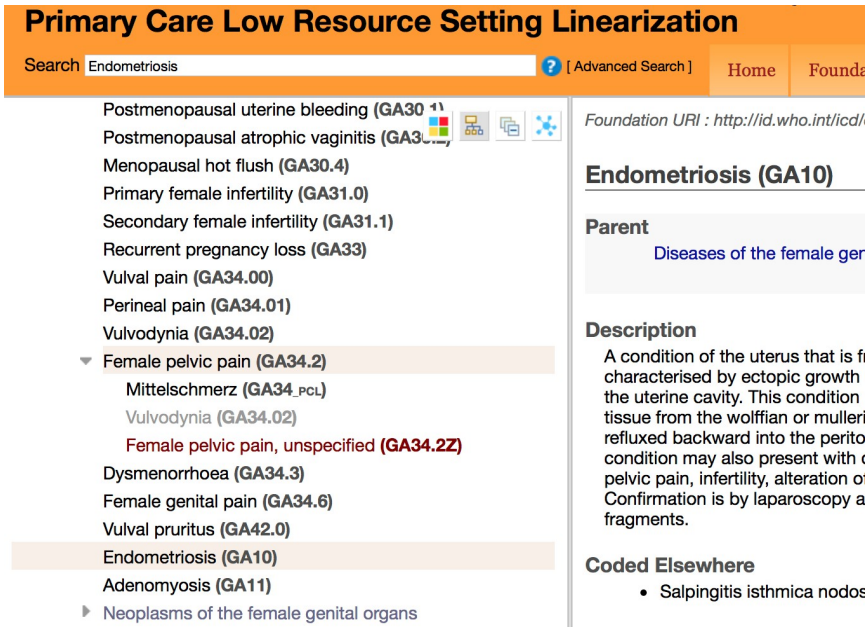
GA10 Endometriosis

Mostrar todos los ancestros

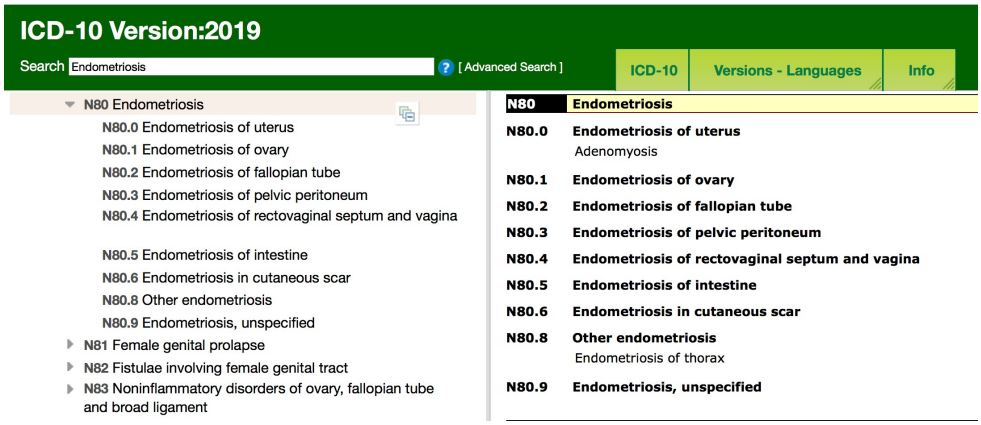
Descripción

Las lesiones de endometriosis torácica pueden afectar el diafragma, la pleura, los pulmones y los bronquios. Puede haber una mayor afinidad por el hemitórax derecho y el parénquima se afecta con mayor frecuencia en los lóbulos inferiores. Macroscópicamente, los implantes endometriósicos aparecen como nódulos de color marrón amarillento y, a veces, rojos rodeados de neovascularización. Los síntomas incluyen: disnea, dificultad para respirar, latidos cardíacos rápidos, tos con sangre y una variedad de patrones de dolor que incluyen escápula, pecho, cuello y hombros ipsolaterales, abdomen superior y epigástrico. La endometriosis torácica puede presentarse con neumotórax catamenial (neumotórax recurrente que ocurre dentro de las 72 horas posteriores a la menstruación), hemoptisis en caso de localización bronquial, hemotórax, derrames pericárdicos. El diagnóstico de endometriosis torácica es sencillo cuando están presentes tanto el estroma como la glándula endometrial. En los casos de endometriosis solo con estroma, podría ser necesaria una clasificación adicional de "patrón agregado", en el que la inmunohistoquímica es ER-, PR- y CD10-positiva para el diagnóstico.

Low Resource Codes



ICD10 Mapping



Global Patient Action Plan

Patient safety is a framework of organized activities that creates cultures, processes, procedures, behaviours, technologies and environments in health care that consistently and sustainably lower risks, reduce the occurrence of avoidable harm, make errors less likely and reduce impact of harm when it does occur. It is often only the patient, family member or carer who has a complete view of the entire journey of care surrounding an event; this emphasizes the value of involving patients, families and carers in investigating and understanding what happened and the circumstances surrounding an incident. The best reporting systems also include and encourage patient generated reports. Good practice around the world suggests that patients who suffer harm and their families should be fully informed about what has happened, how it happened and what will be done to prevent another similar occurrence. More than this, they should be fully engaged (should they so wish) in working with the organization to make change. Patient and family engagement is already an integral feature of the best reporting systems.

Medication Without Harm

Unsafe medication practices and medication errors are a leading cause of injury and avoidable harm in health care systems across the world. Globally, the cost associated with medication errors has been estimated at $42 billion USD annually. Errors can occur at different stages of the medication use process. Medication errors occur when weak medication systems and/or human factors such as fatigue, poor environmental conditions or staff shortages affect prescribing, transcribing, dispensing, administration and monitoring practices, which can then result in severe harm, disability and even death. Multiple interventions to address the frequency and impact of medication errors have already been developed, yet their implementation is varied.

www.who.int/teams/integrated-health-services/patient-safety

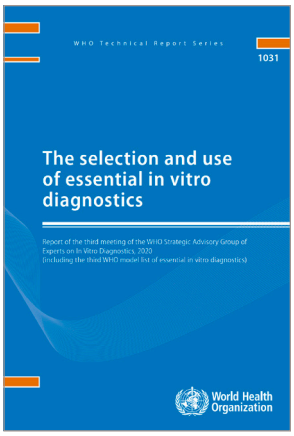
New patient safety incident reporting and learning systems: technical report and guidance.

Patient safety is fundamental to the provision of health care in all settings. However, avoidable adverse events, errors and risks associated with health care remain major challenges for patient safety globally. This global action plan was adopted by Seventy-Fourth World Health Assembly in 2021 with a vision of "a world in which no one is harmed in health care, and every patient receives safe and respectful care, every time, everywhere". The purpose of the action plan is to provide strategic direction for all stakeholders for eliminating avoidable harm in health care and improving patient safety in different practice domains through policy actions on safety and quality of health services, as well as for implementation of recommendations at the point of care. The action plan provides a framework for countries to develop their respective national action plans on patient safety, as well to align existing strategic instruments for improving patient safety in all clinical and health-related programmes

www.who.int/publications/i/item/9789240010338

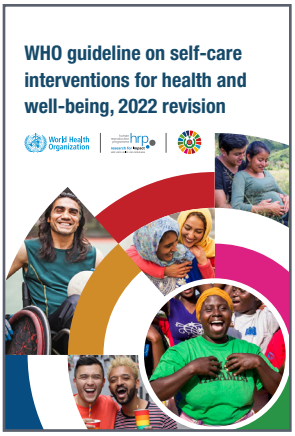
Effective coding is key to the development and use of the WHO Essential Diagnostics List

The WHO new Essential Diagnostics List (EDL) aims to provide a structure for identifying, promoting, and increasing the supply and availability of the most effective and important in-vitro diagnostics. The EDL is not prescriptive, but is instead "expected to provide guidance and serve as a reference". International information technology (IT) standards and medical codes are essential to modern medicine: by agreeing on clinical terms, the health-care ecosystem can prevent errors, improve documentation, and facilitate efficient research and quality improvement. In all health systems, patients frequently move between different health-care providers and facilities, and their health records should be available and understandable to all. In high-income countries, coding systems such as SNOMED CT, ICD11, and Logical Observation Identifiers Names and Codes (LOINC) together provide precise clinical vocabularies that allow medics to very specifically describe medical conditions and treatments in electronic health record systems. The different coding systems and data standards are the result of a long history of gradual development, with different stakeholders requiring different types of data. Data standards designed for medical billing or for aggregating data at a national or regional level might not offer the level of detail needed for data used by clinicians in their day-to-day work, viewing laboratory test results, or entering information into electronic health record systems. The diversity of these applications can result in multiple coding systems being implemented in different clinical IT systems even within the same health-care institution, which can add to complexity and increase the difficulty of linked data analysis.



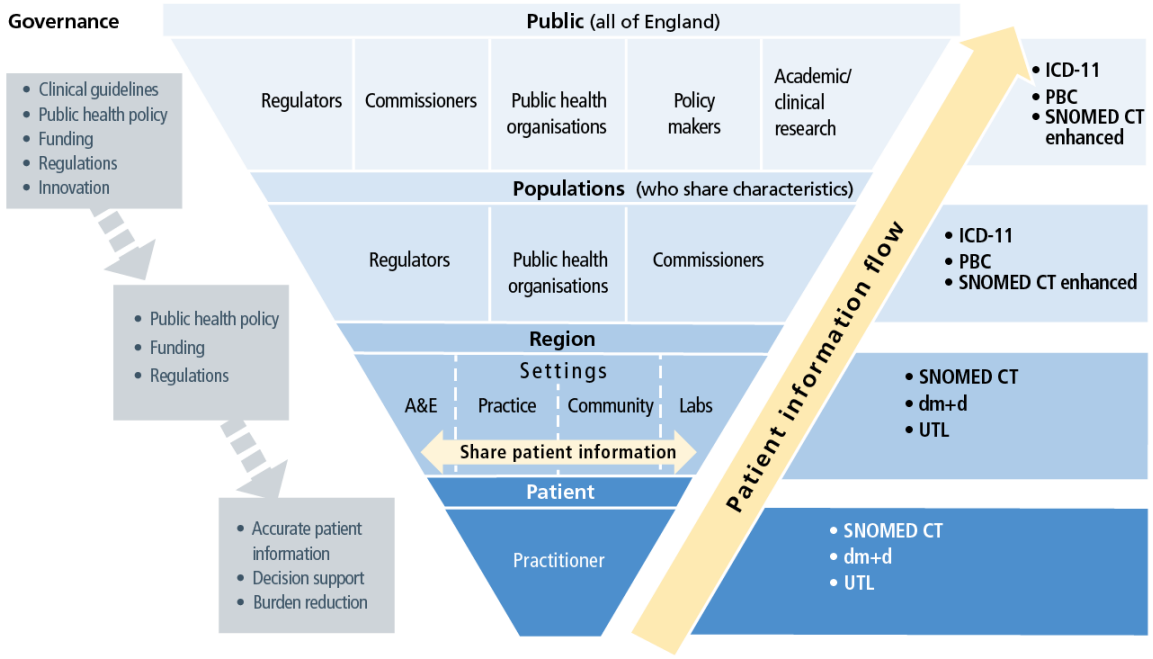
https://www.who.int/publications/i/item/9789240019102

Self-care interventions are among the most promising and exciting approaches to improve health and well-being, both from a health systems perspective and for the users of these interventions. While risk and benefit calculations may be different in different settings and for different populations, with appropriate normative guidance and a safe and supportive enabling environment, self-care interventions promote the active participation of individuals in their healthcare and are an exciting way forward to reach improved health outcomes by addressing various aspects of healthcare. A global shortage of an estimated 18 million health workers is anticipated by 2030, a record 130 million people are in need of humanitarian assistance.



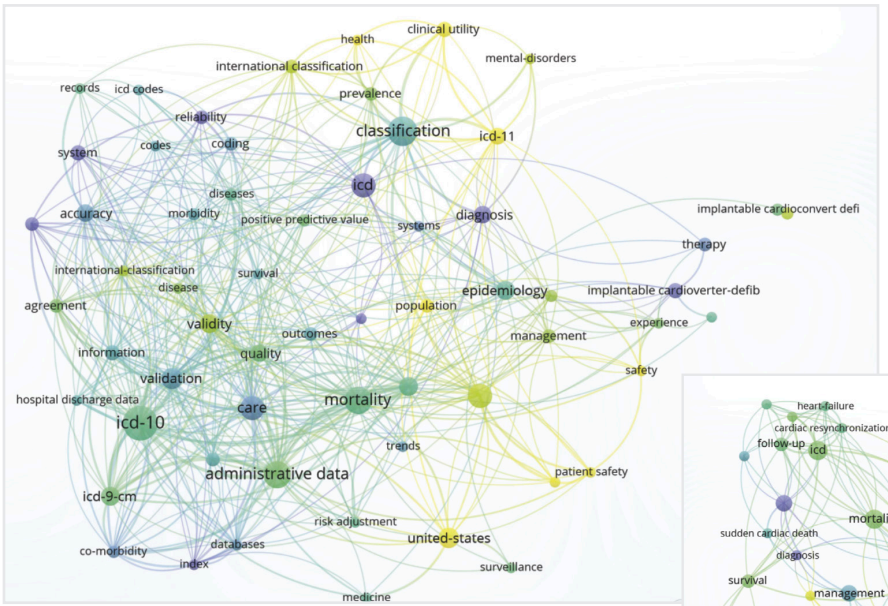
https://www.who.int/news-room/fact-sheets/detail/self-care-health-interventions

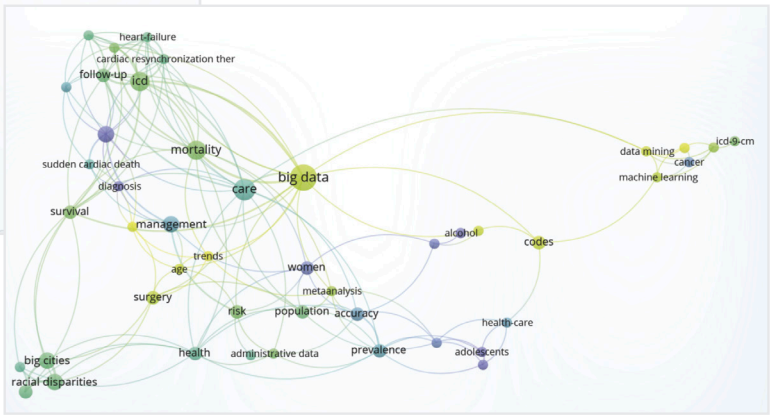
ICD11 in Action



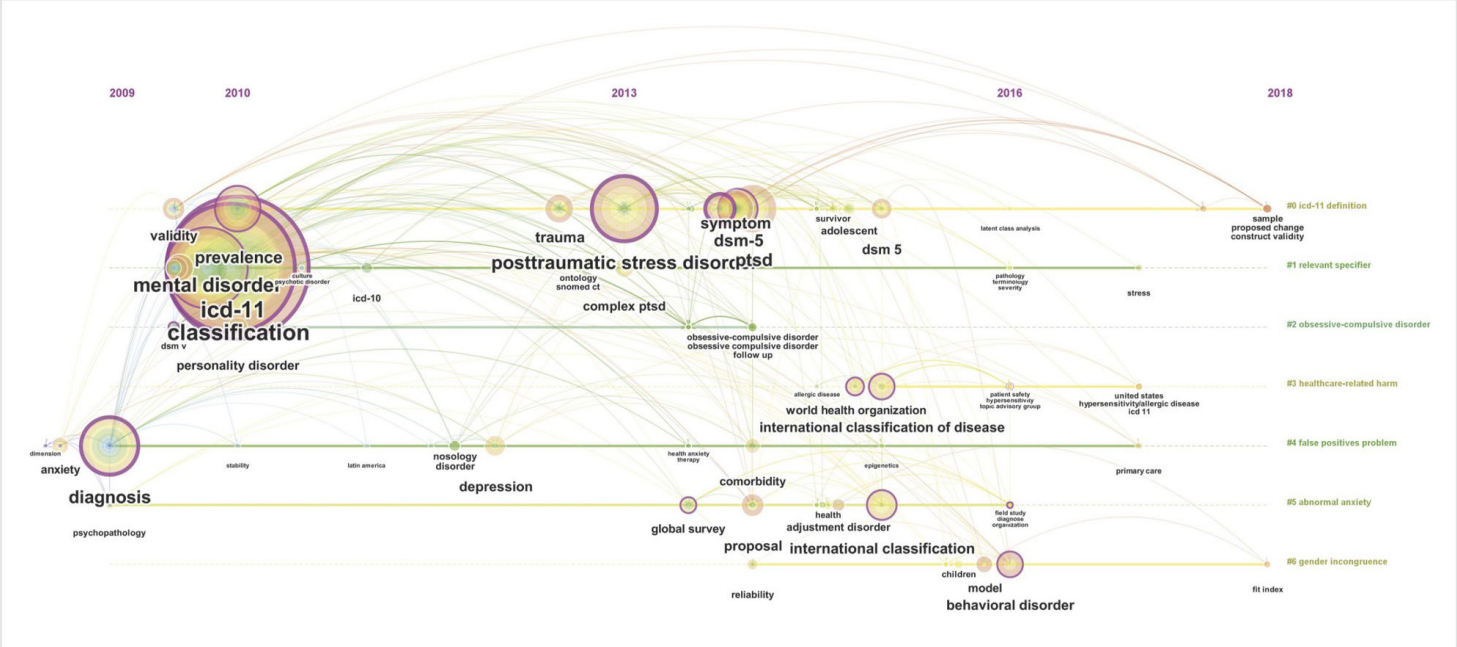
https://digital.nhs.uk/about-nhs-digital/our-work/nhs-digital-data-and-technology-standards/clinical-information-standards

ICD11 Mapping



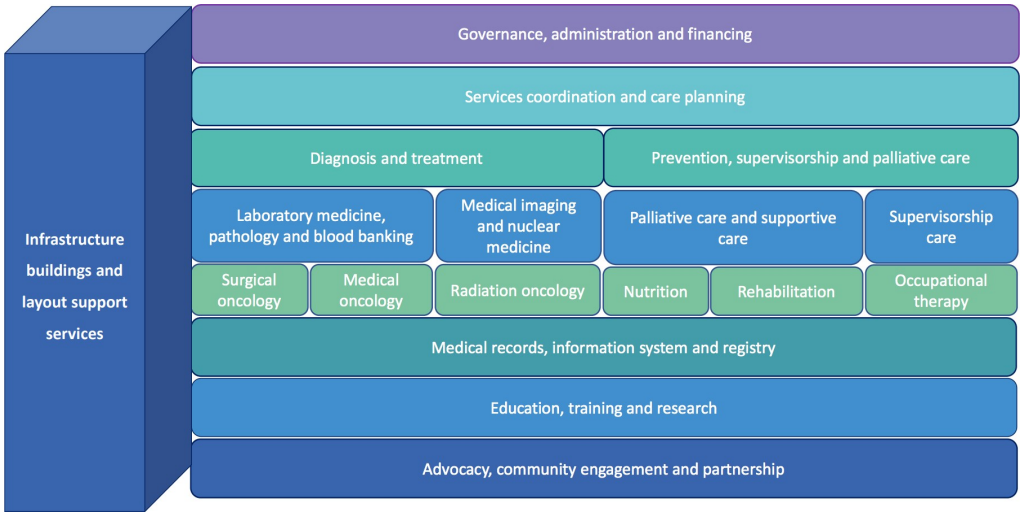


ICD11 Research Example



IAEA Framework for Cancer Centers

The first benefit is patient choice: in most LMICs, medical laboratories in the public sector struggle with shortages and human resource issues that lead to patients seeking medical tests in the private sector. The second benefit is specificity. Approximately 70% of medical laboratory errors occur before the analytical phase. Interoperability is the third benefit of appropriate EDL coding. Networking medical laboratories together in a way that would allow smaller laboratories to send samples to more capable laboratories is a longstanding aim of global health policy makers.



https://www.iaea.org/publications/15052/setting-up-a-cancer-centre-a-who-iaea-framework-

Burnout Assessment Tool (BAT)

Although the burnout syndrome appeared in the 1970s, it is still a global issue such that the 11th revision of the International Classification of Diseases of World Health Organization (ICD-11) defines it as an occupational phenomenon with risk of harming health. The adopted definition of burnout in the ICD-11 comprises three factors (exhaustion, cynicism, and reduced professional efficacy). However, the conceptualization of burnout is somewhat controversial; for example, a meta-analytical study on the physicians' burnout found 142 unique definitions of burnout with at least 47 unique definitions using MBI. Some constructs, such as depression and fatigue, are conceptually linked to job burnout. These phenomena are potentially part of the process of long-term sick leave. At the core of burnout lies severe fatigue (i.e., exhaustion); however persistently fatigued workers are not necessarily (by definition) in burnout, nor must burned-out workers necessarily report fatigue as the main complaint. Occupational fatigue has been linked to an imbalance between the intensity and duration and timing of work with recovery time. Studies over decades have shown evidence that burnout syndrome predicts various negative consequences to individuals and organizations, such as cardiovascular diseases, hypercholesterolemia, type 2 diabetes, coronary heart disease, musculoskeletal disorders, prolonged fatigue, headaches, gastrointestinal issues, mood disturbance, depressive symptoms, absenteeism, poor performance, insomnia, depressive symptoms, and life and job dissatisfaction.

Sinval J, Vazquez ACS, Hutz CS, Schaufeli WB, Silva S. Burnout Assessment Tool (BAT): Validity Evidence from Brazil and Portugal. Int J Environ Res Public Health. 2022 Jan 25;19(3):1344. doi: 10.3390/ijerph19031344. PMID: 35162366; PMCID: PMC8834921.

Item	English					Brazil				Portugal
	Never	Rarely	Sometimes	Often	Always	Nunca	Raramente	Algumas vezes	Frequentemente	S
	1	2	3	4	5	1	2	3	4	
	Exhaustion					Exaustão				
1 S	At work, I feel mentally exhausted					No trabalho, sinto-me mentalmente exausto			No trabalho, sinto-me mentalmente exaust	
2	Everything I do at work requires a great deal of effort					Tudo o que faço no trabalho exige muito esforço			Tudo o que faço no t exige muito esforço	
3 S	After a day at work, I find it hard to recover my energy					Acho difícil recuperar minha energia depois de um dia de trabalho			Depois de um dia no trabalho, acho difícil recuperar a minha er	
4 S	At work, I feel physically exhausted					No trabalho, sinto-me fisicamente exausto			No trabalho, sinto-me fisicamente exausto(	
5	When I get up in the morning, I lack the energy to start a new day at work					Ao levantar pela manhã, me falta energia para começar um novo dia no trabalho			Quando me levanto d manhã, falta-me a er para começar um no no trabalho	
6	I want to be active at work, but somehow I am unable to manage					Quero ser ativo no trabalho, mas de alguma forma não consigo			Quero estar ativo(a) trabalho, mas de alg forma sou incapaz de fazer	
7	When I exert myself at work, I get tired quicker than normal					Quando eu me esforço no trabalho, me canso mais rápido do que o normal			Quando me esforço trabalho, fico rapidam cansado(a)	
8	At the end of my working day, I feel mentally exhausted and drained					No final do meu dia de trabalho, eu me sinto mentalmente exausto e esgotado			No final de um dia de trabalho, sinto-me mentalmente exaust esgotado(a)	
	Mental distance					Distância mental				
9 S	I struggle to find any enthusiasm for my work					Eu luto para encontrar algum entusiasmo pelo meu trabalho			Tenho dificuldade em encontrar algum ent pelo meu trabalho	
10 S	At work, I do not think what I am doing and I function on autopilot					Não penso no que estou fazendo no meu trabalho, eu funciono em piloto automático			No trabalho, não pen muito no que estou a e funciono em piloto automático	
11	I feel a strong aversion towards my job					Sinto forte aversão pelo meu trabalho			Sinto uma forte avers relação ao meu traba	
12	I feel indifferent about my job					Sinto-me indiferente em relação ao meu trabalho			Sinto-me indiferente relação ao meu traba	
13 S	I am cynical about what my work means to others					Sou pessimista sobre o que meu trabalho significa para os outros			Sou cínico(a) sobre meu trabalho signific os outros	

ICD 11: Impact on Payer Market

The World Health Organization (WHO) released the new International Classification of Disease (ICD-11) which would come into effect in January 2022. This document takes a closer look at revisions made to the document and its possible impact on healthcare payers.

Application Programming Interface (API services)

API allows programmatic access to the International Classification of Diseases (ICD). Users must first egister via the site and may then use it to access upto-date documentation on using the API as well as managing the keys needed for using the API.

Reconciliations

A mapping platform is in a restricted area of the ICD11 Online browser. This platform supports the manual creation of transition tables between ICD-10 and ICD11. The links are made between the corresponding entries of ICD-10 and ICD-11. In ICD-11, the logical hierarchical structure does not end with the level of coding, but extends up to 12 levels of branching, such as roots, from the chapter level to the depth.

Benefits for Payers

- Impact on Health Plan Eligibility and Underwriting processes
- Impact on Provider network management
- Impact on Claims Processing
- Impact on Healthcare IT systems and Software

Challenges

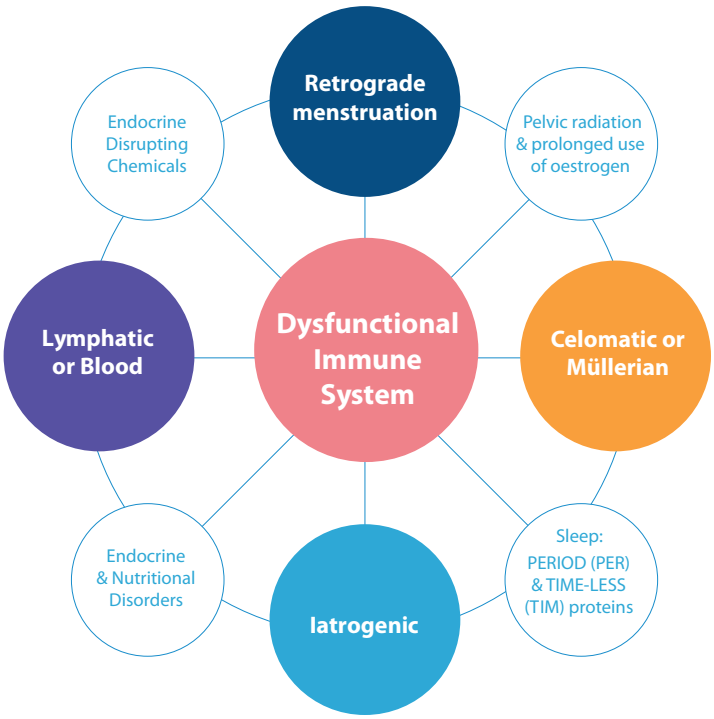
- Conversion of ICD-10 codes to ICD-11 codes is extremely complicated. ICD-11 vastly increases the number and complexity of disease and procedure codes over ICD-10 as single code in ICD 10 might be translated to multiple codes in ICD 11.
- There may be challenges in determining the National coverage determinations, Local coverage decisions, Pharmacy coverage policies, Laboratory/Device/DME, DRG/ case mix cases.
- Risk of Providers taking advantage of the new ICD11 codes for claiming multiple claims for single diagnosis which results in more payments. For e.g. D53.8 in ICD 10 is translated into eight codes in ICD11, in this scenario there is possibility of fraud as provider might submit multiple claims with different codes of ICD 11 instead of single code as per ICD 10which results in multiple payments leading to revenue loss.
- To estimate the possible costs and revenue loss from the transition from ICD-10 to ICD11 is a potential challenge for payer due to complexity of adoption process as it involves changes that are not limited within the organization's boundaries, but are also to be expected from trading partners, vendors, regulatory agencies and business partners.

https://www.slideshare.net/citiustech/icd-11-impact-on-payer-market-174066618

Endometriosis

ICD-11

Pathways



Retrograde menstruation

Retrograde menstruation is the process in which endometrial cells and fragments of the tissue shed during menstrual bleeding and are transported into the peritoneal cavity due to the retroperistaltic movements of the fallopian tubes. Implantation of these particles and subsequent proliferation during the menstrual cycle leads to the damage of pelvic organs at positions of implantation

Dissemination via Lymphatic / Blood

Endometriosis can develop due to endometrial cells transferred through the lymphatic system to other parts of the body, where they further grow and proliferate. Circulating blood cells originating from bone marrow differentiate into endometriotic tissue at various body sites.

Celomatic or Müllerian Origin

Ectopic EM can originate from mesothelial totipotent cells of the peritoneum through metaplasia. This notion is considerably sound due to the fact that the celomatic epithelium, from which the epithelial cells of the Müllerian ducts originate, also differs in pleural and peritoneal epithelial cells, as well as in cells of the ovarian surface.

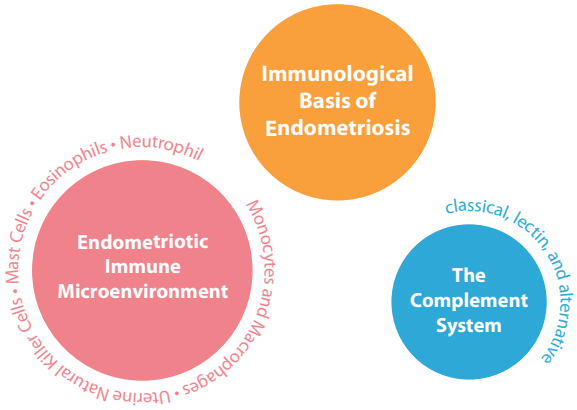
Iatrogenic endometriosis

Iatrogenic endometriosis" may occur after operations of the uterine cavity (myomectomy and metroplasty), or in the case of surgical interventions carried out on pelvic organs, which may account for localization at the vulvo-perineal level

Dysfunctional Immune System

Endometriosis is due to an alteration in the immune system in terms of immune-cell recruitment, cell- adhesion, and upregulated inflammatory processes, which can facilitate the implantation and survival of endometriotic lesions. A distinct epigenetic profile can be observed between eutopic and ectopic endometrial tissues. By analysing global promoter methylation patterns, researchers have demonstrated that differentially methylated genes are associated with immune surveillance, inflammatory response, cell adhesion and negative regulation of apoptosis. There is a paramount role of immune cells in the pathogenesis.

Agostinis, C., Balduit, A., Mangogna, A., Zito, G., Romano, F., Ricci, G., Kishore, U., & Bulla, R. (2021). Immunological Basis of the Endometriosis: The Complement System as a Potential Therapeutic Target. Frontiers in immunology, 11, 599117. https://doi.org/10.3389/ fimmu.2020.599117



Immunological Basis of Endometriosis

Endometriosis (EM) is a chronic disease characterized by the presence and proliferation of functional endometrial glands and stroma outside the uterine cavity. The cyclic and recurrent bleeding, the progressive fibrosis and the peritoneal adhesions of ectopic endometrial glands cause different symptoms depending on the origin involved. The risk of developing EM depends on a complex interaction between genetic, immunological, hormonal, and environmental factors. It is largely considered to arise due to a dysfunction of immunological surveillance. In fact, women with EM exhibit altered functions of peritoneal macrophages, lymphocytes and natural killer cells, as well as levels of inflammatory mediators and growth factors in the peritoneal fluid. Peritoneal macrophages are able to regulate the events that determine the production of cytokines, prostaglandins, growth factors and complement components.

Origins of the endometriotic lesions include surgical dissemination, transplantation of endometrial tissue through retrograde menstruation, and in situ coelomic metaplasia of the peritoneal lining. Vascular or lymphatic metastasis occurs rarely, in cases of extrapelvic lesions. Superficial and deep endometriotic lesions are established and maintained through interacting molecular mechanisms that promote cellular adhesion and proliferation, systemic and localized steroidogenesis, localized inflammatory response and immune dysregulation. There is a paramount role of immune cells in the pathogenesis of EM. Recently, it has been shown that the complement system is one of the most preponderant pathways impaired in the EM.

The Complement System

The complement system plays a very important role in the recognition and clearance of pathogens, apoptotic and necrotic cells. The complement system is represented by over 50 proteins, including soluble activation precursor components, regulators and cell surface receptors. The complement system is very efficient at tagging or flagging the non-self (pathogens), altered self (apoptotic/necrotic cells, and protein aggregates), and transformed self (tumor cells), which can result in lysis of target cells/pathogens, opsonization and subsequent enhanced uptake by phagocytic cells of the immune system via complement receptors, and generation of inflammaton mediators. In addition, the complement system can also modulate the adaptive immune response, and act as a link between innate and adaptive immunity. The complement system can be activated through three major pathways: classical, lectin, and alternative.

Endometrial stem/progenitor cells and their roles in immunity

Endometrial stem/progenitor cells have been proved to exist in periodically regenerated female endometrium and can be divided into three categories: endometrial epithelial stem/progenitor cells, CD140b+CD146+ or SUSD2+ endometrial mesenchymal stem cells (eMSCs), and side population cells (SPs). Endometrial stem/progenitor cells in the menstruation blood are defined as menstrual stem cells (MenSCs). Endometrial stem/progenitor cells also participate in the occurrence and development of endometriosis by entering the pelvic cavity from retrograde menstruation and becoming overreactive under certain conditions to form new glands and stroma through clonal expansion. The limited bone marrow mesenchymal stem cells (BMDSCs) in blood circulation can be recruited and infiltrated into the lesion sites, leading to the establishment of deep invasive endometriosis. On the other hand, cell derived from endometriosis may also enter the blood circulation to form circulating endometrial cells (CECs) with stem cell-like properties, and to migrate and implant into distant tissues. Circulating endometrial cells (CECs) are identified in the peripheral blood of all the acknowledged endometriosis stages: minimal, mild, moderate, and severe. The CECs captured during the menstrual cycle phases display stem cell-like characteristics. CECs are also found in the patients with pelvic endometriosis and spontaneous pneumothorax, with the properties of epithelial, stroma-like, glandular, or stem cell-like cells.

Inflammatory Mediators and Pain in Endometriosis

Cytokines-chemokines expression in endometriosis: the pathophysiology of endometriosis involves biological mechanisms that induce pain. There's a direct correlation between the pain score and the expression of insulin-like growth factor-1 (IGF-1) in peritoneal fluid from women with endometriosis.

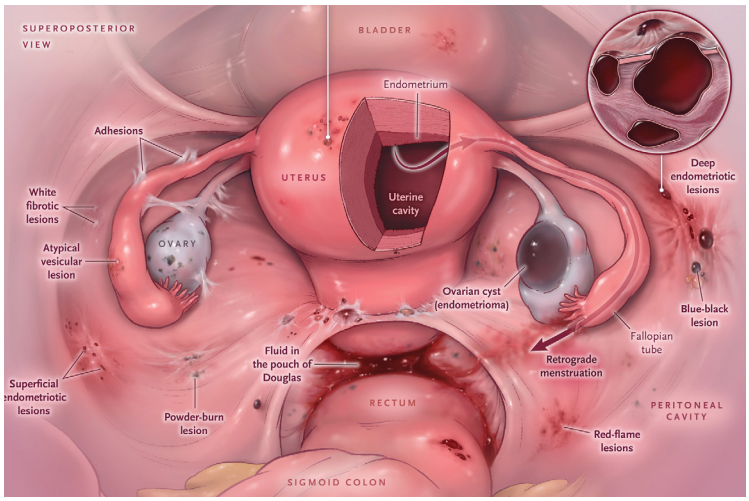
L-6 has been found to be involved and control the homeostasis of cell processes, which include the neuroendocrine system, neuropsychological behavior, lipid metabolism, and mitochondrial activities. These findings have made IL-6 a tool to improve the condition of a patient in terms of pain, mood, depression, fatigue, and sleep. Its function also includes the maintenance of the functional integrity of tissues and organs. The expression rate of IL-6 was also higher in patients with endometriosis and it had a dependence on the stage of the disease.
IL-7 Higher expression in eutopic DIE
IL-8 Overexpression in the endometrium In endometriosis, the IL-8 levels are increased under oxidative stress IL-10 Higher in the peritoneal fluid and serum/anti-inflammatory
IL-15 Higher in ectopic DIE
IL-32 High concentration in the peritoneal fluid-severity IL-33 Higher levels in ectopic lesions
IL-37 Higher expression in serum—anti-inflammatory role TNF- Overexpression in endometrium
CXCR4 Depends on the type of lesion

NETs is another factor, which has been related to autoimmune and inflammatory conditions. It's detected in the plasma of patients with endometriosis.

Kong, Y., Shao, Y., Ren, C. et al. Endometrial stem/progenitor cells and their roles in immunity, clinical application, and endometriosis. Stem Cell Res Ther 12, 474 (2021). https://doi. org/10.1186/s13287-021-02526-z
Machairiotis N, Vasilakaki S, Thomakos N. Inflammatory Mediators and Pain in Endometriosis: A Systematic Review. Biomedicines. 2021;9(1):54. Published 2021 Jan 8. doi:10.3390/ biomedicines9010054

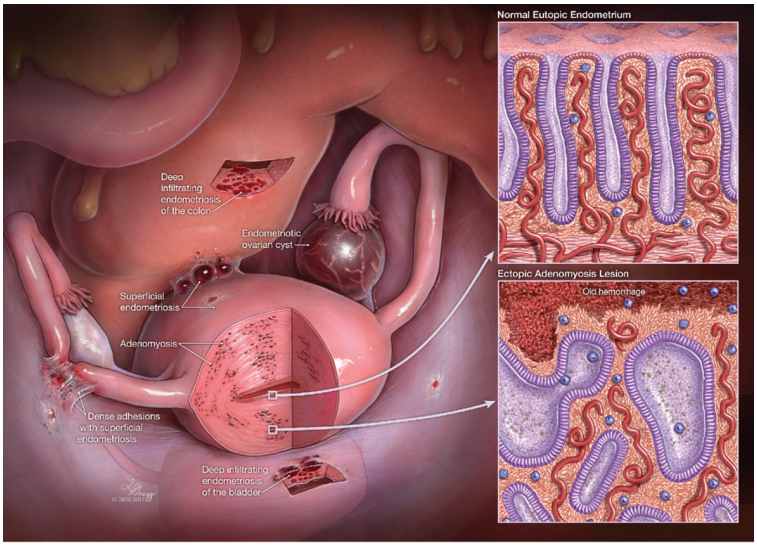
Endometriosis Pathways

Endometriotic lesions are established and maintained through interacting molecular mechanisms that promote cellular adhesion and proliferation, systemic and localized steroidogenesis, localized inflammatory response and immune dysregulation, and vascularization and innervation. Endometrial stromal cells display adhesive capacity as a result of altered integrin profiles, and a localized inflammatory response favors cellular adhesion.



Pathology and Pathogenesis of Adenomyosis

The identification of somatic mutations has provided unequivocal evidence that adenomyosis develops from eutopic endometrium. Adenomyosis and associated eutopic endometrium are progeny of the same endometrial epithelial progenitor cells. Adenomyosis and eutopic endometrium also harbor distinct mutations.

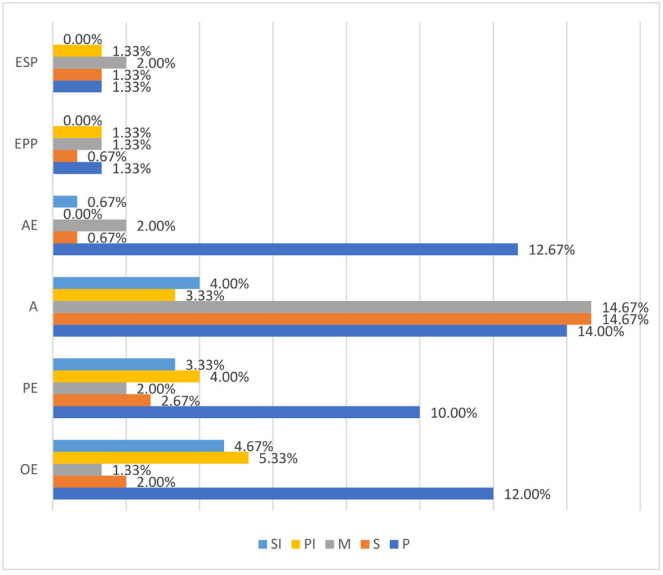


Zondervan, Krina T., Becker, Christian M., Missmer, Stacey A., Endometriosis. N Engl J Med 2020;382:1244-56. DOI: 10.1056/NEJMra1810764
Antero MF, Ayhan A, Segars J, Shih IM. Pathology and Pathogenesis of Adenomyosis. Semin Reprod Med. 2020;38(2-03):108-118. doi:10.1055/s-0040-1718922

Ectopic endometrial epithelium associates a wide spectrum of symptomatology. Their evolution can be influenced by inflammatory and vascular changes, that affect not only the structure and cell proliferation rate, but also symptoms. This prospective study involved tissue samples from surgically treated patients, stained using classical histotechniques and immunohistochemistry. We assessed ectopic endometrial glands (CK7+, CK20-), adjacent blood vessels (CD34+), estrogen/progesterone hormone receptors (ER+, PR+), inflammatory cells (CD3+, CD20+, CD68+, Tryptase+), rate of inflammatory cells (Ki67+) and oncoproteins (BCL2+, PTEN+, p53+) involved in the development of endometriosis/adenomyosis. A CK7+/CK20- expression profile was present in the ectopic epithelium and differentiated it from digestive metastases. ER+/PR+ were present in all cases analyzed. We found an increased vascularity (CD34+) in the areas with abdominal endometriosis and CD3+-:T-lymphocytes, CD20+-:B-lymphocytes, CD68+:macrophages, and Tryptase+: mastocytes were abundant, especially in cases with adenomyosis as a marker of proinflammatory microenvironment. In addition, we found a significantly higher division index-(Ki67+) in the areas with adenomyosis, and inactivation of tumor suppressor genes-p53+ in areas with neoplastic changes. The inflammatory/vascular/hormonal mechanisms trigger endometriosis progression and neoplastic changes increasing local pain. Furthermore, they may represent future therapeutic targets. Simultaneous-multiple immunohistochemical labelling represents a valuable technique for rapidly detecting cellular features that facilitate comparative analysis of the studied predictors.

The need to investigate and research tissue changes associated with endometriosis and adenomyosis has increased, due to the rising incidence and improvement of diagnosis techniques during the last decades [8,9,10,11]. Premalignant transformation, complex atypical hyperplasia, and malignant transformation of endometriosis foci can be highlighted by identifying the typical glandular structure in malignant areas by classical histological staining and later confirmed by immunolabeling to accomplish the differential diagnosis.

The presence of endometrial structures and adjacent stroma were diagnosed by the presence of endometrial glands and endometrial stroma, accompanied by varying degrees of fibrosis, acute or chronic hemorrhage, and lympho-monocyte inflammatory infiltration.



Proportion of symptomatic patients depending on the location of endometriosis. OE = Ovarian endometriosis, PE = Peritoneal/pelvic endometriosis, A = Adenomyosis, AE = Abdominal wall endometriosis, EPP = Endometrium—proliferative phase, ESP = Endometrium—secretory phase, CD = cluster of differentiation, p = pain, S = spotting, M = menorrhagia, PI = primary infertility, SI = secondary infertility.

Evolution Predictors for Endometriosis/Adenomyosis Foci

- Cytokeratin
- Hormone Receptors
- Perilesional Vascularization
- Cell Proliferation and the Presence of Tumor Proteins

The Implications of Perilesional Inflammation

Inflammatory factors secreted by the periglandular immune system cells, can influence the evolution and transformation of the abnormal cells, with carcinogenetic implications. Thus, inflammation can lead to atypical aspects of endometrial cells, altering the nucleocytoplasmic ratio, the nuclei can become hyper- or hypochromic, and the cell layers can multiply [8]. The inflammatory cells invading the stroma and can influence the transformation of this benign pathology into a hyperplastic or even malignant pathology. This inflammatory microenvironment associated with endothelial dysfunction participates in carcinogenesis [8]. The intense perilesional inflammatory response plays a double role, in defense and creating an environment favorable to hyperplastic transformations.

Involved in the development of endometriosis/adenomyosis

Ectopic endometrial glands (CK7+, CK20-)

Adjacent blood vessels (CD34+)

Estrogen/progesterone hormone receptors (ER+, PR+)

Inflammatory cells (CD3+, CD20+, CD68+, Tryptase+)

Rate of inflammatory cells (Ki67+)-

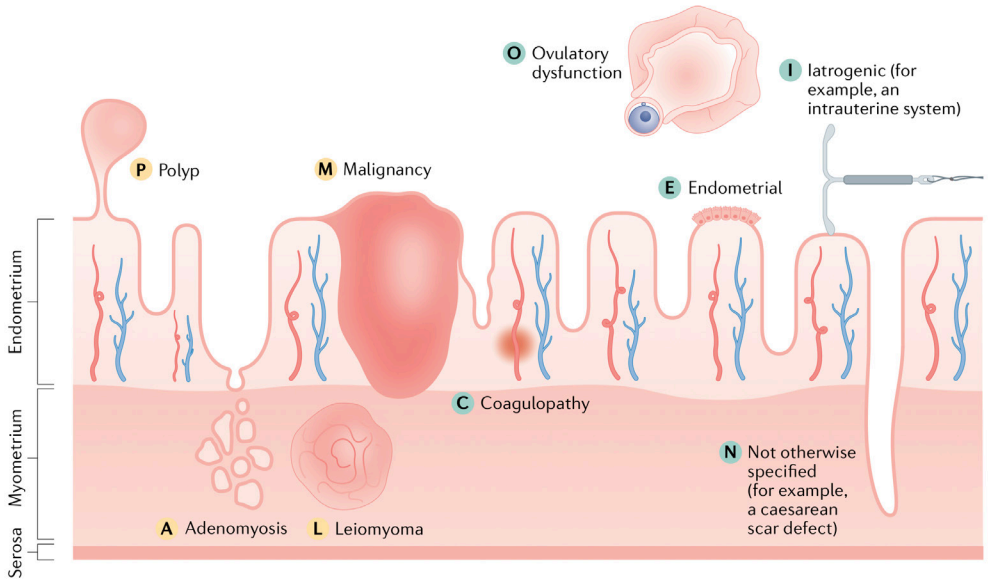
Oncoproteins (BCL2+, PTEN+, p53+)

Istrate-Ofițeru AM, Berbecaru EI, Zorilă GL, Roșu GC, Dîră LM, Comănescu CM, Drăguşin RC, Ruican D, Nagy RD, Iliescu DG, Mogoantă L, Pirici D. Specific Local Predictors That Reflect the Tropism of Endometriosis-A Multiple Immunohistochemistry Technique. Int J Mol Sci. 2022 May 17;23(10):5614. doi: 10.3390/ijms23105614. PMID: 35628423; PMCID: PMC9145853.

FIGO Classification: abnormal uterine bleeding (AUB)

The causes of abnormal uterine bleeding are classified using the acronym PALM-COEIN, with each letter denoting a cause. The structural causes (denoted by yellow letters) are discrete entities and include polyp, adenomyosis, leiomyoma (uterine fibroids) and malignancy. The non-structural causes (denoted by green letters) are depicted for the illustration; however, they cannot be measured or imaged. They include coagulopathy, ovulatory dysfunction, endometrial, iatrogenic and not otherwise classified (for example, a caesarean scar defect).

Uterine bleeding: how understanding endometrial physiology underpins menstrual health. One third of women globally will be affected by abnormal uterine bleeding (AUB)



The terminology and definitions for diagnosing causes of AUB are now standardized in the International Federation of Gynecology and Obstetrics Systems 1 and 2, and should be followed for ease of clinical and research synchrony.

Classification	Definition	Global prevalence	Further details
Polyp (AUB-P)	Focal outgrowths of vascular, glandular, fibromuscular and connective tissue	10–15% of women without AUB have polyps; 20–30% of women with AUB have polyps201	Located in uterine cavity or endocervix
Adenomyosis (AUB-A)	The presence of ectopic endometrial glands and stroma within the myometrium12	Varies depending on method of diagnosis and concurrent symptoms in population being studied;202 however, an estimate of 20–35% on average in women with AUB164,203,204	Can be focal or diffuse; primarily affects the posterior uterine wall143; an 'elusive' disease, poorly understood and difficult to diagnose with a vague, ill-defined pattern of symptoms12
Leiomyoma (AUB-L; uterine fibroids)	Excessive proliferation of smooth muscle cells and fibroblasts	80% of all women by age 50 years (varies with ethnicity)189	Benign uterine lesions; individuals can have one or multiple fibroids; sub-classification is dependent on their uterine location2
Malignancy and hyperplasia (AUB-M)	An abnormal proliferation of cells of the reproductive tract	Atypical endometrial hyperplasia and genital tract malignancy are uncommon; prevalence depends on the tissue of origin of the malignancy or hyperplasia	An important potential cause to consider in all women with AUB; the risk of AUB-M increases with age, especially in perimenopause, in people with anovulatory cycles, and/or in people with obesity. WHO or FIGO classification systems should be followed
Coagulopathy (AUB-C)	A spectrum of systemic disorders of haemostasis that can be associated with AUB	~13% of patients with HMB have a detectable coagulopathy and von Willebrand disease is the most common cause112	Pharmacological intervention that can impair blood coagulation is included in AUB-I2
Ovulatory dysfunction (AUB-O)	AUB-O is linked with endocrinopathies, such as -PCOS and hyperprolactinaemia (diagnosed with blood tests); AUB-O can be linked with mental stress and extreme (high or low) weight10	Dependent on cause	AUB-O leads to varying bleeding patterns, from amenorrhoea to HMB; ovulatory disorders linked with iatrogenic pharmaceutical interventions are classified under AUB-I2
Endometrial (AUB-E)	Primary disorder of the endometrium; diagnosis of exclusion10,205	Prevalence unknown	Can involve dysregulation of the mechanisms regulating the control of endometrial bleeding at the time of menstruation, such as local endometrial vasoconstriction, haemostasis and endometrial repair
Iatrogenic (AUB-I)	Medical interventions and devices, pharmacological agents that lead to AUB	Dependent on cause	Medical interventions and devices such as medicated intrauterine systems (for example, LNG-IUS) or inert intrauterine systems; pharmacological agents such as sex steroids, drugs influencing dopamine metabolism or ovulatory function, or anticoagulants; it is important to decipher the origin of unscheduled and/or breakthrough bleeding2,10
Not otherwise classified (AUB-N)	A spectrum of conditions, only some of which can be evaluated or measured using imaging modalities or histopathology	Dependent on cause	Includes rarely encountered or ill-defined entities such as uterine arteriovenous malformations, lower segment or upper cervical niche (or an isthmocele) associated with a caesarean section scar defect2,10

Jain, V., Chodankar, R.R., Maybin, J.A. et al. Uterine bleeding: how understanding endometrial physiology underpins menstrual health. Nat Rev Endocrinol 18, 290–308 (2022). https://doi.org/10.1038/s41574-021-00629-4

FIGO Classification: abnormal uterine bleeding (AUB)

Menstruation is a fine balance between proliferation, decidualization, inflammation, hypoxia, apoptosis, haemostasis, vasoconstriction and, finally, repair and regeneration. Poor menstrual health has a negative impact on a person's physical, mental, social, emotional and financial well-being. On a global scale, iron deficiency and iron deficiency anaemia are closely linked with AUB, and are often under-reported and under-recognized.

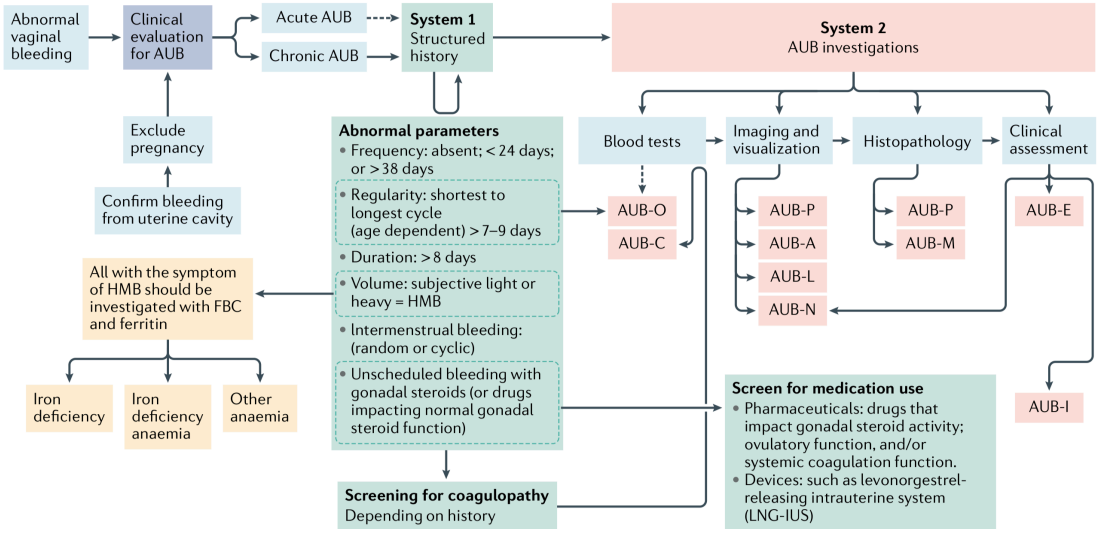
The endometrium is highly responsive to the endocrine environment. The main cellular components within the endometrium are the epithelial cells, stromal cells, vascular cells and a variety of innate immune cells. The numbers of immune cells vary according to the cycle stage. The endometrium is a target tissue for steroid hormones and its form and function is entirely governed by the prevailing endocrine environment. Therefore, both endogenous and exogenous hormone exposure affects endometrial bleeding patterns. Oestradiol and progesterone induce their physiological effects ina the endometrium primarily via their cognate receptors, the oestrogen receptor (ER) and the progesterone receptor (PR). These receptors, along with receptors for androgens, glucocorticoids and mineralocorticoids, belong to a superfamily of nuclear receptors that act as ligand- activated transcription factors.

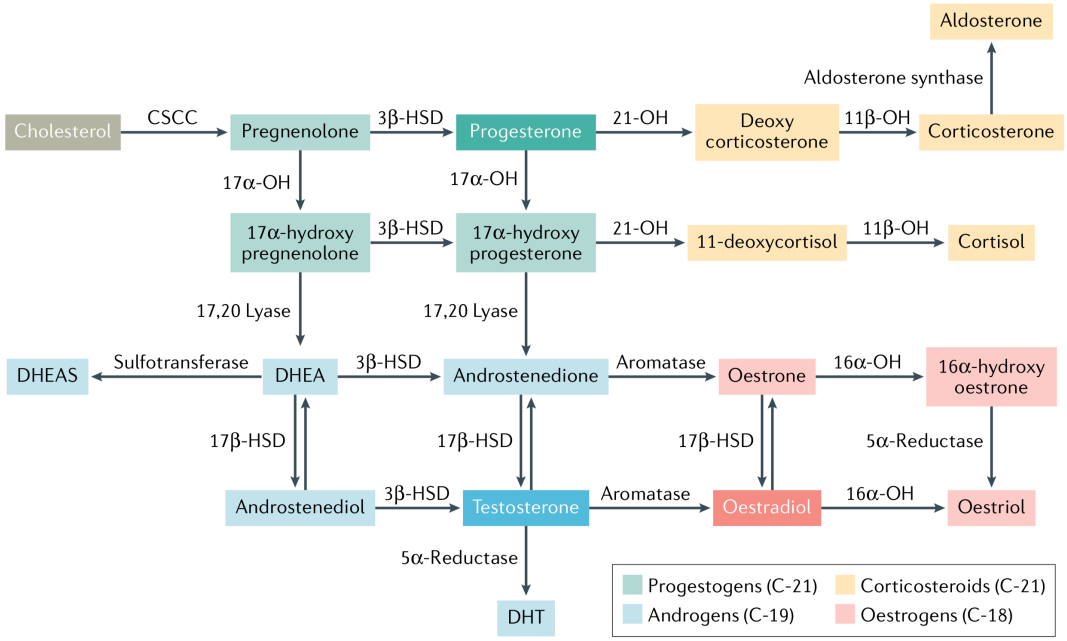
Chronic AUB is "bleeding from the uterine corpus that is abnormal in volume, regularity, and/or timing, and has been present for the majority of the past 6 months".

Acute AUB is "an episode of heavy bleeding that, in the opinion of the clinician, is of sufficient quantity to require immediate intervention to prevent further blood loss"10. Acute AUB can occur in the presence of chronic AUB or as an independent episode. AUB can be frequent or infrequent, prolonged, irregular or heavy.

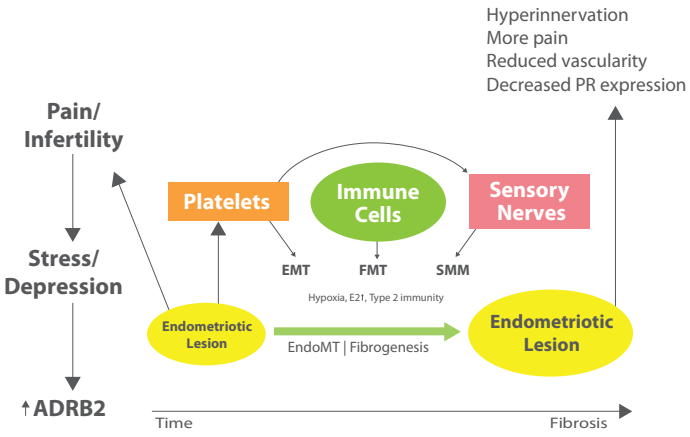
Heavy menstrual bleeding (HMB) is defined as "excessive menstrual blood loss which interferes with a woman's physical, social, emotional and/or material quality of life".

Intermenstrual bleeding is the spontaneous bleeding occurring between menstrual cycles that can be either cyclical or random.





Natural history of endometriotic lesions.
This diagram sketches, in broad strokes, the progression of endometriotic lesions, which interact with various mediators and players in their microenvironment, such as estrogen (E2), hypoxia, platelets, various immune cells, and sensory nerve fibers, through epithelial-mesenchymal transition (EMT), endothelial-mesenchymal transition (EndoMT), fibroblast-to-myofibroblast transdifferentiation (FMT), mesothelial-mesenchymal transition (MMT), smooth muscle metaplasia (SMM), and type 2 immunity, leading ultimately to fibrosis. In addition, pain or infertility resulting from endometriosis may also induce stress, depression, and anxiety, resulting in the activation of the hypothalamic-pituitary-adrenal (HPA) and sympatho-adreno-medullary (SAM) axes, which, in turn, release copious amount of catecholamines. When these catecholamines reach the endometriotic lesions, adrenaline β2 receptor (ADRB2) would be activated, causing further progression of endometriosis. The progression of endometriosis would cause increased nerve fiber density within or surrounding the lesions (hyperinnervation) and as the fibrogenesis progresses, result in reduced vascular density and progesterone receptor (PR) expression, causing more pain and making lesions resistant to drug treatment. Note that all these players in the lesional microenvironment could engage in crosstalk through various mechanisms (the arrows). ADRB2, adrenaline β2 receptor; E2, estrogen; EMT, epithelial-mesenchymal transition; EndoMT, endothelial-mesenchymal transition; FMT, fibroblast-to-myofibroblast transdifferentiation; MMT, mesothelial-mesenchymal transition; PR, progesterone receptor; SMM, smooth muscle metaplasia.



Age-dependent phenotypic variations in OE are discernable. These variations may have important implications in ascertaining their pathogenesis and devising strategies for intervention or even prevention. For example, on average the OE lesions in adolescents would be more likely to be cystic and less fibrotic than those in adults, which would mean that these patients would be more likely to respond to non-steroid anti-inflammatory drugs (NSAIDs) therapy since the PGE2 signaling is less likely to be attenuated. They may also respond to therapies that target the EP2 and/or EP4 receptors. In contrast, OE lesions in adults may not respond well to either NSAID treatment or therapies that target the EP2 and/or EP4 receptors, especially when the lesions are highly fibrotic.

Adolescence
The most characteristic difference between juvenile and adult OE consists of the progressive fibrotic process that involves the wall of OE. Adolescent disease, the initial stages of an OE are not characterized by fibrosis; rather, they involve neo-angiogenesis. To speed up the identification of an OE in a young woman, a number of practical ways to diagnose it as early as possible. The first suggestion is to never underestimate the pain symptom; this means that a physician should always consider endometriosis as a possible cause of severe cyclic pain. Pain should be immediately treated with hormonal therapies and analgesics; if the symptom persists, imaging technology should be employed without delay; however, it is important to obtain a detailed and accurate history before performing clinical evaluation and pelvic sonography. Finally, for these patients, frequent follow-up visits to reevaluate the situation should be planned.

Postmenopausal
Symptomatic postmenopausal endometriosis should be managed surgically because of the risk of malignancy, with medical treatments limited to cases with pain recurrence after surgery. This may be sensible or justifiable, since the detrimental impact of either OE lesions or surgery on ovarian cortex no longer matters any more for postmenopausal women. In contrast, the risk of malignancy cannot be dismissed lightly, since the chance of acquiring new lesions after menopause is low and since the lesions are likely already in existence prior to the menopause. As such, they may be in existence for a long time, likely to have acquired certain cancer-associated mutations (CAMs) already. Guidelines describing appropriate imaging surveillance in postmenopausal women are lacking. This variant appears to have a greater predisposition to malignant change, may have a greater tendency to spread to extragonadal organs, and may develop into constrictive and/or obstructive lesions; for these reasons, it should be preferably treated surgically.

In terms of pathogenetic mechanisms, besides HRT, importance must be given to extra-ovarian estrogen production by the skin and adipose tissue, giving a role to obesity in its pathogenesis. Such extra-ovarian sites of estrogen neosynthesis have been identified in several cases. In addition, locally produced estrogens may play a significant role. Estrogen dependence is central to the pathophysiological process since recent studies confirmed the presence in endometriotic lesions of the enzymes necessary for estrogen synthesis; thus, this local source represents a likely pathogenic contributor.

Benagiano, G, Guo, S-W. Age-dependent phenotypes of ovarian endometriomas. Reprod Med Biol. 2022; 21:e12438. doi:10.1002/rmb2.12438

Evidence indicaties that peritoneal endometriosis and ovarian endometriosis are caused by the retrograde, ectopic, and presence of endometrial cells and stroma; fibrosis and muscle metaplasia are almost ubiquitous but secondary phenomena. Endometriosis is a condition that starts with the ectopic deposition of endometrial epithelium and stroma, which undergo cyclic bleeding and thus repeated tissue injury and repair, resulting in gradual and progressive smooth muscle metaplasia and fibrogenesis.

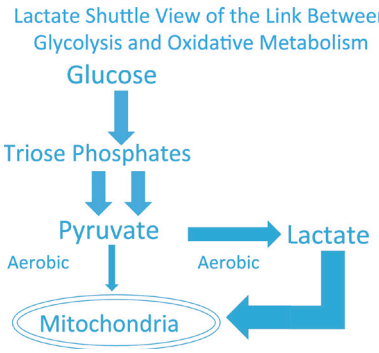
- In a nutshell, endometriotic lesions, once established, experience epithelial-mesenchymal transition (EMT), fibroblast-to-myofibroblast transdifferentiation (FMT), and smooth muscle metaplasia (SMM), ultimately culminating in fibrosis.
- Endometriotic lesions can recruit various cells, including endothelial and mesothelial cells, into the lesions through endothelial-mesenchymal transition (EndoMT) and mesothelial-mesenchymal transition (MMT).
- The lesional microenvironment, as a nexus of lesion and host, as well as a transducer of lesional signals and of host lifestyle, is of vital importance, dictating the tempo and pace of lesional progression and determining the fate and destiny of lesions.

OE can occur in human females of almost all ages and can cause harm to the ovarian cortex either by its mere presence, or because of surgery to eliminate it, or both. Characteristics of the various phenotypes of endometriosis differ greatly according to the age of the patient. In contrast to the situation in older patients, in young patients red lesions are more prevalent, predominantly located at the site of the invagination stigma, and are highly indicative of a mucosa-type implant. In most cases the OE is formed by invagination of the cortex and active, vascularized implants are located at the site of invagination. In the younger woman, the invaginated cortex is fully or patchily covered by an angiogenic mucosa.

The molecular and cellular characterization of the natural history of endometriotic lesions views them as wounds undergoing repeated tissue injury and repair (ReTIAR). In a nutshell, endometriotic lesions, once established, experience epithelial-mesenchymal transition (EMT), fibroblast-to-myofibroblast transdifferentiation (FMT), and smooth muscle metaplasia (SMM), ultimately culminating in fibrosis. Of note, endometriotic lesions can recruit various cells, including endothelial and mesothelial cells, into the lesions through endothelial-mesenchymal transition (EndoMT) and mesothelial-mesenchymal transition (MMT). In addition, the lesional microenvironment, as a nexus of lesion and host, as well as a transducer of lesional signals and of host lifestyle, is of vital importance, dictating the tempo and pace of lesional progression and determining the fate and destiny of lesions. Looking through this prism of ReTIAR, it can be understood as why there are a hyperestrogenis and aberrant expression of estrogen receptor β (ERβ), why there is a reduced cytotoxicity of natural killer (NK) cells in endometriosis, and why there is histological difference, in OE between younger and older patients or between OE and deep endometriosis. Above all, we can understand why OE is a progressive disease if unimpeded.

Identified risk factors include recurrence of endometriosis, previous hysterectomy, with or without bilateral salpingo-oophorectomy before menopause, and estrogen-only HRT for a relatively long time.

	Infancy and early adolescence	**Post-menarche and adolescenceA**	**dulthood**	**Postmenopausal**
Possible source/ origin	Neonatal uterine bleeding (NUB), obstructive anomaly, celomic metaplasia, embryonic Müllerian rests, genetic	NUB, obstructive anomaly, retrograde menstruation celomic metaplasia, embryonic Müllerian rests, genetic susceptibility, and environmental or lifestyle factors	NUB, obstructive anomaly, retrograde menstruation, celomic metaplasia, embryonic Müllerian rests, genetic susceptibility, and environmental or lifestyle factors	Pre-existing or residual lesions
Size	6.5 × 3 × 3 cm (a) 9 cm in diameter (b)	Mean cyst size 75 ± 29 mm (c)	Up to the size of a grapefruit (d)	Up to 3121 g (e)
Cyst wall lining	Endometrial epithelium, stroma, and hemosiderin-laden macrophages, but no glandular structures	A thin wall composed of the ovarian cortex itself	Progressive smooth muscle metaplasia leading to fibrosis	Different grades of metaplasia, hyperplasia, atypia; endometrioid carcinoma may arise out of the endometriotic wall tissue
Morphological/ Histological appearance	Cystic	Cystic	Various, can be cystic and fibrotic	Cystic
Pattern of pain	Acute (?)	Absent or cyclic	Usually, cyclic	Persistent
Pattern of vascularity			Reduced vascularity concomitant with increased fibrosis	Statistically significant lower incidence of hemorrhage
Extent of fibrosis	Absent	Largely absent	Increasingly fibrotic	Presence of constrictive and/or obstructive lesions



The endometrium is one of the first tissues to be evaluated spectroscopically.

The main endometrial metabolites, choline, creatine, and lactate levels are measured in mid-luteal phase and compared to metabolite values of fertile women. Spectroscopy analysis of patients in both groups provided Cho, Cr, and lactate peaks. Compared to the fertile group, a decrease in Cr signal and an increase in lactate signal were detected in patients with endometrial polyps. Endometrial polyps are the most common benign pathologies of the uterus and are considered to cause subfertility. Subfertility effects of polyps occur in two different ways (i) mechanical effect and (ii) non-mechanical effect. Broad- based polyps located close to the tubal ostia or internal cervical os may impair sperm transport and lead to infertility. However, endometrial polyp located far from the tubal ostia can cause subfertility. The subfertility-producing effects of small and non- obstructing endometrial polyps occur non-mechanically

NF-kB p65 expression in patients with endometrial polyp is important evidence that endometrial polyp stimulates pathological endometrial inflammation. Since NF-kB p65 is a cellular indicator of inflammation and its expression decreased to the level of healthy controls after polypectomy, it is important evidence that endometrial polyps cause pathological inflammation in the endometrium. Concordantly, it has been reported that the synthesis and release of molecules involved in receptivity and inflammation, such as TNF-alpha, osteopontin, IGFBP-1 and glycodelin, which are measured in the endometrial flushing of patients with polyps, are impaired and polypectomy reverses their secretion

Cr is a metabolite that indicates that the energy pathways of the cell are healthy. In general, this metabolite is considered stable. The decrease in Cr levels in women with endometrial polyp compared to control group suggests that there maybe a defect in energy production in endometrial cells. Since there is a high energy requirement for decidua formation, the presence of decreased Cr suggests that endometrial polyp impairs energy production and leads to subfertility. The increased lactate peak in women with endometrial polyp is another important evidence of disruption of energy pathways. In healthy tissues, the lactate peak is detected within physiological limits. The presence of increased lactate peak indicates activation of the anaerobic glycolysis. Increased lactate and decreased Cr are the clear evidence of impaired energy production in the endometrium containing polyp.

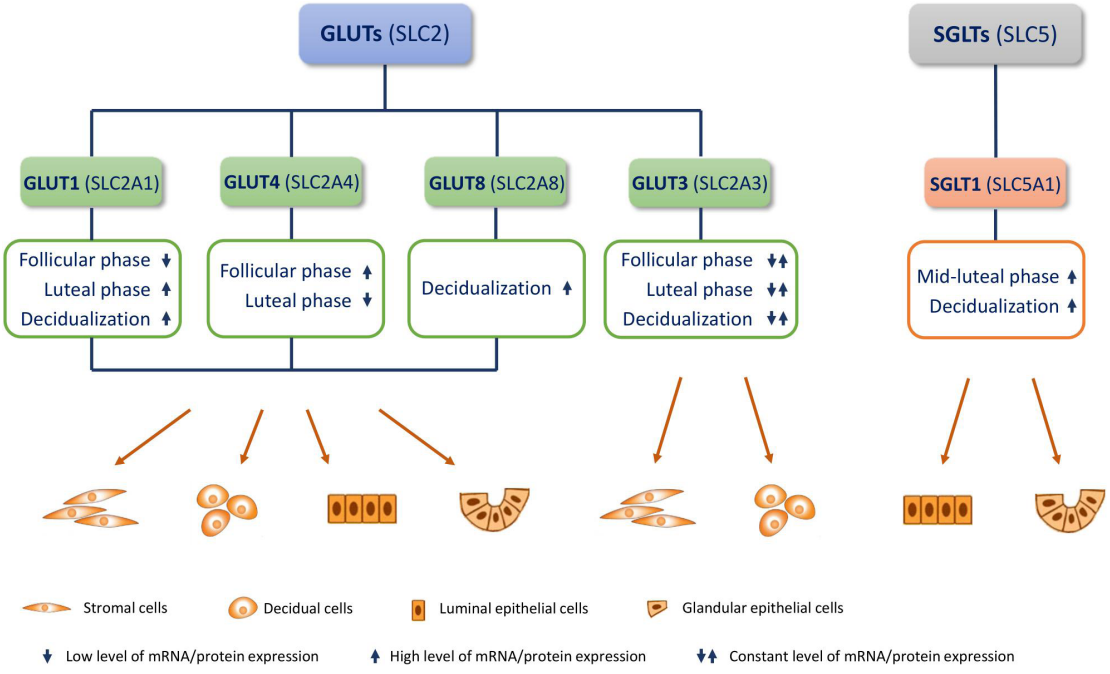
Ozyurt R, Turktekin N. Endometrial polyps prevent embryo implantation via creatine and lactate pathways. Eur Rev Med Pharmacol Sci. 2022 May;26(9):3278-3281. doi: 10.26355/eurrev_202205_28746. PMID: 35587079.

Endothelial Cell: Lactate Metabolic Player in Organ Regeneration

Endothelial cells (ECs), the "gatekeeper", control the extravasation of circulating cells into tissues, playing an essential role in regulating tissue homeostasis. By altering their production of cytokines, chemokines, and adhesion molecules, endothelial cells control the traffic of immune cells into injury sites. Injury or dysfunction of ECs is known to contribute to many pathologies, including metabolism-related disease. Lactate interactions affect the microenvironment through two pathways except for the classical angiogenesis pathway; 1. Lactate uses endothelium as a gatekeeper to regulate the microenvironment through immune cells, affecting the regeneration of the damaged tissues 2. ECs secrete lactate to repair the organ regeneration caused by the damaged tissues. Lactate uses the "lactate shuttle" in ECs to shuttle between cells and affect cell differentiation in cancers. Even under quiescent conditions, ECs can use glycolysis to convert glucose into lactate. Lactate metabolism plays a vital role in the regeneration of tissues (especially in the nervous system). The accumulation of lactate often leads to neurodegenerative diseases. The brain is an excellent example of lactate going through ECs for tissue regeneration for the "gatekeeper" role. Exercise can increase lactate production from skeleton muscle and promote lactate penetration through the blood–brain barrier. The primary mechanism is that lactate (after exercise) undergoes anaerobic metabolism in ECs and finally changes from glucose to lactate, following an amount of lactate accumulated in ECs.

ECs are no longer a simple barrier but are activated by tissue damage and activated ECs, which become a reservoir of metabolites such as lactate. ECs with a large amount of lactate are used as raw material and fuel to combine with the lactic acid transporter of immune cells to promote the release of cytokines, amplifying the repairing effect of immune cells in damaged tissues. ECs are the blood barrier in which oxygen, nutrients, and metabolites can be transported and exchanged with the blood flow, among which lactate is a vital metabolite shuttled through the "switch" action of ECs. Lactate passes through the transporter of ECs, allowing the lactate produced by other tissues (such as muscles) to be carried through the blood to the targeted organs (such as neurons), promoting tissue regeneration. However, ECs can also serve as a "reservoir" for the release of lactate, allowing the lactate with "angiocrine" function to be released from ECs, and the damaged tissue can be repaired with lactate. Therefore, the "gatekeeper" role of ECs can allow activated ECs to act as a gated channel to release lactate when repairing other tissues. However, the angiocrine function of ECs is achieved by endothelial activation. Then, lactate is released, and immune cells are recruited, which are undergoing tissue regeneration and repair.

Zhang L, Gui X, Zhang X, Dai Y, Wang X, Tong X and Li S (2021), Endothelial Cell: Lactate Metabolic Player in Organ Regeneration. Front. Cell Dev. Biol. 9:701672. doi: 10.3389/ fcell.2021.701672



Endometriosis, Glucose and Lactate

Endometrial Glucose Transporters in Health and Disease
The endometrium is composed of stromal cells, luminal and glandular epithelial cells, and endothelial cells. The endometrium is incapable of synthesizing glucose, which thus must be delivered into the uterine lumen by glucose transporters (GLUTs) and/or the sodium-dependent glucose transporter 1 (SGLT1). Investigation of the GLUTs function in different endometrial cells is of high importance, as numerous glucose transporters are associated with infertility, polycystic ovary syndrome, and gestational diabetes. Intrauterine or early pregnancy loss occurs due to fetal chromosomal abnormalities, irregular maternal hormone secretion/action, or inappropriate nutritional support of uterine endometrium or embryos. More than 50% of pregnancies are lost in humans, mostly before or during embryo implantation, when there is high glucose demand. Glucose, a major source of metabolic energy, is crucial for endometrial decidualization and embryonic development.

When glucose enters uterine fibroblasts, it is metabolized via multiple pathways to support decidualization, which is an essential process of endometrial stromal cells (ESCs) to support pregnancy. In decidua, the Warburg metabolism, a mechanism of glucose- derived carbon metabolism, is increased in this scenario, providing ATP and lactate for cell proliferation. High glucose concentrations can be toxic to embryos, suggesting that there is an optimal glucose requirement for pre-implantation and embryo survival. Embryo implantation is a synchronized process between an activated blastocyst and a receptive endometrium requiring glucose concentration sustained within a narrow range to optimize endometrial decidualization and embryo development. Otherwise, too high, or too low glucose levels could severely impair its development.

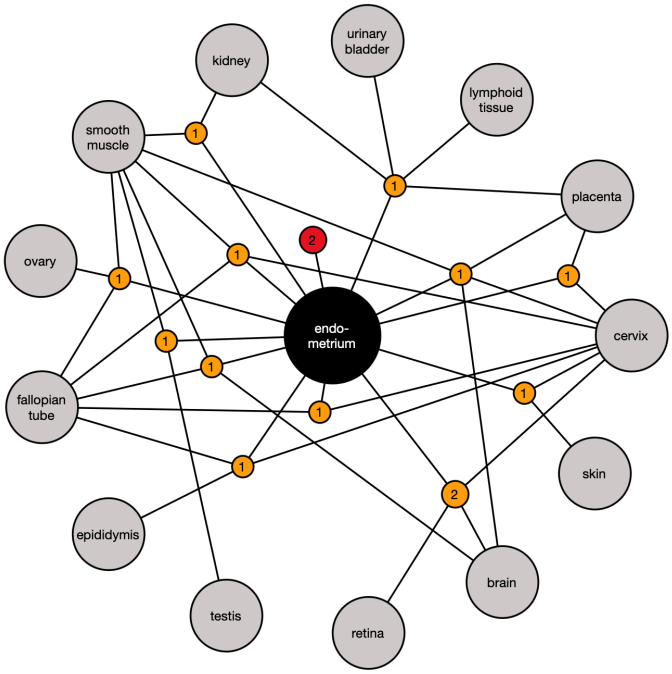
Vrhovac Madunić I, Karin-Kujundžić V, Madunić J, Šola IM, Šerman L. Endometrial Glucose Transporters in Health and Disease. Front Cell Dev Biol. 2021 Sep 6;9:703671. doi: 10.3389/fcell.2021.703671. PMID: 34552924; PMCID: PMC8450505.

Endometriosis, Glucose and Lactate

Lactate is a metabolically valuable carbohydrate. 80% of lactate is disposed of immediately within tissue with significant uptake and oxidation for gluconeogenesis. The importance lactate shuttling in healthful living is further emphasized when dysregulation occurs in cancer and other conditions. A post-trauma neuro-protective role of lactate is the preferred brain fuel for post injury and surgery to hasten and improve outcomes.4

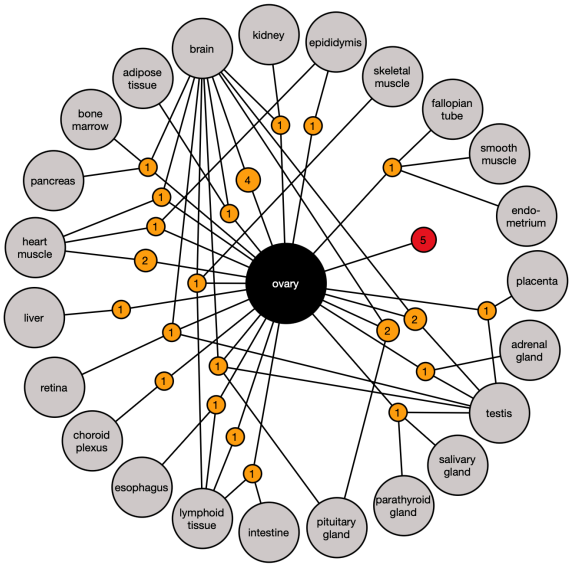
Endometrial polyps prevent embryo implantation via creatine and lactate pathways Endometrial polyps are benign lesions that occur in the presence of high estrogen and rarely show malignant transformation. They can be stalked, sessile, single or multiple. Its incidence increases with advancing age and increase in BMI. Its incidence in infertile cases approaches 40%. Evaluating receptivity by performing a biopsy is not preferred because it is invasive. With MR spectroscopy, it is possible to determine what kind of changes occur in the endomtrium at the base of the polyp without performing a biopsy. Spectroscopy provides information about the cell's living conditions non-invasively by detecting metabolite levels in living tissues. In a healthy tissue, choline signals indicate cell integrity, while creatine signals indicate the integrity of energy pathways. Lactate signals indicate that the physiological conditions of the cell are disturbed.

George A. Brooks, Lactate as a fulcrum of metabolism, Redox Biology, Volume 35, 2020, 101454, https://doi.org/10.1016/j.redox.2020.101454.



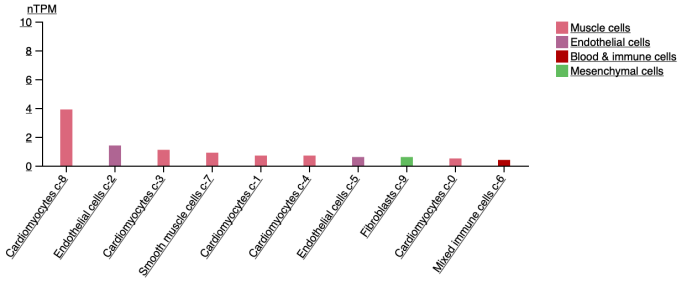
Human Protein Atlas

The Human Protein Atlas initiated with the aim to map all the human proteins in cells, tissues, and organs using an integration of various omics technologies, including antibody-based imaging, mass spectrometry- based proteomics, transcriptomics, and systems biology. All the data in the knowledge resource is open access to allow scientists both in academia and industry to freely access the data for exploration of the human proteome. The Human Protein Atlas consists of ten separate sections, each focusing on a particular aspect of the genome-wide analysis of the human proteins.

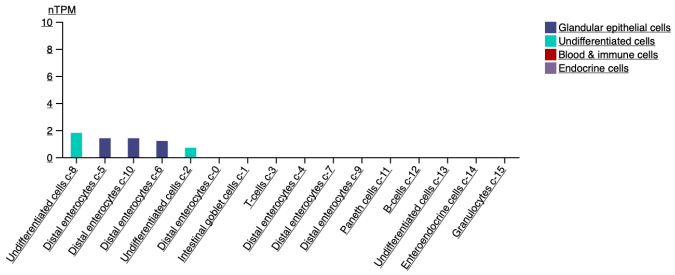


gut-brain-axis

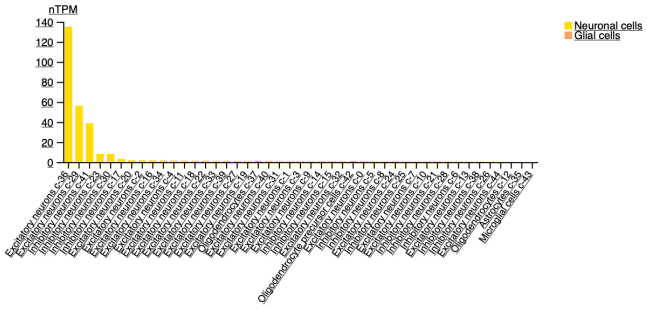
Heart muscle



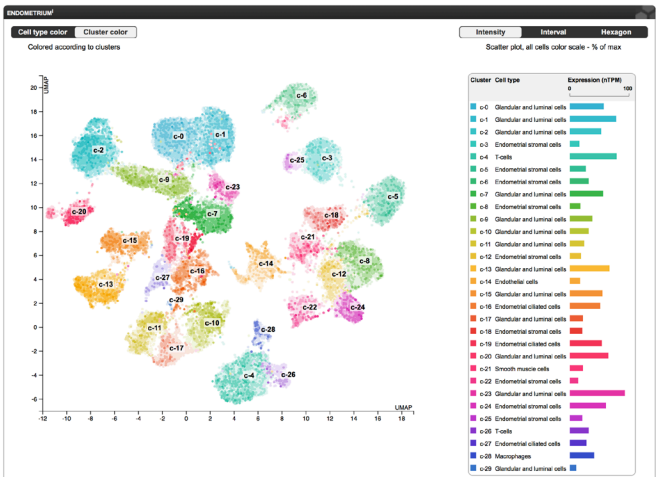
Colon

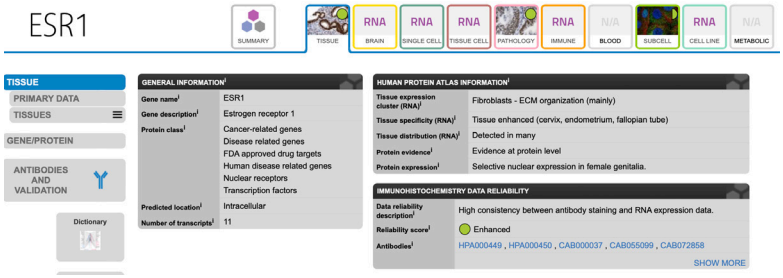


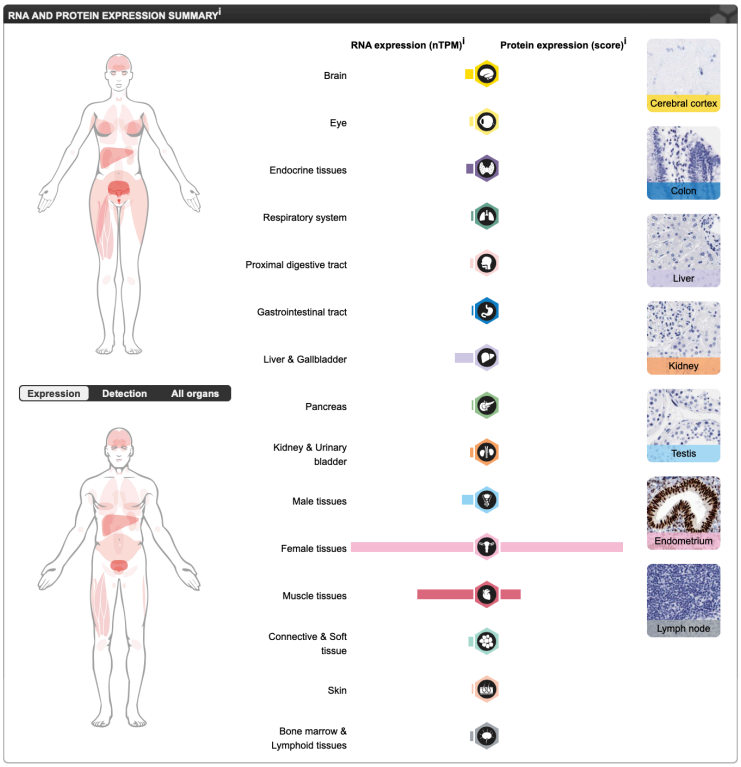
Brain

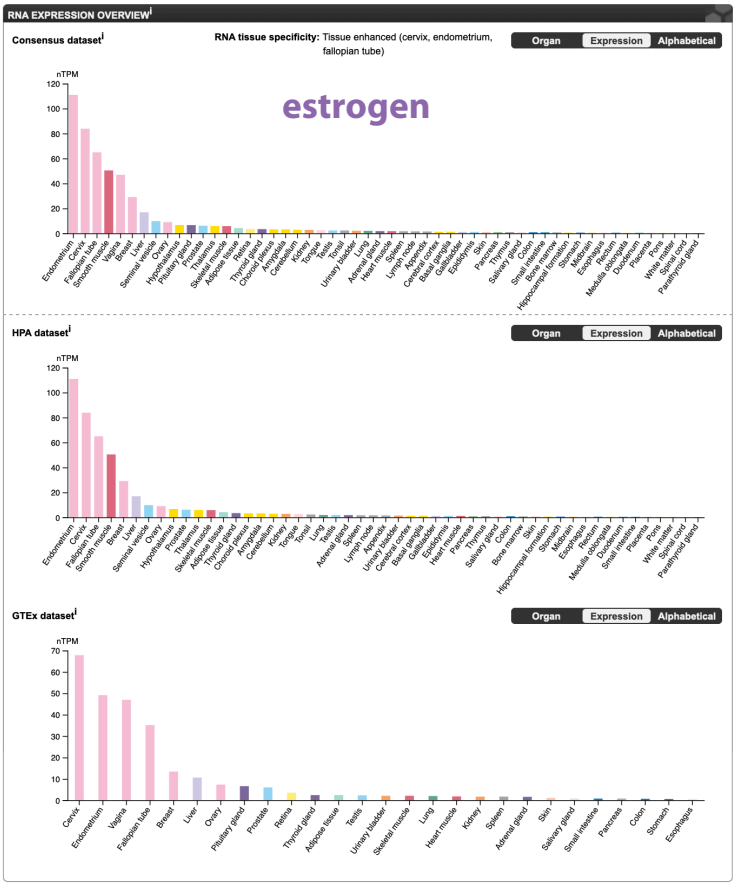


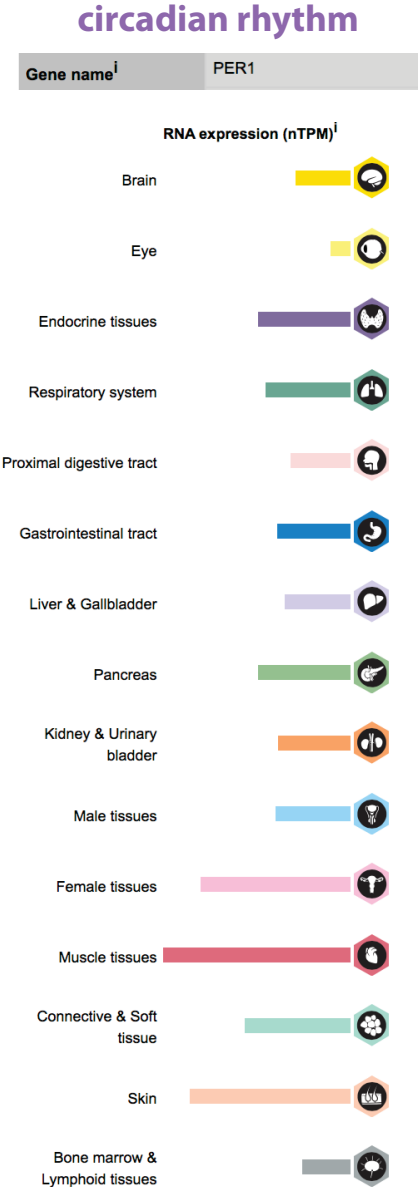
endometrium











Endometriosis, Metabolism and Oxidative Stress

A crucial physiological mechanism explains circadian adaptation with important implications for human health and disease. Clock genes exert a profound influence on metabolism through the control of gluconeogenesis, insulin sensitivity and systemic oscillation of blood glucose. If the human body or cells experience significant stress, their ability to regulate internal systems, including circadian rhythms, may become impaired. For a more efficacious management of disease, targeting both circadian rhythm and oxidative stress components in tandem is far more successful. Targeting oxidative stress looks to be a promising strategy to both curb

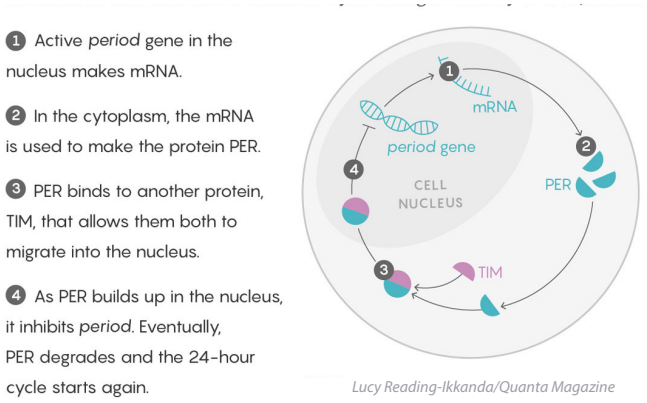
Discoveries of Molecular Mechanisms Controlling the Circadian Rhythm

Circadian rhythms are driven by an internal biological clock that anticipates day/night cycles to optimize the physiology and behavior of organisms. Observations that organisms adapt their physiology and behavior to the time of the day in a circadian fashion have been documented for a long time, but the existence of an endogenous circadian clock would only finally become established well into the 20th century. Chronobiology has an impact on many aspects of our physiology. For example, circadian clocks help to regulate sleep patterns, feeding behavior, hormone release, blood pressure and body temperature. Molecular clocks also play critical roles locally in many tissues. Clock genes also exert a profound influence on metabolism through the control of gluconeogenesis, insulin sensitivity and systemic oscillation of blood glucose. Sleep is vital for normal brain function and circadian dysfunction has been linked to sleep disorders, as well as depression, bipolar disorder, cognitive function, memory formation and some neurological diseases. The circadian program is regulated at both a central and peripheral level. In mammals, the central pacemaker is located in the suprachiasmatic nucleus (SCN) of the hypothalamus and functions as the master circadian clock. The retina receives photic input and relays this information to the SCN, which synchronizes its own neuronal cellular clocks. The central clock regulates circadian rhythms across the entire body via humoral factors and the peripheral autonomic nervous system.

A Transcription- Translation Feedback Loop (TTFL). In this mechanism, the transcription of period and its partner gene timeless are repressed by their own gene products – the PERIOD (PER) and TIME- LESS (TIM) proteins, generating an autonomous oscillation. At the time, a transcriptional mechanism was not obvious, and the discovery of the self- sustained circadian TTFL was a new paradigm. Further studies revealed a series of interlocked transcription-translation feedback loops, together with a complex network of reactions. These involve regulated protein phosphorylation and degradation of TTFL components, protein complex assembly, nuclear translocation and other post-translational modifications, generating oscillations with a period of ~24 hours. Circadian oscillators within individual cells respond differently to entraining signals and control various physiological outputs, such as sleep patterns, body temperature, hormone release, blood pressure, and metabolism. The seminal discoveries by Hall, Rosbash and Young have revealed a crucial physiological mechanism explaining circadian adaptation, with important implications for human health and disease.

Nobel Prize in Physiology or Medicine 2017

An interesting recent study examined the relationship of breakfast to the development of future reproductive diseases. Missing this first meal interferes with the start of the active phase during the circadian rhythm that is regulated by the central clock system. Since both food intake and the light/dark cycle are the main regulators of circadian rhythms, skipping breakfast can lead to changes in light stimulation within the central clock system.



Lucy Reading-Ikkanda/Quanta Magazine

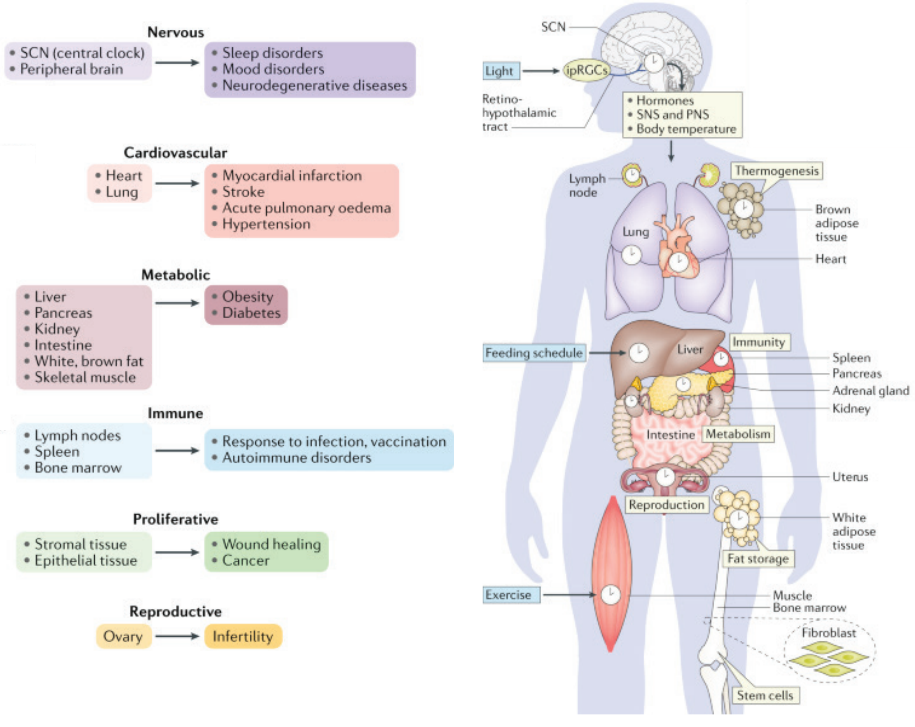
How Do Our Cells Tell Time?

Short-term sleep loss
– Trouble concentrating
– Increased stress
– Emotional distress
– Feeling unwell
– Memory problems and difficulty learning
– Poor physical performance and coordination

Long-term sleep loss or circadian confusion
– Mood disorders and psychological problems
– Heart and blood pressure issues
– Obesity and diabetes
– Reduced immune response
– Increased risk of cancer
– Worsening of existing medical conditions

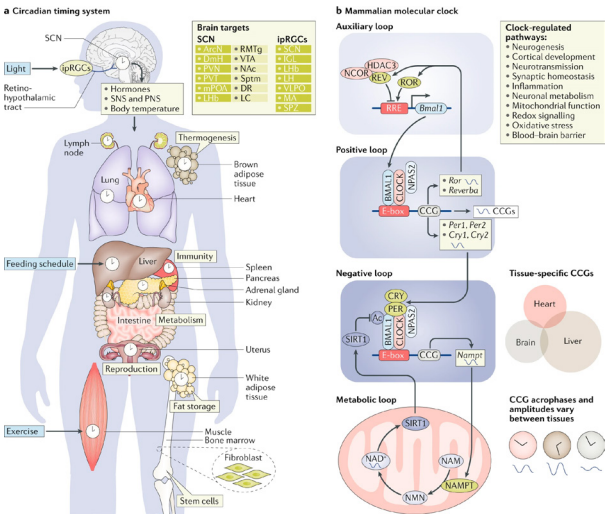
Addison K and Harris J (2019) How Do Our Cells Tell Time?. Front. Young Minds. 7:5. doi: 10.3389/frym.2019.00005

Molecular mechanisms and physiological importance of circadian rhythms

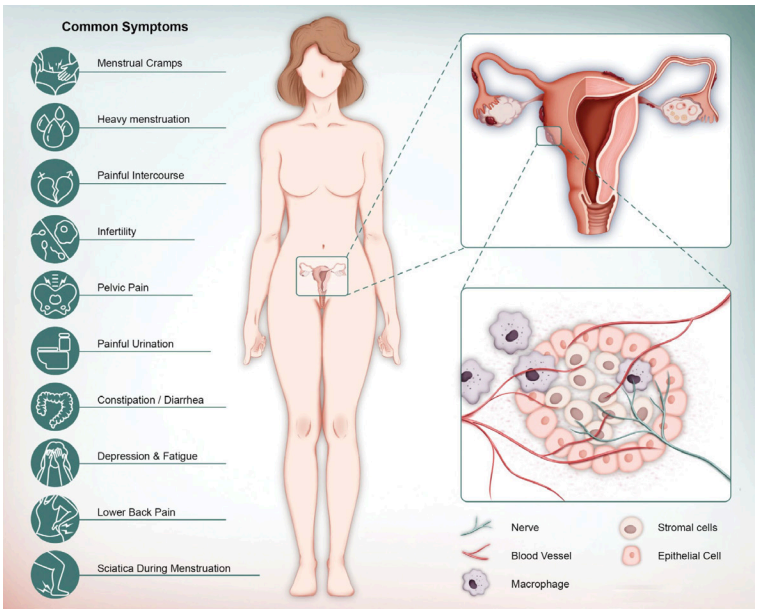


Patke, A., Young, M.W. & Axelrod, S. Molecular mechanisms and physiological importance of circadian rhythms. Nat Rev Mol Cell Biol 21, 67–84 (2020). https://doi.org/10.1038/s41580-019-0179-2

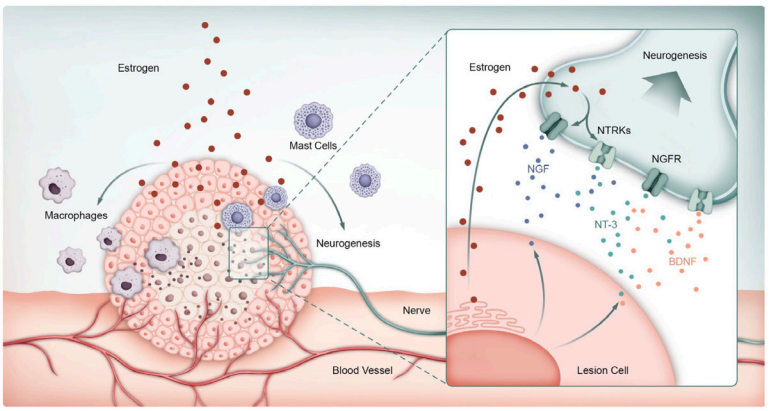
The circadian timing system synchronizes clocks across the entire body to adapt and optimize physiology to changes in our environment. Light is received by specialized melanopsin-producing photoreceptive retinal ganglion cells (ipRGCs) in the eye. These ipRGCs project through the retinohypothalamic tract to the suprachiasmatic nucleus (SCN), among other brain regions. The SCN relays timing information to other areas of the brain via direct projections (dark green boxes) and indirect projections (light green boxes). Humoral signals and the peripheral nervous system (that is, the sympathetic nervous system (SNS) and parasympathetic nervous system (PNS)) convey information from the SCN to orchestrate peripheral clocks. Feeding schedules and exercise can also entrain central and peripheral clocks. Circadian rhythms are key regulators of thermogenesis, immune function, metabolism, reproduction and stem cell development. The positive loop is driven by the heterodimerization of either circadian locomotor output cycles protein kaput (CLOCK) or neuronal PAS domain-containing protein 2 (NPAS2) with brain and muscle ARNT-like 1 (BMAL1) in the nucleus. The resulting heterodimers bind to enhancer boxes in gene promoters to regulate the transcription of clock-controlled genes (CCGs), including those encoding period (PER) proteins and cryptochrome (CRY) proteins. PER and CRY proteins accumulate in the cytoplasm during the circadian cycle, eventually dimerizing and shuttling to the nucleus to inhibit their own transcription, thus closing the negative-feedback loop. The auxiliary loop includes the nuclear retinoic acid receptor-related orphan receptors (RORα and RORβ) and REV-ERBs (REV-ERBα and REV-ERBβ), which are also transcriptionally regulated by CLOCK–BMAL1 heterodimers. REV-ERBα (REV in the figure) and RORα repress and activate the transcription of Bmal1, respectively, by inhibiting and activating the ROR or REV-ERB response elements (RREs). CLOCK–BMAL1 complexes also control the expression of nicotinamide phosphoribosyltrans.



The Role of Peripheral Nerve Signaling in Endometriosis



Overview of the broad and disparate symptoms associated with endometriosis. In endometriosis, lesion growth of endometrial tissue occurs outside of the endometrium. Lesions are composed of an abundance of distinct cell types including immune, stromal and epithelial cells as well as infiltrating blood vessels and nerves



Multifaceted role of estrogen in endometriosis: Estrogen can mediate the recruitment of immune cells, nerve fibers, and blood vessels to lesions. Macrophages and mast cells once recruited, contribute to neurite outgrowth and peripheral nerve sensitization, respectively. Estrogen strongly induces neurotrophin production, including NGF, BDNF, and NT3 by macrophages which signal through NTRK receptors on nerves to promote neurogenesis. Mast cell degranulation and the subsequent release of pro-inflammatory mediators can be triggered by estrogen release. Release of pro-inflammatory mediators from mast cells sensitizes peripheral nerve endings in endometriotic lesions, contributing to the pain. An estrogen-dependent detrimental cycle of macrophage mediated neurogenesis and mast-cell mediated inflammation and sensitization drives the pro-growth cycle necessary for endometriosis progression. BDNF, Brain-Derived Neurotropic Factor; NGF, Nerve Growth Factor; NGFR, Nerve Growth Factor Receptor; NT-3, Neurotrophin-3; NTRK, Neurotrophic Tyrosine Receptor Kinase

Godin SK, Wagner J, Huang P, Bree D. The role of peripheral nerve signaling in endometriosis. FASEB Bioadv. 2021 Aug 2;3(10):802-813. doi: 10.1096/fba.2021-00063. PMID: 34632315; PMCID: PMC8493968.

Endometriosis

ICD-11

Endocrine, nutritional and metabolic systems

Common standards for a connected world

Metabolic Profile of Patients with Severe Endometriosis

Metabolomic strategy is used to discover new biomarkers in endometriosis and to clarify the metabolic pathways involved in the pathogenesis of this disease. Omics science has transformed biology and has the potential of transforming medicine. Genomics and proteomics carry the resulting information from the expression of genes and proteins, whereas metabolomics provides the possibility of quantifying and identifying metabolites with low molecular weight, which are the final products of physio- pathological processes and may be used for a better understanding of upstream biological events. The metabolomics approach offers an integrated perspective of the metabolic change during a different physiological or pathological status, thus serving as a useful tool in the study of different pathways and biomolecules. Metabolomics combines the use of several technologies, such as mass spectrometry (MS) and nuclear magnetic resonance (NMR) spectroscopy, with pattern recognition techniques. Endometriosis can be considered an inflammatory disease with evidence of elevated levels of peritoneal fluid cytokines and growth factors, alterations in B cell activity, and an increased incidence of autoantibodies. In immunological and other chronic inflammatory diseases (such as endometriosis), the activation of the immune system consumes vast amounts of energy (up to 2000 kJ/day and more, and immune cells use glucose, glutamine, ketone bodies, and fatty acids in different amounts. In particular, glucose and glutamine are the main energy-rich sources. Glutamine is also found to be increased in the serum of our endometriosis patients. Glutamine is a non-essential amino acid, structurally correlated to glutamate. The most relevant glutamine-producing tissue is the muscle mass, but glutamine is also released, in small amounts, by the lungs and the brain where it seems to be correlated with neural pain modulation.5

Cortisol is an essential hormone; it helps the body respond to stress, such as surgery and illness, and recover from infections.

Cortisol also helps maintain blood pressure and cardiovascular functions and regulates the metabolism of proteins, carbohydrates and fatty acids. Aldosterone plays a key role in sodium and potassium balance. Cortisol is the main glucocorticoid hormone produced by the adrenal gland. It is secreted in response to stimulation of the adrenal gland by adrenocorticotropic hormone (ACTH), produced by the pituitary. Patients with adrenal insufficiency, both central and primary, often present with hypotension, anorexia, vomiting, weight loss, fatigue and recurrent abdominal pain. Reproductive complaints typically occur in women (amenorrhoea, loss of libido, decreased axillary and pubic hair). As endometriosis patients have higher stress levels, their hypothalamic pituitary adrenal axis is altered.

CHAPTER 5 : Endocrine, nutritional or metabolic diseases

Endocrine disorders

5A41 Hypoglycaemia without diabetes

Women with Endometriosis can have hypoglyceamia (a drop in blood sugar) even though women can have normal insulin levels

Metabolic disorders

5C64.41 Hypomagnesaemia

This is an electrolyte disturbance in which there is an abnormally low level of magnesium in the blood. Normal magnesium levels in humans fall between 1.5 - 2.5 mg/dL. Usually a serum level less than 0.7 mmol/L is used as reference for hypomagnesemia

Extension Codes

Electrolytic, caloric and water-balance agents

XM1P36 Glutamine
XM9UX0 Ketones

Disorders of the adrenal glands or adrenal hormone system

5A74.0 Acquired adrenocortical insufficiency

Androgens, Endometriosis and Pain

There's a strong inverse relationship between androgen levels and days per month of pelvic and period pain. Androgens can influence pain at different stages of life and when different pathologies are present. Endometriosis lesions exhibit estrogen, progesterone and androgen receptors, with variable activity across the menstrual cycle. Three conditions develop through independent mechanisms, which may all be exacerbated by the presence of inflammation. Dysmenorrhea occurs when prostaglandin levels within the uterus rise following progesterone withdrawal with resolution of the corpus luteum. Where inflammation is present, cyclooxygenase activity is enhanced, and prostaglandin formation is increased further. Endometriosis lesions develop following retrograde menstruation. Where inflammation is present, macrophage phagocytic activity is impaired and the clearance of endometrial cells from the peritoneal cavity is reduced, facilitating the development of lesions. Symptoms including chronic pain, fatigue, poor sleep, anxiety, low mood, nausea, sweating, bowel or bladder dysfunction and myofascial pain syndromes are due to excess activation of the uterine-central nervous system neuroimmune circuit. This circuit includes the sensory afferent innervation of the uterus, circulating immune cells, circulating cytokines, and immune competent cells within the central nervous system. Inflammation results in excess activation of the neuroimmune cells within the circuit and an increase in symptoms. Antidromic neural signaling induces bowel or bladder symptoms. Orthodromic neural signaling induces myofascial pain syndromes. Menstrual suppression by medications that inhibit ovulation to treat dysmenorrhea leads to the unintended collateral effect of dramatically reducing androgens in young females.

Murgia, F., Angioni, S., D'Alterio, M.N. et al. Metabolic Profile of Patients with Severe Endometriosis: a Prospective Experimental Study. Reprod. Sci. 28, 728–735 (2021). https://doi.org/10.1007/s43032-020-00370-9
Evans SF, Hull ML, Hutchinson MR and Rolan PE (2021) Androgens, Endometriosis and Pain. Front. Reprod. Health 3:792920. doi: 10.3389/frph.2021.792920

CHAPTER 3 : Nutritional or metabolic anaemias

3A00 Iron deficiency anaemia

3A00.0 Acquired iron deficiency anaemia due to blood loss

3A00.1 Acquired iron deficiency anaemia due to low intake

3A01 Megaloblastic anaemia due to vitamin B12 deficiency

A disease caused by inadequate dietary intake of vitamin B12, impaired absorption of vitamin B12, surgical removal of the small bowel, coeliac disease or inherited mutations affecting absorption of vitamin B12. This disease is characterised by decreased levels of vitamin B12 in the body presenting with or without anaemia. This disease may present with fatigue, pallor, dizziness, seizures, or symptoms of dementia.

3A03.3 -Copper deficiency anaemia

Anaemia due to copper deficiency arises from impaired utilization of iron and is therefore a conditioned form of iron deficiency anaemia.

CHAPTER 5 Metabolic disorders

5C64.0 Disorders of copper metabolism

5C64.1 Disorders of iron metabolism

5C64.10 Iron overload diseases

Iron overload is the accumulation of excess iron in body tissues. Iron overload usually occurs as a result of a genetic predisposition to absorb and store iron in excess amounts, the most common form of which is hereditary hemochromatosis. Iron overload can also occur as a complication of other hematologic disorders that require chronic transfusion therapy, repeated injections of parenteral iron, or excessive iron ingestion. Excessive iron stores usually accumulate in the reticuloendothelial tissues and cause little damage ("hemosiderosis"). If overload continues, iron eventually begins to accumulate in tissues such as hepatic parenchyma, pancreas, heart and synovium, causing hemochromatosis.

5C64.21 Zinc deficiency syndrome

Endometriosis and Trace Elements

Zinc is one of the most crucial elements responsible for the proliferation and differentiation of the reproductive system cells. It takes part in the ovulation process, development of spermatozoa, fetal development, physiological pregnancy. Proper zinc levels ensure correct testosterone homeostasis, sperm parameters as well as proper folate cycle. Blood zinc level in women who suffer from endometriosis is decreased, and it can confirm that this trace element may possibly affect the multifactorial pathogenesis of endometriosis. Zinc is suspected of interfering with many biological processes, such as inflammation and immunity, which seem to be essential in the development of endometriosis lesions.

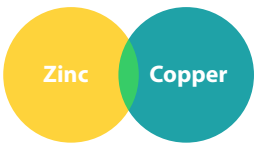
Copper plays a crucial role in cell division processes. This particular trace element is also an important factor of fertility process, including gametogenesis, and plays a structural role in testical somatic cells and sperm and prostate liquids. It is responsible for the distribution of androgen and regulation of the hypothalamic pituitary testis line. The improper homeostasis may result in different male fertility abnormalities such as improper production of hormones, sperm levels, etc.

The Cu/Zn ratio is used as a marker of oxidative stress and has been used in diagnostic processes in immune dysfunction, inflammation as well as gynecological tumors.

Diet. A positive effect of antioxidant supplementation (vitamin C, vitamin E, selenium, copper, and zinc) in women with confirmed endometriosis. An inverse correlation was noted in patients on an antioxidant diet with the intensity of the disease.

Nickel has been recently marked as a risk factor of endometriosis. Ni allergic contact mucositis prevalence of about 90% in patients with endometriosis. A low-Ni diet for a period of three months, achieved a significant improvement of all symptoms typical of endometriosis.

Cadmium	**Formation of ROS - Reactive oxygen species Decreases estrogen levels**
Chromium	**Cytotoxic properties**
Cobalt	**Cytotoxic properties**
Iron	**Participation in angiogenesis**
Lead	**Inducing oxidative stress**
Mercury	**Inducing oxidative stress**
Nickel	**Interfere with the hormone receptors**
Copper	**Decreases estrogen levels**
Zinc	**Proliferation and differentiation of the reproductive system cells. Key role in anti- inflammatory, antioxidant, and immune regulation processes**



Osuchowska-Grochowska, I.; Blicharska, E.; Gogacz, M.; Nogalska, A.; Winkler, I.; Szopa, A.; Ekiert, H.; Tymczyna-Borowicz, B.; Rahnama-Hezavah, M.; Grochowski, C. Brief Review of Endometriosis and the Role of Trace Elements. Int. J. Mol. Sci. 2021, 22, 11098. https://doi.org/10.3390/ijms222011098

Nutrition in Gynecological Diseases

Diet and nutrition are fundamental in maintaining the general health of populations, including women's health. Health status can be affected by nutrient deficiency and vice versa. Gene–nutrient interactions are important contributors to health management and disease prevention. Nutrition can alter gene expression, as well as the susceptibility to diseases, including cancer, through several mechanisms. Nutrients and their deficiencies can be associated with gynecological diseases, namely polycystic ovary syndrome, infertility, uterine fibroids, endometriosis, dysmenorrhea, and infections, as well as cervical, endometrial, and ovarian cancers. All these diseases significantly impact women's quality of life, and many of them, unfortunately, are still lacking efficient treatment plans. Promoting both primary and secondary prevention is essential for the sake of these afflicted women and their reproductive health. Sometimes, applying such preventive approaches is as or even more important than curative procedures. Nutrigenomics and nutrigenetics are defined as sciences that investigate the relationship between genetic variations and nutrient requirements. Gene–nutrient interactions are central contributors to health management and disease prevention. Interestingly, it was recently reported that nutrients can drive epigenetic changes that can influence such requirements. Nutrition can alter gene expression, as well as the susceptibility to several diseases, including cancer, through genetic and epigenetic changes. During the past decade, it has become clearer that nutrition can exert imprinting effects on the human genome, with many studies indicating that early life nutrition could influence the risk of developing chronic diseases in adulthood. For example, with regard to the role of nutrition in cancer development, existing evidence suggests that dietary components can impact disease pathogenesis via the activation of tumor suppressor genes, cellular apoptosis, protein translation, and noncoding microRNAs (miRNAs) with roles in messenger RNA (mRNA) stability and translation. Lactobacillus dominance is that the high starch content of human diets leads to high glycogen levels in the vaginal tract, creating a suitable Lactobacillus environment. Lactobacilli and other fermentative bacteria and vaginal epithelial cells produce lactic acid and are responsible for acidifying the vaginal microenvironment pH to <4.5, which gives the vaginal microbiota a certain level of balance and ability to withstand some infections. This microbiota is shown by a low degree of diversity and the high dynamics of its structure changes under the control of various exogenous and endogenous factors. Nutrients play an important role in altering the vaginal microbiome diversity.

Polyphenols

Plants are sources of bioactive compounds that demonstrate broad-spectrum health-promoting effects and interact with molecular targets associated with endometriosis, such as cell proliferation, apoptosis, invasiveness, inflammation, oxidative stress, and angiogenesis. Anti-endometriotic properties are exhibited mainly by polyphenols, which can exert a potent phytoestrogen effect, modulating estrogen activity. Polyphenols comprise a large group of bioactive compounds synthesizedby plants that are an integral part of the human diet, widely recognized for their multiple functional health-promoting benefits, mainly anti-oxidant and anti-inflammatory properties, with importance in endometriosis.

Adult Nutritional Status Scale Value

XS11 Underweight BMI Below 18.5
XS43 Normal weight BMI 18.5–24.9
XS7R Pre-obesity BMI 25.0–29.9
XS3Y Obesity class I BMI 30.0–34.9
XS6N Obesity class II BMI 35.0–39.9
XS2B Obesity class III BMI Above 40

CHAPTER 5: Nutritional disorders

Undernutrition

5B55	Vitamin A deficiency
5B56	Vitamin C deficiency
5B57	Vitamin D deficiency
5B58	Vitamin E deficiency
5B59	Vitamin K deficiency
5B5A	Vitamin B1 deficiency
5B5B	Vitamin B2 deficiency
5B5C	Vitamin B3 deficiency
5B5D	Vitamin B6 deficiency
5B5E	Folate deficiency
5B5F	Vitamin B12 deficiency
5B5G	Biotin deficiency
5B5H	Pantothenic acid deficiency
5B5J	Choline deficiency
5B5K	Mineral deficiencies

Overweight or obesity

5B80	Overweight or localised adiposity
5B81	Obesity

Certain specified nutrient excesses

5B90	Vitamin excesses

PHYTOESTROGENS

Collectively, plants contain several different families of natural products among which are compounds with weak estrogenic or antiestrogenic activity.

Phytoestrogens, include certain isoflavonoids, flavonoids, stilbenes, and lignans. Their perceived health beneficial properties extend beyond hormone-dependent breast and prostate cancers and osteoporosis to include cognitive function, cardiovascular disease, immunity and inflammation, and reproduction and fertility.

In addition to being a source of compounds necessary for human nutrition, certain plant foods also contain compounds that may have long-term effects on human and animal health.

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Goła¸bek, A.; Kowalska, K.; Olejnik, A. Polyphenols as a Diet Therapy Concept for Endometriosis—Current Opinion and Future Perspectives. Nutrients 2021, 13, 1347. https://doi.org/10.3390/nu13041347
Balan, A.; Moga, M.A.; Dima, L.; Dinu, C.G.; Martinescu, C.C.; Panait, D.E.; Irimie, C.A.; Anastasiu, C.V. An Overview on the Conservative Management of Endometriosis from a Naturopathic Perspective: Phytochemicals and Medicinal Plants. Plants 2021, 10, 587. https://doi.org/10.3390/plants10030587

Menorrhagia

Menorrhagia is excessive uterine bleeding, in terms of flow and duration, during regular cyclical intervals. Its clinical definition includes blood loss greater than 80 mL per cycle or menses lasting longer than 7 days. Diet should be considered when managing menorrhagia. Ideally, the diet should be low in animal fat and rich in fish oils and linolenic and linoleic acids.
Iron: Blood loss is one of the major causes of iron deficiency anemia. However, it is less well known that chronic iron deficiency can be a contributor to menorrhagia, in turn. Women experiencing heavy blood loss should consume iron-rich foods such as Brewer's yeast, wheat germ, blackstrap molasses, organic liver and kidneys, apricots, eggs, ground beef, raisins, beans, cooked spinach, and chicken. In addition, yogurt, sour fruits, and citrus juices can aid in the absorption of iron.

Vitamin A: Adult women experiencing menorrhagia may have low levels of vitamin A. Vitamin A is used to treat women with menorrhagia showed that those who received 60,000 IU of vitamin A for 35 days experienced both a return to normal and a reduction in blood loss.

Vitamin B Complex: Vitamin B complex deficiencies result in failure of the liver to inactivate estrogen. Thus, the excess estrogen's effect on the endometrium ends up with more bleeding, while vitamin B complex may help normalize estrogen metabolism and thus reduce bleeding.

Vitamin C and Bioflavonoids: Vitamin C and bioflavonoids improve heavy bleeding via making the capillary walls less fragile. Moreover, vitamin C can benefit women with iron deficiency due to menorrhagia by increasing iron absorbency.

Some herbal and nutritional supplements have shown beneficial effects against menorrhagia, including the chaste tree or chasteberry (Vitex agnus castus. In addition, astringent herbs such as shepherd's purse have a long history of use for inhibiting gynecological hemorrhage. Tonic herbs such as life root, also known as ragwort, have been used for conditions such as menstrual cramps, menorrhagia, and subdued menstruation. Traditional herbs such as yarrow have been used since medieval times to treat bleeding wounds. Yarrow is a uterine stimulant that increases muscular tone, stimulates reproductive activity, and effectively treats menstrual problems.

76%

with endometriosis use non-pharmacological practices and lifestyle choices like relaxation techniques, movement, and nutrition.

Phytochemicals & Medicinal Plants and their bioactive compounds exhibit anti-angiogenic, anti-oxidative, sedative and pain-alleviating properties, and the beneficial effects encourage their use for the management of endometriosis.*

Dysmenorrhea

Dysmenorrhea is commonly described as painful menstruation in the form of lower abdominal pain. Symptoms include nausea, vomiting and loss of appetite, fatigue, diarrhea, headache, restlessness, insomnia, and fainting. Primary dysmenorrhea has been primarily associated with the extra production of prostaglandins and leukotrienes. Prostaglandins (PGF2-α) temporarily limit or stop the blood supply to the uterus by stimulating its contraction, which reduces the amount of blood perfusing the uterus through myometrial compression of the blood vessels. This deprives the uterus of oxygen, which results in cramping and abdominal pain.

Calcium and Magnesium: Dietary calcium and magnesium intake has a protective effect against dysmenorrhea. Following absorption from the upper intestine, they can manage the muscle cells' response to nerve stimuli through numerous functions.

Olive Oil: The polyphenolic compound oleocanthal in extra virgin olive oil has been shown to have anti-inflammatory and antioxidant effects. Its inhibitory effect on prostaglandin-induced uterine hypercontraction shows that oleocanthal, dose-dependently, inhibited the PGF2α-induced contraction amplitude. Extra virgin olive oil and oleocanthal can reduce oxidative stress and uterine hypercontraction.

Dietary Fiber: Fiber intake reduces blood estrogen levels, whereas fat has been associated with increased estrogen levels. Intake of dietary fiber is significantly inversely correlated with the menstrual pain scale after adjusting for age, smoking status, age at menarche, and total energy intake.

Omega-3 and Omega-6 Fatty Acids: Western diets are rich in omega-6 fatty acids (e.g., vegetable oil, eggs, and margarine) but poor in omega-3 fatty acids (e.g., fish, canola oil, and wheat germ). Omega-6 fatty acids contribute to the formation of pro- inflammatory eicosanoids, such as Prostaglandin E2 (PGE2), thromboxane A2, and leukotriene B4, whereas omega-3 fatty acids, specifically eicosapentanoic and docosahexanoic acids, lead to the formation of less inflammatory eicosanoids (e.g., PGE3, thromboxane A3, and leukotriene B5).

Vitamin D: Vitamin D receptors are located in the human uterus, and vitamin D inhibits the synthesis of prostaglandins. Calcitriol (1,25[OH]2D) decreases, in vitro, the level of pro-inflammatory cytokines such as interleukin 6 and tumor necrosis factor and regulates the expression of several key genes involved in the prostaglandin pathway, causing decreased biological activity of prostaglandins.

Vitamin E: The positive effects of vitamin E on the alleviation of primary dysmenorrhea pain shows a significant reduction in pain severity in women treated with this vitamin.

Qixuehe: QiXueHe Capsule (QXHC) can alleviate pathological changes in menstrual disorders. Targets in the treatment of menstrual disorders are significantly associated with several biological pathways, such as VEGF and chemokine signaling pathways and alanine, aspartate, and glutamate metabolism, which are involved in the major pathological processes of menstrual disorders.

Vitamin K: Treatment with vitamin K may shorten the length of the extended menstrual flow due to its action on prothrombin, which is a coagulation protein produced in the liver and is dependent on vitamin K.

M. (2021). Nutrition in Gynecological Diseases: Current Perspectives. Nutrients, 13(4), 1178. https://doi.org/10.3390/nu13041178

Endometriosis

ICD-11

Microbiome Science

WHO International Reference Reagents for Gut Microbiome Analysis by Next-Generation Sequencing

Developing standards for the microbiome field. Microbiome 2020.

Effective standardisation of methodologies to analyse the microbiome is essential to the entire microbiome community. These can act as global working standards and will be evaluated as candidate World Health Organization International Reference Reagents. Developments in next-generation sequencing (NGS) technologies have facilitated the rapid expansion of the microbiome field. As new technologies have been developed, the cost per read of sequencing has decreased, meaning sequencing-based cohort studies have become more accessible to the wider scientific community. The creation of global standards for the microbiome field has the potential to improve method development, prevent erroneous results being reported, and allow for effective commutability of results globally. These improvements will be essential for effective translation of research to clinical application. Furthermore, standards can open up innovation in the field, as they negate the requirement for everyone to use the same protocol as long as users validate their protocol with respect to the global standard.

DNA-Gut-Mix (NIBSC 20/302), different strains = equal ratios

DNA-Gut-HiLo (NIBSC 20/304) different strains = staggered ratios.

$$\textbf{Sensitivity} = \frac{\text{Number of Correctly Identified Species}}{\text{Total Number of Species in Regent}} \times 100$$

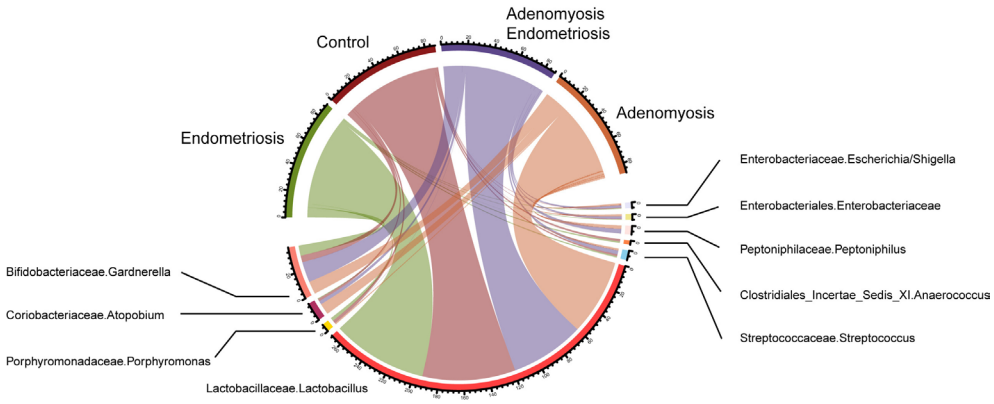
$$\textbf{False Positive = Relative Abundance} = \frac{\text{Abundance of All False Positive Species}}{\text{Total Abundance of All Species}} \times 100$$

Diversity + Total Number of All Observed Species (True Positive + False Positive

$$\textbf{Similiarity [jk]} = 1 - \frac{sumabs(x[ij] - x[ik])}{sum(x[ij] + x[ik]}$$

Akkermansia muciniphila
Alistipes finegoldii
Anaerostipes hadrus
Bacteroides thetaiotaomicron
Bacteroides uniformis
Bifidobacterium longum subsp. infantis
Bifidobacterium longum subsp. longum
Blautia wexlerae
Clostridium butyricum
Collinsella aerofaciens
Escherichia coli
Eubacterium/Anaerobutyricum hallii
Faecalibacterium praunitzii
Lactobacillus gasseri/paragasserii
Parabacteroides distasonis
Prevotella copri
Prevotella melaninogenica
Roseburia hominis
Roseburia intestinalis
Ruminococcus gauvreauii

Endometriosis and adenomyosis related microbiota in female lower genital tract www.



Endometriosis and adenomyosis

Endometriosis is an immune-dysfunction-related disease, contributing to the diversity of microbiota in the lower genital tract. An increased release of proinflammatory cytokines from endometriotic lesions contribute to the excessive sensory innervation and development of chronic pelvic pain. Immune system dysfunction greatly impacts the development of endometriosis, which involves various types of immune cells and cytokines.

Dysmenorrhea

The investigation on dysmenorrhea by random forest regression identified the importance of the features of microbiota. The cervical canal samples displayed more OTUs with negative impacts, while the posterior fornix samples showed several OTUs with only positive impacts. It proved that posterior fornix is a better sampling location to analyze the microbiota feature in dysmenorrhea investigation. Endometriosis dysmenorrhea is correlated to some imbalanced immune factors, such as IL-6 and IL-8. Microbiota features this during the menstrual cycle. Estrogen is associated with interleukin (IL)33 as well as macrophages34; the change of IL is also correlated to the bacterial micro-environment.

Adonis test shows that eight factors are significantly related to microbiota

Gravidity	**Menstrual cycle**
Parity	**Visual Analogue Score**
Weight	**Infertility**
BMI	**GnRHa treatment**

Environmental factors are statistically significantly related to microbiota feature. GnRH-a treatment was the most critical factor influencing the microbiota feature, followed by BMI and weight, but each leads to different feature characteristics of the microbiotas. Infertility, days of menstrual cycle and dysmenorrhea showed similar effectiveness in different extents. For GnRH-a-treated patients, their vaginal environments were similar to post-menopause women, and bacterial contamination can be detected in the uterine cavity and endometriosis cystic fluid. Infertility, menstrual cycle, and GnRH-a treatment are all associated with ovarian function; research has also demonstrated that estrogen and macrophages' cross talk contributes to endometriosis .dysmenorrhea.

Glycome and the microbiome

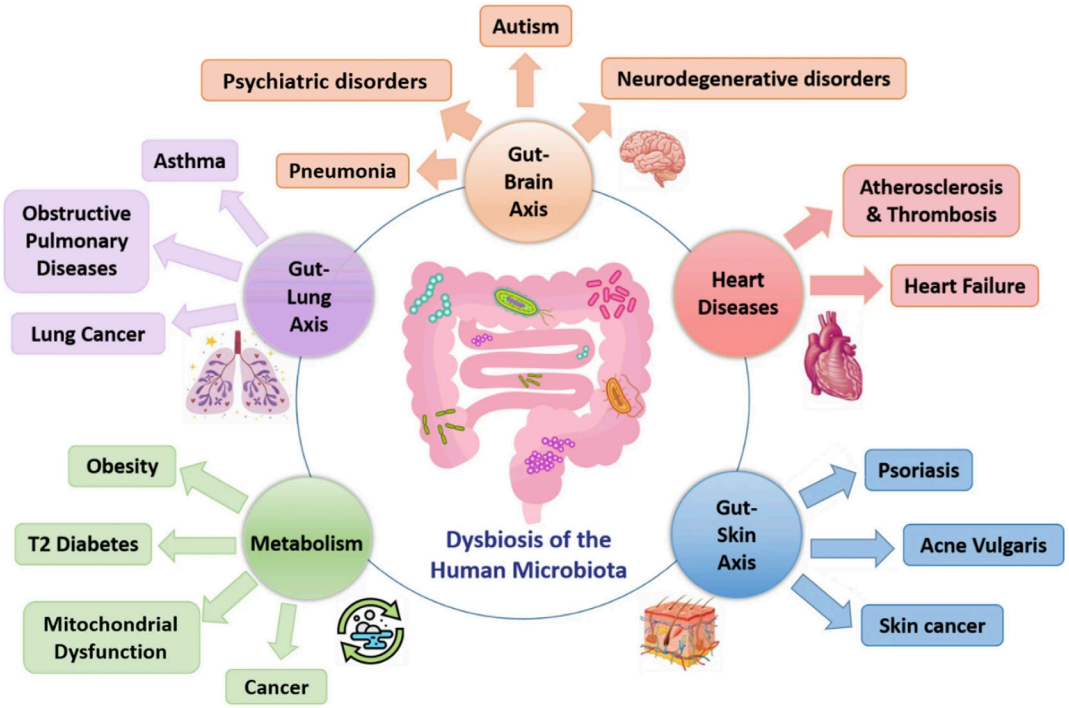
Endometriosis (EMS) is a condition of multifactorial aetiology; involving genetic predisposition, prenatal exposure to endocrine-disrupting chemicals, the microbiome, the immune system and sex hormones. Associations between gastrointestinal and genital tract microbial health and endometriosis have been identified. For instance, irritable bowel syndrome is more common in women with endometriosis, and hormonal imbalance has a negative impact on the microbiome of both the genital tract and the gastrointestinal system. Hormones, especially estrogen, can regulate a number of anti-microbial peptides. Bacteria can spread through endometrial influx in retrograde menstruation, when hormone

levels are low. LPS/endotoxin from these bacteria was found to promote growth of EMS through TLR4. The emerging discipline of glycomics holds promise as a new 'omics' approach to understanding complex diseases. Glycomics is a discipline for the study of carbohydrates and indirectly provides an opportunity to discover new glyco-biomarkers. Glycans play an essential role in the functioning and regulation of living organisms. Under pathological conditions, in addition to changes at the proteomic, metabolic, and genetic levels, glycan structures are also modified. The relevance of the vaginal microbiota to health and homeostasis of the female genital tract is well known and its alteration has been observed in many gynaecological diseases including EMS. There is substantial evidence pointing to the role of the gut microbiome in modulating extra intestinal host health. Indeed, changes in circadian rhythms and immune function have been linked to intestinal microbial processing and the resulting metabolites like short-chain fatty acids.

Sikai Chen, Zhiyue Gu, Wen Zhang, Shuangzheng Jia, Ping Zheng, Yi Dai, Jinhua Leng, The study of endometriosis and adenomyosis related microbiota in female lower genital tract in Northern Chinese population, Gynecology and Obstetrics Clinical Medicine, Volume 1, Issue 3, 2021, https://doi.org/10.1016/j.gocm.2021.07.007.

Zsuzsanna Kovács, Louise Glover, Fiona Reidy, John MacSharry, Radka Saldova, Novel diagnostic options for endometriosis – Based on the glycome and microbiome, Journal of Advanced Research, Volume 33, 2021, https://doi.org/10.1016/j. jare.2021.01.015

Microbe host interactions exist not only within an organ, but also constitute an inter-kingdom crosstalk linking automatically distinct organs together.



Pregnancy

The diversity and the functions of the gut microbiota are shown to be affected by naturally occurring physiological changes that accompany pregnancy, including the immunological and hormonal gestational balance. In fact, the estrogen and progesterone affect the prenatal and postpartum intestinal motility in women as well as the gut microbial diversity through their effect on bacterial metabolism, growth and virulence. In one of the most recent cohort studies, it was demonstrated that the gut bacterial repertoires largely differ in pregnant women under the effect of multiple factors such as gestational age, body mass index, ethnicity, nutritional state and others . The effect of the gut microbiota dysbiosis throughout the different pregnancy trimesters has been of special concern as it may significantly contribute to different metabolic disorders during the pregnancy stages. Recent evidence demonstrated a connection between gut microbiome and gestational diabetes mellitus (GDM) referred to as a glucose intolerance in pregnancy, at the first, second and the third trimester of pregnancy. It was also shown, in a recent study, that GDM pregnant women show special food preferences such as lower intake of vegetables, fish, poultry, and fish paste. This correlates with microbiome diversity. In this context, the use of probiotics as a novel therapeutic strategy appears to be appealing in the prevention of type 2 diabetes mellitus in post-GDM women. The consumption of multi-strain probiotics can actually contribute to the modulation of the gut microbiota composition, the improvement of the intestinal epithelial integration and others. Further investigations on the probiotics selection, the dosage, the timing and the duration are needed. The imbalance in the gut microbiota during pregnancy is associated to pre- eclampsia (PE) which is a pregnancy-specific systemic disorder involving hypertension, proteinuria and other complications. One recent study revealed a reduction in the bacterial diversity. The gut microbial community was enriched by opportunistic pathogens, such as Fusobacterium and Veillonella, but lacked the beneficial bacteria.

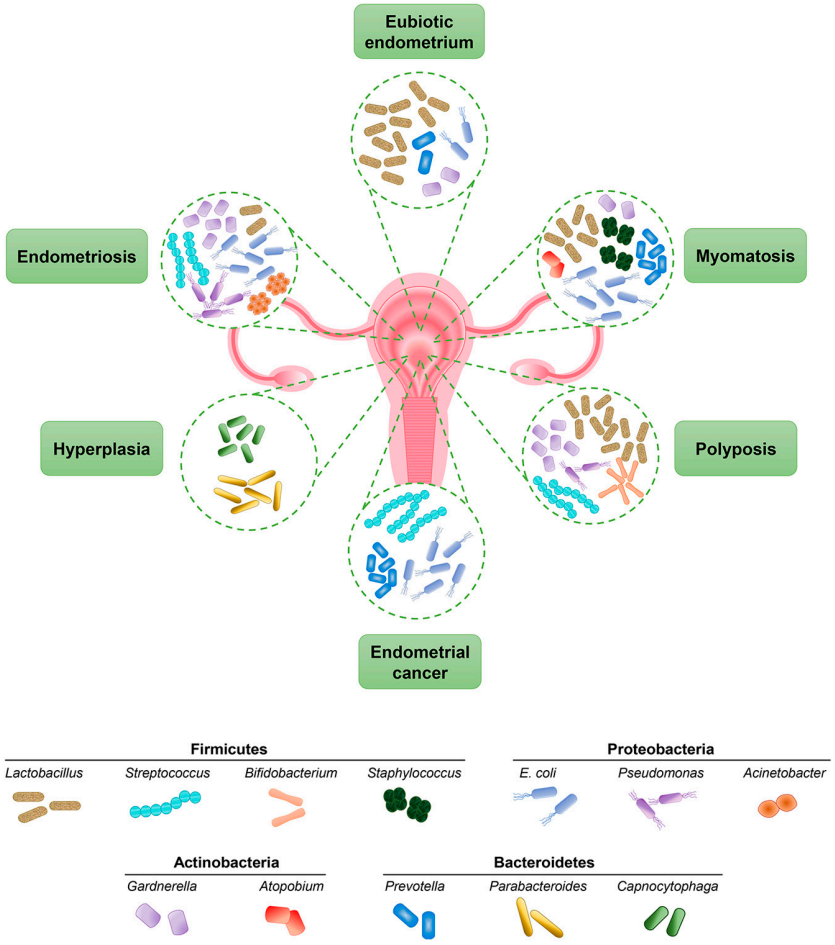
This striking dysbiosis was correlated to an increase in the blood pressure, as well as in the proteinuria, aminotransferase and creatinine levels. Moreover, the T regulatory/ helper -17 cells balance was greatly disturbed in the intestines and the spleen of mice with transplanted fecal microbiota from PE patients.

Endometriosis

Treatment with one or two probiotics, have different but both favorable effects on clinical, immune and physiologic parameters in endometriosis. Because of its better results on pain and a greater ease of handling, Saccharomyces boulardii seems to be more suitable to be used as a new therapeutic strategy for endometriosis.

Gebrayel, P., Nicco, C., Al Khodor, S. et al. Microbiota medicine: towards clinical revolution. J Transl Med 20, 111 (2022). https://doi.org/10.1186/s12967-022-03296-9

Current findings in endometrial microbiome: impact on uterine diseases



Schematic representation of the endometrial microbiome composition in uterine-related diseases. The most representative genera from each bacterial phylum are shown across the physiological and pathological conditions. Lactobacillus and some Proteobacteria are abundant in the eubiotic endometrium, while changes in the microbiome from uterine diseases are observed. Myomatosis displays a high diversity of bacteria, including Firmicutes, Proteobacteria, and Actinobacteria. Lactobacillus, Bifidobacterium, and Gardnerella predominantly compose the endometrial microbiome in polyposis. In endometrial cancer, the bacterial community is mainly composed of Streptococcus, E. coli, and Prevotella. The presence of Parabacteroidetes and Capnocytophaga characterizes endometrial hyperplasia. Endometriosis is characterized by a predominance of E. coli, Pseudomonas, Acinetobacter, and Gardnerella, whereas a decrease in Lactobacillus is observed.

Medina-Bastidas D, Camacho-Arroyo I, García-Gómez E. Current findings in endometrial microbiome: impact on uterine diseases. Reproduction. 2022 Mar 24;163(5):R81-R96. doi: 10.1530/REP-21-0120. PMID: 35195535.

LOINC / loinc.org

88849-5 Microbiology CNAMTS panel - Vaginal fluid

Lactobacillus sp Ab.IgG
Lactobacillus sp Ab.IgM
Lactobacillus is a genus of Gram-positive facultative anaerobic or microaerophilic bacteria. They are a major part of the lactic acid bacteria group, named as such because most of its members convert lactose and other sugars to lactic acid. They are common and usually benign. In humans they are present in the vagina and the gastrointestinal tract, where they are symbiotic and make up a small portion of the gut flora. Many species are prominent in decaying plant material. The production of lactic acid makes its environment acidic, which inhibits the growth of some harmful bacteria.

Inflammatory Bowel Syndrome

8085-3 Neutrophil cytoplasmic Ab.perinuclear [arb'U]/mL
31032-6 Baker's yeast IgA Ab [Units/volume] in Serum k[IU]/L
35538-8 Baker's yeast IgG Ab [Mass/volume] in Serum ug/mL
42723-7 OmpC Ab [Units/volume] in Serum [arb'U]/mL

Endometriosis

ICD-11

Diagnostic Codes and Descriptions

PATIENT EXPERIENCE

Person goes to a doctor

- Code concern of the patient

Data inform planning of care

Practitioner identifies Endometriosis symptoms

- ICD11: Code Clinical Findings
- Code Diagnostic Test
- Code Imaging Test
- Code Diagnostic Findings

Data inform blood test, resource planning, testing and imaging

Monitoring of fitness and function

- Monitoring function -WHODAS
- ICF: Code full functioning detail

Data inform planning of support

Referral to Pain Specialist / Physical Therapy / Nutritionlist / Therapist

- ICHI: Code therapies and procedures

Referral to secondary care: Endometriosis Specialist

- Code Diagnostic Test
- Code Imaging Test
- ICHI: Code therapies and procedures
- ICD-O: Histopathology

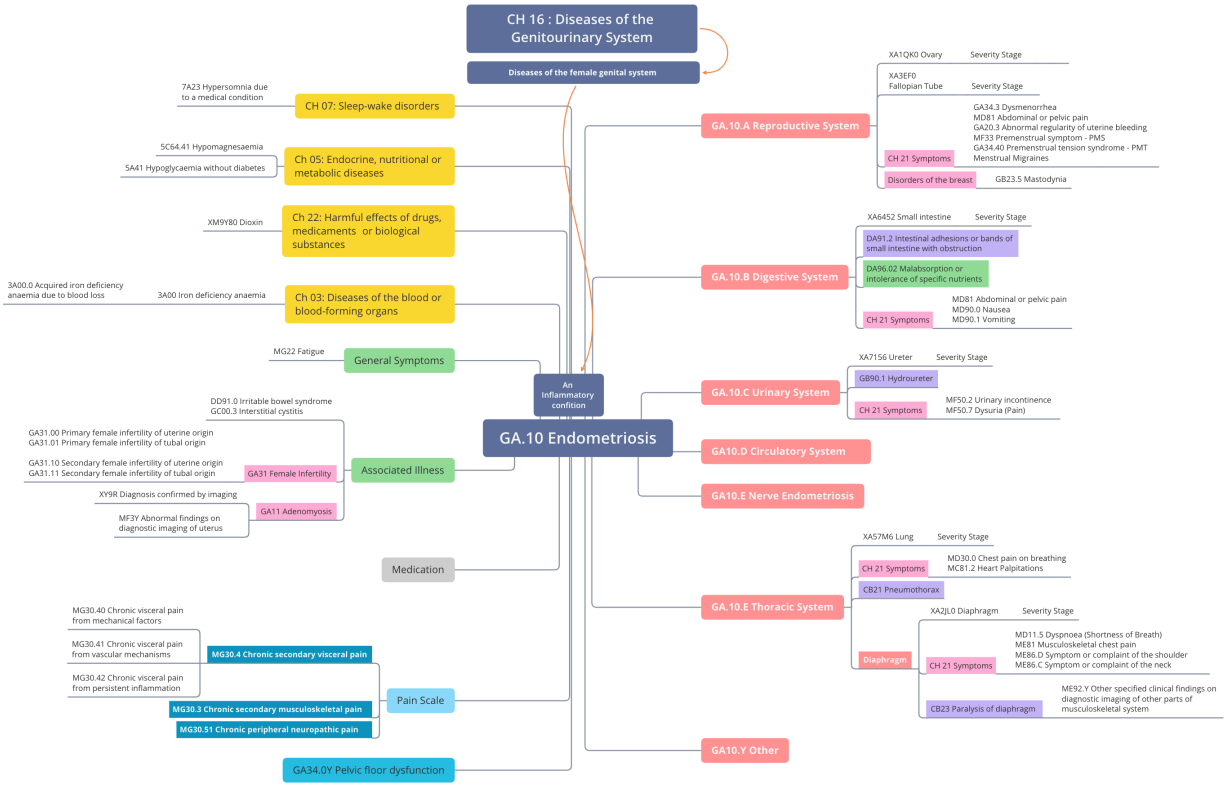
Data inform surgery resource planning, service availability and insurance

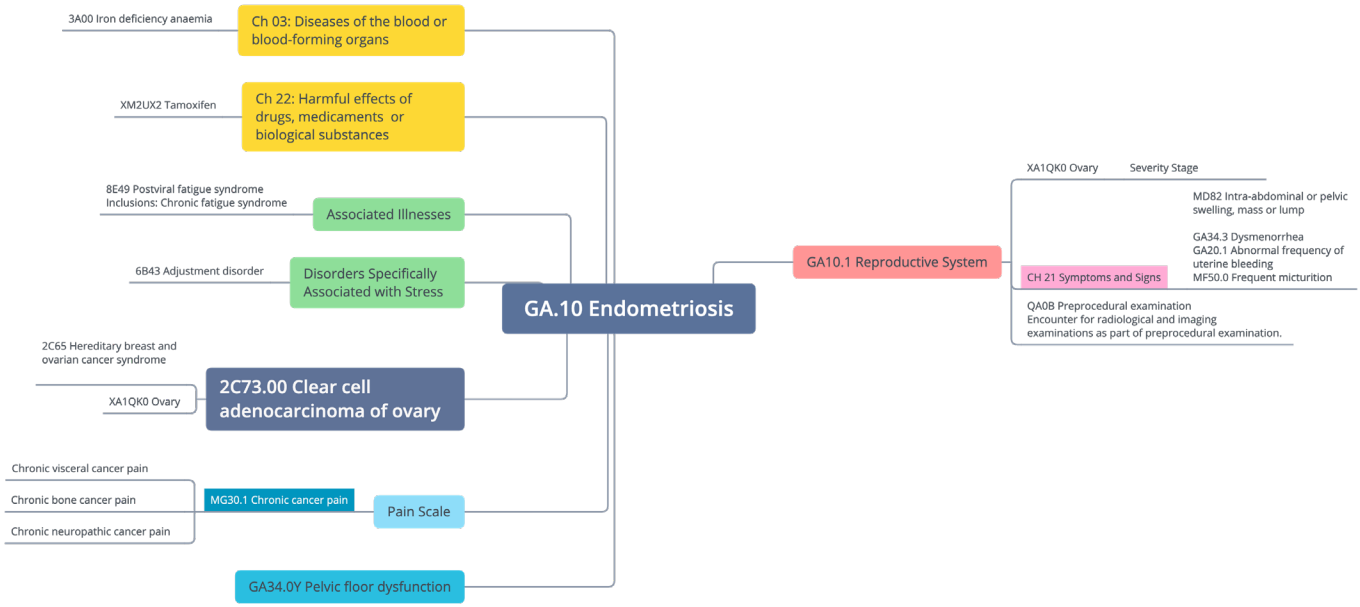
- ☑ Medical History
- ☑ Blood Panels review for overall health
- ☑ Physical Exam
- ☑ Interpreting new diagnostic imaging or a second review of prior imaging for errors
- ☑ Review of prior surgery photos and video

Endometriosis

ICD11 Linearization

Examples of Patient Coding and Mapping





Lesions
1.
2.
3.
4.

Adhesions
XS3V No endometriosis
XS5N Filmy endometriosis
XS55 Dense endometriosis

ICD-O
WHO Classification of Tumours

GA10. Endometriosis of the reproductive system

Parent
GA10 Endometriosis
Show all ancestors

Exclusions
- Endometriosis of the uterus (GA11)

Postcoordination

Add detail to **Endometriosis of the reproductive system**

Relational *(use additional code, if desired .)*
XK7F Superficial
XK16 Deep

Specific anatomy *(use additional code, if desired .)*

Search
Has manifesta
Search

Specific anatomy
- **Specific anatomy**
  - XA78U5 Vulva
  - XA1LK7 Vagina
  - XA9HG1 Parametrium
  - XA5CW9 Pelvic floor
  - XA29C1 Pelvic wall
  - XA60B5 Rectovaginal septum
  - XA37K5 Rectovesical septum
  - XA1DP8 Uterine wall
  - XA57Q2 Vaginal wall

GA10.J Endometriosis-related adhesions

Foundation URI: http://id.who.int/icd/entity/938154534

Code: GA10.J ✓ Select

Exclusions from above levels Show all [4]

Postcoordination

Specific anatomy *(use additional code, if desired .)*
search in axis: Specific anatomy
- **XA2GU7** Female genital organs
  - **XA78U5** Vulva
  - **XA1LK7** Vagina
  - **XA99N3** Uterus
  - **XA1QK0** Ovary
  - **XA7E69** Uterine adnexa
  - **XA90F8** Placenta

Has manifestation *(use additional code, if desired .)*
MG30.40 Chronic visceral pain from mechanical factors
MG30.42 Chronic visceral pain from persistent inflammation

Has severity *(use additional code, if desired .)*
XS3V No endometriosis
XS5N Filmy endometriosis
XS55 Dense endometriosis

2C73.01 Endometrioid adenocarcinoma of ovary

Parent
2C73.0 Carcinomas of ovary
Show all ancestors

Description
An endometrioid adenocarcinoma arising from the ovary. It comprises 10% to 25% of all primary ovarian carcinomas. Grossly, endometrioid carcinoma may present as a cystic or solid mass. Microscopically, the tumour greatly resembles the appearance of the ordinary type of endometrial adenocarcinoma. As a group, endometrioid carcinoma has a prognosis twice as good as that of serous or mucinous carcinoma.

Postcoordination

Add detail to **Endometrioid adenocarcinoma of ovary**

Laterality *(use additional code, if desired .)*
XK9J Bilateral
XK8G Left
XK9K Right
XK70 Unilateral, unspecified

Histopathology *(use additional code, if desired .)*
XH9508 Endometrioid adenocarcinoma, ciliated cell variant
XH0718 Endometrioid adenocarcinoma, secretory variant
XH0SD2 Endometrioid adenocarcinoma, NOS

Has manifestation *(use additional code, if desired .)*
MG30.10 Chronic cancer pain

2C73.00 Clear cell adenocarcinoma of ovary

Parent
2C73.0 Carcinomas of ovary
Show all ancestors

Description
A malignant glandular epithelial tumour characterised by the presence of clear and hobnail cells. The tumour is highly associated with ovarian endometriosis, pelvic endometriosis and paraendocrine hypercalcemia.

Postcoordination

Add detail to **Clear cell adenocarcinoma of ovary**

Laterality *(use additional code, if desired .)*
XK9J Bilateral
XK8G Left
XK9K Right
XK70 Unilateral, unspecified

Histopathology *(use additional code, if desired .)*
XH2Q13 Clear cell adenocarcinofibroma
XH6YS0 Clear cell adenocarcinoma, mesonephroid

Has manifestation *(use additional code, if desired .)*
MG30.10 Chronic cancer pain

XH1S94 Endometrial stromal sarcoma, low grade

Parent
Complex mixed and stromal neoplasms, malignant
Show all ancestors

Inclusions
- Stromal endometriosis
- Endometrial stromatosis
- Endolymphatic stromal myosis
- Endometrioid stromal sarcoma, low grade
- Stromal myosis, NOS

The color appearance of lesions and activity of these lesions by analysis of a panel of activity markers.

Translucent	Nonopaque lesions containing either watery, serous, or mucinous secretion and there is no collection of blood in the stroma by histology. The lesions of early endometriosis are either transparent or translucent because they still lack formation ofvasculatures around them.
Red	Opaque red lesions are defined as nontransparent (blood-filled) lesions, including polypoid excrescence, blood bled, or ecchymosis. Overproliferation of microvessels in the growing endometriotic lesions causes oozing of blood in the stroma and appears as blood-filled opaque red lesions by laparoscope. Early endometriosis with red peritoneal lesions induces a higher inflammatory response in the pelvic cavity than advanced endometriosis.
Black-Blue	With the progression of time, there is deoxygenation from hemoglobin to methemoglobin or hemosiderin leading to color changes of these opaque red lesions to black or related lesions. At this stage, collection of blood in the stroma disappears.
White-yellow	Black lesions again changes to white lesions due to the collection of bilirubin or biliverdin and accumulation of fibrous tissue. White lesions are due to the collection of bilirubin or biliverdin and accumulation of fibrous tissue. In this stage, the gland gradually becomes smaller and stroma sometimes disappears due to a deposition of fibrous tissue. Finally, old lesions disappear and there is a new focus of endometriosis due to continuation of menstrual reflux.
Invisible	Three patterns of Occult Microscopic Endometriosis: (1) presence of typical gland/stroma, (2) reactive hyperplastic change of endometrioid epithelium with surrounding stroma, and (3) single-layered mesothelium or epithelium-lined cystic lesions with a surrounding rim of stromal cells. OME lesions are confirmed by their immunoreactivity to Ber-EP4 (marker of gland epithelium), CD10 (marker of stroma), and nonreactivity to calretinin (marker of mesothelial cells). OME lesions are detected at a depth of 10–80 μm from the surface of the peritoneum.

Atypical endometriosis, stromal endometriosis, polypoid endometriosis, and the association of endometriosis with florid mesothelial hyperplasia

Recurrence

Lesion recurrence on reoperation or imaging after previous complete excision of the disease

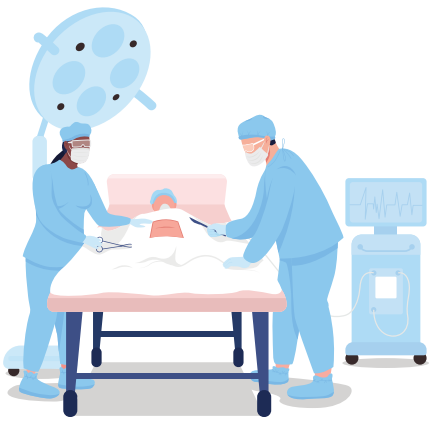
1. Suspected recurrence, based on patient history and symptoms, but not proven/confirmed by imaging and/or surgery
2. Imaging based suspected recurrence in patients with or without symptoms
4. Recurrence of histologically proven endometriosis during laparoscopy

• Endometriosis lesions not completely removed at the time of prior surgery

Risk Stratification Score

Risk factors that increase the likelihood of perioperative morbidity and mortality may include the patient's underlying health problems as well as factors associated with each specific type of surgery. By combining risk scores for patient co-morbidity and the complexity of surgery, we can stratify overall risk and determine which patients should undergo more extensive preoperative evaluation. If a patient who is scheduled for a non-emergency procedure is found to have medical conditions that are not under ideal control, this preoperative evaluation process can include optimization, or "prehabilitation", so that the patient can be in the best possible health before surgery. This process may address blood pressure control, diabetes management, nutritional status, exercise tolerance, smoking cessation, and treatment of anemia, as examples.

1.	**Symptoms +**	Microbiome, Endocrine, Metabolic Test, etc.
2.	**Symptoms +** Intermediate Risk Mild renal insufficiency Imaging Findings Superficial / Deep Infiltrating Pathology Findings	**Surgery Procedures associated with moderate changes in hemodynamics, risk of blood loss** Gynecologic and urologic surgery Nerve and spine surgery **Intermediate Risk**
3.	**Symptoms +** Imaging Findings Superficial / Deep Infiltrating Pathology Findings	Intra-abdominal surgery without bowel or bladder resection Intra-thoracic surgery without lung resection **Intermediate Risk**
4.	**Symptoms +** High Risk Renal insufficiency: creatinine > 2 Imaging Findings Ruptured Ovary Organ Obstruction Associated Tumors Pathology Findings	**Surgery Procedures with possible significant effect on hemodynamics, blood loss** Colorectal surgery with bowel or bladder resection Urinary artery erosion Kidney loss Major oncologic general surgery or gynecologic surgery **High Risk**
5.	**Symptoms +** Imaging Findings/ Lung Collapse Diaphragm Paralysis Pathology Findings	**Surgery Procedures with major impact on hemodynamics, fluid shifts, possible major blood loss** Cardiac surgery Intra-thoracic procedures with lung resection **Very High Risk**



UCLA https://www.uclahealth.org/anes/risk-stratification

GA10 Endometriosis
GA10.A Reproductive Endometriosis
GA10.B Digestive Endometriosis
GA10.C Urinary Endometriosis
GA10.D Circulatory Endometriosis
GA10.E Nerve Endometriosis
GA10.F Thoracic Endometriosis
GA10.Y Other

Caused By
GA10.H Endometriosis in cutaneous scar
GA10.J Endometriosis-related adhesions
GA10.Y Endometriosis of other specified sites
GA10.Z Endometriosis of unspecified site

Post-coordination: Extension Codes:

- **Severity Stage 1-4: by size**
- **Anatomy**
- **Pain Codes**
- **Histopathology**

Endometriosis Severity Scale Value

XS3V	No endometriosis
XS5N	Filmy endometriosis
XS55	Dense endometriosis

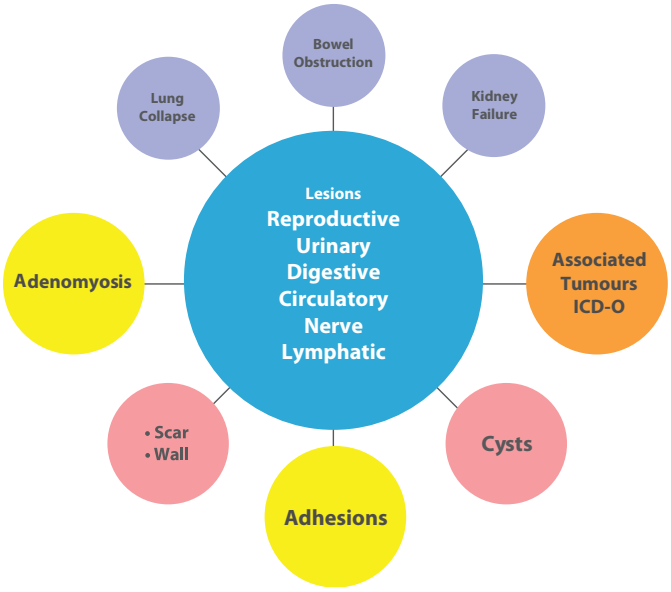
Additional Information:
Due to: endometriosis
Caused by: external factors
Manifestation: chronic pain
Associated: illnesses

Infertility

GA31 Female infertility

GA31.00 Primary female infertility of uterine origin
Female infertility caused by uterine abnormalities on the level of the endometrium or myometrium, with more detailed description classified elsewhere, i.e. under genitourinary infections, STDs and noninflammatory benign gynaecological disease

GA31.01 Primary female infertility of tubal origin
Female infertility caused by dysfunction of one or both fallopian tubes, usually related to pelvic adhesions or occurring after pelvic surgery, with or without hydrosalpinx



GA10 Endometriosis

Parent

Diseases of the female genital system

Show all ancestors

Description

A condition of the uterus that is frequently idiopathic. This condition is characterised by ectopic growth and function of endometrial tissue outside the uterine cavity. This condition may be associated with remaining vestigial tissue from the wolffian or mullerian duct, or fragments endometrium refluxed backward into the peritoneal cavity during menstruation. This condition may also present with dysmenorrhoea, dyspareunia, nonmenstrual pelvic pain, infertility, alteration of menses, or may be asymptomatic. Confirmation is by laparoscopy and histological identification of ectopic fragments.

Coded Elsewhere

- Salpingitis isthmica nodosa (GA17.4)

Postcoordination

Add detail to **Endometriosis**

Relational *(use additional code, if desired .)*

XK7F	Superficial
XK16	Deep

Specific anatomy *(use additional code, if desired .)*

Search

Has manifestation *(use additional code, if desired .)*

MG30.40	Chronic visceral pain from mechanical factors
MG30.42	Chronic visceral pain from persistent inflammation

Associated with *(use additional code, if desired .)*

PK80.71	Obstetric procedure associated with injury or harm, percutaneous approach
PL11.0	Cut, puncture or tear, as mode of injury or harm

GA11 Adenomyosis

Parent

Diseases of the female genital system

Show all ancestors

Description

A condition of the uterus characterised by endometrial tissue growth in the myometrium, hypertrophy of the myometrium, and heavy or prolonged menstrual bleeding, dysmenorrhoea, dyspareunia, bleeding between menstruation, infertility, or is asymptomatic. Confirmation is by histopathology or ultrasound.

Exclusions

- Leiomyoma of uterus (2E86.0)

Postcoordination

Add detail to **Adenomyosis**

Relational *(use additional code, if desired .)*

XK7F	Superficial
XK16	Deep

Specific anatomy *(use additional code, if desired .)*

Search

Has manifestation *(use additional code, if desired .)*

MG30.40	Chronic visceral pain from mechanical factors
MG30.42	Chronic visceral pain from persistent inflammation

Add Endometriotic Cyst

Endometriomas are cystic lesions that stem from endometriosis. Endometriomas are most commonly found in the ovaries. These lesions are commonly referred to as chocolate cysts, due to the thick dark brown appearance of the fluid that is contained within them. Endometriomas indicate a more severe disease state in patients with endometriosis and can lead to specific issues in these patients, such as decreased ovarian reserve.

GA18 Acquired abnormalities of ovary
GA18.0 Follicular cyst of ovary
GA18.1 Corpus luteum cyst
GA18.2 Theca lutein cyst
GA18.4 Para ovarian cyst
GA18.5 Torsion of ovary, ovarian pedicle or fallopian tube
GA18.6 Other or unspecified ovarian cysts
GA18.7 Acquired atrophy of ovary or fallopian tube

ICD-11 extension codes support detailed clinical abstraction and comprehensive classification

Coded hospital morbidity data are used internationally for many reasons, including in the assessment of quality of care and healthcare provider performance. A feature in such data, which substantially facilitates the capture of quality and safety events within health care settings, is the ability to time the onset of conditions.

Drösler, S.E., Weber, S. & Chute, C.G. ICD-11 extension codes support detailed clinical abstraction and comprehensive classification. BMC Med Inform Decis Mak 21 (Suppl 6), 278 (2021). https://doi.org/10.1186/s12911-021-01635-2

Head categories: all parents in ICD-11 chapter X	Type of Extension codes	Examples in hierachical Subheading (Parent)
Severity Scale Value	1	Disease Specific Severity Scale Value
Temporality	1	Duration of pregnancy
Aetiology	1	Infectious Agents
Topology Scale Value	1	Laterality
Anatomy and topography	1	Functional anatomy
Histopathology	1	Adenomas and adenocarcinomas
Dimensions of injury	1	Whether fracture is open or closed
Dimensions of external causes	1	Aspects of transport injury events
Consciousness	1	Pupil reaction score
Substances	1	Medicaments
Diagnosis code descriptors[#]	2	Diagnosis certainty
Capacity or context*	2	
Health devices, equipment and supplies	1	Respiratory and anaesthesia devices

Post-coordination

Postcoordination of concepts allows more detail to be added about associated or causing conditions, specific anatomy, laterality or infectious agent.

EXTENSION CODES

Severity Stage
1
2
3
4

Histopathology

Specific anatomy

Topology scale value
Laterality
XK97 Bilateral
XK8G Left
XK9K Right
XK70 Unilateral, unspecified

Relational
XK7F Superficial
XK16 Deep

Time Related Pain
Temporal pattern and onset
XT5G Intermittent
XT6Z Persistent
XT5T Persistent with overlaid attacks

Causality
XB8M Congenital
XB7K Hereditary
-
XB5F Idiopathic
XB1Y Familial
XB4Q Environmental

Chemical agent
Substances, chiefly nonmedicinal

Medication

Discharge diagnosis types
XY0Y Main condition
XY7B Main resource condition
XY6E Initial reason for encounter or admission

Diagnosis timing
XY6M Present on admission
XY69 Developed after admission
XY85 Uncertain timing of onset relative to admission

Diagnosis timing in relation to surgical procedure
XY9U Preoperative
XY9N Intraoperative
XY7V Postoperative

Diagnosis method of confirmation
XY3B Diagnosis confirmed by laboratory examination
XY0E Diagnosis confirmed by serology
XY9Q Diagnosis confirmed by histology
XY8K Diagnosis confirmed by genetics
XY9R Diagnosis confirmed by imaging
XY19 Diagnosis confirmed by microscopy
XY0K Diagnosis confirmed by culture

Diagnosis certainty
XY7Z Provisional diagnosis
XY75 Differential diagnosis

Activity when injured
XE245 Being taken care of by health care professional

In
XE9VC Medical service area
XE28K Hospital
XE8DZ Outpatient clinic or health centre

Reproductive Endometriosis

Endometriosis is associated with severe pain during periods, sexual intercourse, bowel movements and/or urination, chronic pelvic pain, abdominal bloating, nausea, fatigue, anxiety, and infertility. Common locations of endometrial implants include the ovaries, fallopian tubes, and ligaments that support the uterus. The cyclic and recurrent bleeding, the progressive fibrosis and the peritoneal adhesions of ectopic endometrial glands cause different symptoms depending on the origin involved.

Urinary Endometriosis

Urinary Endometriosis lesions can be in or around the urethra, bladder, ureters, or kidney. UE is usually unilateral, and the distal ureter is the most commonly affected site. Ureteral endometriosis can lead to urinary tract obstruction, with subsequent hydroureter, hydronephrosis, and potential kidney loss. The extrinsic form involves compression of the ureteral wall and is more common than the intrinsic, which involves invasion of the ureter and may originate from lymphatic or venous metastases.Urinary involvement may present with frequency, incontinence, dyspareunia, pain and urgency.

Digestive Endometriosis

Bowel endometriosis symptoms include dyschezia, constipation, diarrhea, abdominal bloating, painful bowel movements, passage of mucus in the stools and cyclical rectal bleeding. Bowel lesions can be present anywhere along the lower gastrointestinal tract, but have a predilection for the distal colon (sigmoid and rectum). Bowel lesions can be superficial or deep; or can invade the bowel wall being associated with fibrosis and adhesions. Gastrointestinal endometriosis can manifest as an acute abdomen with perforation, intussusception, and obstruction.

Thoracic Endometriosis

Thoracic endometriosis lesions can affect the diaphragm, pleura, lung and bronchi. There may be a greater affinity for the right hemi thorax, and the parenchyma is more commonly affected in the lower lobes. Macroscopically, the endometriotic implants appear as brown–yellow and sometimes red nodules surrounded by neovascularization. Symptoms include: dyspnea, shortness of breath, rapid heartbeat, coughing up blood and a variety of pain patterns to include scapula, chest, ipsilateral neck and shoulder, upper abdominal and epigastric. Thoracic endometriosis may present with catamenial pneumothorax (recurrent pneumothorax occurring within 72 hours of menstruation), haemoptysis in case of bronchial location, haemothorax, pleural effusion. A diagnosis of thoracic endometriosis is simple when both endometrial stroma and gland are present. In cases of endometriosis with stroma only, a further classification of "aggregated pattern", in which immunohistochemistry is ER-, PR- and CD10-positive might be necessary for diagnosis.

Circulatory Endometriosis

Pericardial Endometriosis can have mediastinal involvements such as catamenial pericardial effusion, pericardial nodules, hemopericardium accompanied by sudden and excruciating chest pain due to parietal pericardial irritation.

• Lymphatic endometriosis

Lymphatic endometriosis includes mesorectal, pericolic and pelvic lymph nodes. Lymph node endometriotic foci is associated with rectosigmoid, rectovaginal, and bowel endometriosis. It consists of glandular cystic spaces lined by Müllerian serous epithelium and endometrioid stroma. Lymph node endometriosis immunohistochemical panel with antibodies against ER, PR and p53 is useful in diagnosing atypical endometriosis. From a histological and immunohistochemical point of view, deep infiltrating endometriosis and lymph node endometriosis represent the same entity. The marked endometriosis-associated neural changes (endometriotic neuropathy) causes of impaired function of the affected organs after debulking surgery with macroscopic negative resection margins as well as pain symptomatology in macroscopic inapparent endometriotic lesions.

Nerve Endometriosis

Nerve Endometriosis involvement may manifest with neurological symptoms, including pain, muscle weakness, bowel and bladder incontinence, and paraplegia. The neural involvement may be isolated or caused by a direct extension of a deep infiltrating endometriosis of the pelvic structure. Magnetic resonance imaging (MRI) is a reliable imaging modality for detecting neural involvement of endometriosis. Both the disease and radical removal of endometriosis may lead to the destruction of the nerve fibres with corresponding symptoms, which can be very debilitating for the patient. Endometriosis close to the sympathetic and parasympathetic nerve fibres (hypogastric plexus and splanchnic nerves) can lead to a dysfunction of pelvic organs (e.g. dysfunction of the bladder as well as disturbance of vaginal lubrication and intestinal dysfunction). Involvement of somatic nerves, such as the sacral plexus and the sciatic nerve, leads to corresponding neurological symptoms or deficits. Neural entrapment is a possible occurrence and has been described in different pelvic nerves, such as the sciatic, obturator, femoral, and pudendal nerves and the inferior hypogastric and lumbosacral plexus.

Endometriosis Specified: Other Organ Systems

Reproductive
XA2GU7 Female genital organs
- XA78U5 Vulva
- XA1LK7 Vagina

XA99N3 Uterus
- XA3V49 Fundus of uterus
- XA5229 Corpus uteri
  - XA8QA8 Endometrium
    - XA9DM0 Endometrial gland
    - XA3FR4 Endometrial stroma
- XA2LU5 Myometrium
- XA9HG1 Parametrium
- XA3QZ2 Uterine cavity
- XA7F09 Isthmus uteri
- XA5WW1 Cervix uteri

XA1QK0 Ovary
- XA6FA5 Cortex of ovary
- XA44X6 Medulla of ovary

XA7E69 Uterine adnexa
- XA3EF0 Fallopian Tube

Urinary
XA6KU8 Kidney
XA7156 Ureter
XA77K2 Urinary bladder
XA5TA5 Urethra

Digestive
XA9607 Gastrointestinal tract
XA6452 Small intestine
- XA9780 Duodenum
- XA8UM1 Jejunum
- XA0QT6 Ileum

XA1B13 Large intestine
- XA6J68 Caecum
- XA03U9 Colon
  - XA8PW4 Appendix
  - XA3AL5 Ascending colon
  - XA95L3 Hepatic flexure of colon
  - XA49U1 Transverse colon
  - XA1PY9 Splenic flexure of colon
  - XA2G13 Descending colon
  - XA8YJ9 Sigmoid colon
  - XA33J5 Rectosigmoid junction
  - XA7177 Descending colon and splenic flexure of colon
  - XA25P9 Ascending colon and right flexure of colon
- XA4KU2 Rectum

XA5DY0 Liver
XA3QC5 Pancreas
XA0KZ0 Peritoneum
- XA6S21 Retroperitoneum
- XA43V8 Mesentery
- XA6DF7 Omentum
- XA46W1 Mesoappendix
- XA4QM7 Mesocolon

Respiratory
XA26H1 Trachea
XA57M6 Lung
XA2PV7 Connective, subcutaneous and other soft tissues of lung
- XA61M6 Bronchus
- XA8Z62 Lung parenchyma
- XA4646 Pulmonary vasculature

XA5TT2 Pleura
- XA1B59 Visceral pleura
- XA7RC6 Parietal pleura

***Muscle** XA2JL0 Diaphragm

Circulatory
XA2XU0 Pericardium
XA8RK9 Parietal pericardium
XA48H9 Pericardial cavity
XA37Q8 Epicardium

-Immune system
Lymphoid organs
XA33X2 Lymph nodes

Nervous
XA1630 Peripheral nervous system
- XA65L3 Spinal nerve
- XA6EC2 Spinal nerve root
  - XA9F62 Sacral Nerve Root
- XA64F0 Spinal nerve plexus
- XA06U6 Peripheral nerve
  - XA11D4 Femoral nerve
  - XA4548 Obturator nerve
  - XA6WU3 Pudendal nerve
  - XA9KK8 Sciatic nerve
  - XA0SA1 Sacral splanchnic

XA7718 Autonomic nervous system
XA7EA2 Parasympathetic nervous system
XA93B4 Sympathetic nervous system

Ligaments
XA0EJ9 Broad ligament of the uterus
XA23X3 Round ligament of uterus
- XA4T57 Uterine ligament

XA2NB2 Uterosacral ligament

Walls
XA3JR1 Intestinal Wall
XA5CW9 Pelvic floor
XA29C1 Pelvic wall
XA60B5 Rectovaginal septum
XA37K5 Rectovesical septum
XA1DP8 Uterine wall
XA57Q2 Vaginal wall
XA3KX0 Abdominal wall
- XA4SN6 Anterior abdominal wall
- XA0NH8 Iliac region
- XA1DN2 Lateral lumbar region
- XA1LM1 Periumbilical region
- XA3MT8 Umbilicus
- XA0LF4 Suprapubic area
- XA8ZL8 Epigastrium
- XA3TD4 Hypochondrium

XA0R03 Bladder wall
XA55T2 Chest wall

Cavities
XA34B0 Abdominopelvic cavity
- XA9M74 Abdominal cavity

XA25Q2 Pelvic cavity
- XA9CK0 Ischiorectal fossa
- XA53A7 Presacral region
- XA2EG4 Perirectal region
- XA0GN7 Inguinal region

XA7WA2 Mediastinum
XA1XJ5 Thoracic cavity
- XA3LX5 Pleural cavity
- XA2RT1 Precordium

Arteries and Veins
- XA9UT1 Artery of thorax
- XA9JK8 Artery of abdomen
- XA4GP1 Artery of pelvis

CHAPTER 16 :Diseases of the urinary system

DC51.2 Haemoperitoneum
Blood retention in peritoneal cavity.
XT5 Acute
XT8W Chronic

NB97.0 Retroperitoneal haemorrhage or haematoma
Traumatic retroperitoneal haemorrhage or haematoma

GB56 Obstructive or reflux nephropathy

GB56.0 Hydronephrosis with ureteropelvic junction obstruction
A condition caused by any obstruction in or stenosis of the ureteropelvic junction. This condition is characterised by distension of the pelvis and calyces of the kidney with a partial or complete obstructed flow of urine. This condition may present with flank pain, haematuria, pyuria, or hyperpyrexia.

GB56.1 Hydronephrosis with ureteral obstruction
Intrinsic stenosis or stricture or extrinsic obstruction of the ureter, except at the ureteropelvic junction or at the ureteral orifice, causing distension of the pelvis and calices of the kidney with urine.

GB56.2 Hydronephrosis with ureteral orifice obstruction
Dilatation of the renal pelvis and calyces associated with (and presumably due to) obstruction of the ureter at the insertion into the bladder and hence ascending back pressure.

GB56.3 Hydronephrosis due to bladder obstruction
A condition caused by an obstruction in the urinary bladder. It is characterised by distention of the pelvis and calices of one or both kidneys, and lack of free flow of urine from the kidney, and can lead to progressive atrophy of the kidney if untreated. The condition may also present with pain in the flank, haematuria, pyuria, or hyperpyrexi

GB56.4 Other or unspecified hydronephrosis

GB56.5 Hydronephrosis and reflux nephropathy with vesicoureteral or vesico-uretero-renal reflux

GB61 Chronic kidney disease
GFR <60 or presence of kidney damage that is present for more than 3 months. Evidence of kidney damage can include structural abnormalities (imaging or histology), albuminuria above normal limits, urinary sediment abnormalities or electrolyte disturbances due to tubular disorders.

GB90.1 Hydroureter
A condition caused by obstruction, stricture, or stenosis of the ureter, which may be due to prostatic hypertrophy, carcinoma, retroperitoneal or pelvic neoplasms, calculi, or a congenital anomaly. This condition is characterised by distention of the ureter with urine.

CHAPTER 13: Diseases of the digestive system

DA91 Obstruction of small intestine
Hindrance of the passage of luminal contents in the small intestine. Obstruction of the small intestine can be partial or complete, and caused by intrinsic or extrinsic factors. Simple obstruction is associated with diminished or stopped flow of luminal contents. Strangulating obstruction is associated with impaired blood flow to the small intestine in addition to obstructed flow of luminal contents.

DA91.0 Intussusception of small intestine

DA91.1 Volvulus of small intestine

DA91.2 Intestinal adhesions or bands of small intestine with obstruction
Small bowel obstruction resulting from intraabdominal adhesion due to laparotomy, trauma, and intraabdominal inflammation such as endometriosis

DB30 Obstruction of large intestine

DB30.2 Adhesions of large intestine with obstruction
Large bowel obstruction resulting from intraabdominal adhesion due to laparotomy, trauma, and intraabdominal inflammation such as endometriosis.

CHAPTER 12 : Diseases of the respiratory system

CB21 Pneumothorax
Pneumothorax is an abnormal collection of air or gas in the pleural space that separates the lung from the chest wall, and that may interfere with normal breathing.

CB21.Y Other specified pneumothorax
Catamenial pneumothorax

Pleural, diaphragm or mediastinal disorders

CB23 Disorders of diaphragm
Diaphragm Paralysis
This category includes the abnormalities of diaphragmatic position or motion (paralysis, relaxation, and acquired deformity) and the inflammation of the diaphragm, but neoplasms of the diaphragm, congenital malformation of diaphragm, and diaphragmatic hernias are included in other categories.

CB26 Haemothorax
Hemothorax is the presence of blood with or without air in the pleural space. The most common cause is chest trauma. Hemothorax should be considered to be present when the haematocrit of the pleural fluid is more than half that of the peripheral blood. A number of bleeding sites may be responsible for the hemothorax, including pulmonary laceration, intercostal vessel laceration, and rupture of pleural adhesions.

CB27 Pleural effusion
Presence of fluid in the pleural cavity resulting from excessive transudation or exudation from the pleural surfaces.

CHAPTER 11: Diseases of the circulatory system

Pericarditis
BB24 Haemopericardium
Hemopericardium generally refers to blood in the pericardial sac of the heart. It is clinically similar to a pericardial effusion, and, depending on the volume and rapidity with which it develops, may cause cardiac tamponade.

BB25 Pericardial effusion
Pericardial effusion is an abnormal accumulation of fluid in the pericardial sac.

Abdominal Wall Endometriosis and CCC:
The scar of cesarean section (CS) is the most common site of abdominal wall endometriosis (AWE). Tumor degeneration has been reported in an increasing number of cases; the most frequent histological type is clear cell carcinoma (CCC). Lymph nodes involvement was detected in 26% patients. The average time between the last CS and the diagnosis of CCC was around 15 years. 15% patients died of disease, 32% had no evidence of disease, and 17% recurred.

CHAPTER 16

Acquired abnormalities of uterus, except cervix

• GA16.0 Endometrial glandular hyperplasia
A condition of the uterus, caused by chronic, excess oestrogen stimulation due to obesity, anovulation, or oestrogen therapy. This condition is characterised by excessive proliferation of the endometrial gland cells and a greater gland-to-stroma ratio of endometrial cells. This condition may also present with abnormal uterine bleeding, particularly among postmenopausal women and premenopausal women of increasing age. Confirmation is by sampling endometrial tissue through biopsy or dilation and curettage.

• GA16.1 Malposition of uterus
A condition of the uterus, caused by weakened pelvic ligaments, enlargement of the uterus, scarred pelvic tissue from pregnancy, tumour, menopause, endometriosis, inflammation, or salpingitis. This condition is characterised by a deviation in the position of the uterus from normal.

• GA16.2 Intrauterine synechiae
Intrauterine adhesions caused by pelvic inflammatory disease, uterine surgery, or complications related to spontaneous, incomplete or induced abortion. May be asymptomatic or associated with amenorrhea or light menstrual bleeding and subfertility.

Acquired abnormalities of fallopian tube

• GA17.3 Haematosalpinx
A condition of the Fallopian tube, caused by tubal pregnancy, endometriosis, tubal carcinoma, or cryptomenorrhoea. This condition is characterised by bleeding and the presence of blood clots inside the Fallopian tubes, and pelvic pain or uterine bleeding. Confirmation is by imaging.

Symptoms, signs or clinical findings of the immune system

MA01 Enlarged lymph nodes
MA01.0 Localised lymph node enlargement
MA01.1 Generalised lymph node enlargement

CHAPTER 18: Pregnancy, childbirth or the puerperium

JA05 Complications following abortion, ectopic or molar pregnancy
JA05.0 Endometriosis following pregnancy or abortion

CHAPTER 21

GA10.B Endometriosis in cutaneous scar
Clinical history and imaging findings are necessary for the diagnosis of abdominal wall endometriosis. Its management is challenging, and requires close collaboration between gynaecologists and visceral surgeons specially in complex procedures. Endometrial cells, both stroma and epithelium, are mechanically transferred to the abdominal fascia or subcutaneous tissue around sites of incision following procedures such as cesarean sections, hysterectomies, myomectomies appendectomies, tubal ligations and episiotomies.

MG30.4 Umbilicus
XA3KX0 Abdominal wall
- XA4SN6 Anterior abdominal wall
- XA0NH8 Iliac region
- XA1DN2 Lateral lumbar region
- XA1LM1 Periumbilical region
- XA3MT8 Umbilicus
- XA0LF4 Suprapubic area
- XA8ZL8 Epigastrium
- XA3TD4 Hypochondrium
- XA00B4 Inguinal canal

Associated with (use additional code, if desired.)
• PK80.30 Gastrointestinal, abdominal, or abdominal wall procedure associated with injury or harm, open approach

• PK80.32 Gastrointestinal, abdominal, or abdominal wall procedure associated with injury or harm, endoscopic approach

Ferrari, F., Valenti, G., Forte, S., Ardighieri, L., Iraci Sareri, M., Barra, F., Sartori, E. and Odicino, F. (2021), Clear cell degeneration associated with endometriosis of abdominal wall after cesarean section: A case report and systematic review of literature. J. Obstet. Gynaecol. Res., 47: 1243- 1252.

Iatrogenic lesions and artefacts in gynaecological pathology

Increasingly in the field of medicine, new therapeutic modalities, both surgical and non-surgical, are being introduced. Some of these may significantly alter the pathological appearance of normal and neoplastic tissue and result in problems for the pathologist. Iatroogenic include mechanical displacement of normal and neoplastic elements into vascular or tissue spaces and thermal artefacts. Recently described pathological findings in neoplastic and nonneoplastic tissue secondary to hormonal, chemotherapeutic and other medications are discussed. Changes associated with non-surgical management of uterine leiomyomas are also described. It behoves the pathologist to be aware of these iatrogenic lesions and artefacts in order to prevent diagnostic errors.

MECHANICAL ARTEFACTS

Mechanical effects at the time of surgery or routine grossing of pathology specimens may result in artefactual displacement of tissue, normal or neoplastic, into vascular or tissue spaces with obvious resultant diagnostic problems.

- Displacement of endometrial tissue into lymphovascular channels
- Displaced ovarian granulosa cells

THERMAL ARTEFACTS

- Cervix
- Endometrium
- Fallopian tube
- Ovary and peritoneum

CHEMOTHERAPY INDUCED CHANGES

- Neoadjuvant therapy for ovarian cancer
- Taxane effect on the endometrium

HORMONAL THERAPIES

- Mirena coil
- Progesterone receptor modulators (PRMs)

NON-SURGICAL MANAGEMENT OF UTERINE LEIOMYOMAS

- Gonadotropin releasing hormone agonists
- Uterine artery embolisation

XB8D Iatrogenic

Iatrogenic endometriosis (IE) is defined by the appearance of endometrial glands and stroma outside the uterus following certain surgical procedures, including hysterectomy, myomectomy, cesarean section, and the endometrial tissue seeding of surgical scars during these operations. Gynecologic surgery includes adenomyosis, uterine leiomyomas, and fibroids. Iatrogenic mechanism of the endometrial cell spread to the peritoneal cavity and abdominal wall raises awareness of the need for careful management of surgical interventions involving the uterus. Cesarean scars such as skin and uterine scars, trocar insertion sites, sigmoid colon, ovaries, bladder, vaginal vault, and parietal peritoneum are the most prevalent locations.

Clarke B, McCluggage WG. Iatrogenic lesions and artefacts in gynaecological pathology. J Clin Pathol. 2009 Feb;62(2):104-12. doi: 10.1136/jcp.2008.061424. Epub 2008 Oct 6. PMID: 18838400.

Rare types of endometriosis

Intramedullary

Most cases of IEM present a mass with hematoma. Thus, the differential diagnosis includes underlying neoplasm or vascular lesion. Patients who present with occupancy of the nidus in the spinal canal might suffer from spinal cord- or cauda equina-related deficits. IEM demonstrates the importance of maintaining a broad differential diagnosis when evaluating spinal cord injuries and the necessity of a comprehensive history for each patient. Young female patients with acute or menstruation-related neurological symptoms should raise suspicion for IEM. Most IEM reported cases are associated with an actively bleeding mass. However, a mass intraspinal lesion without evident hematoma must also include EM as a differential diagnosis. Moreover, timely intervention and appropriate management in patients with neurological symptoms can control the disease and improve neurological function.

Beck T B, Carbonar M F, Hanel R, et al. (April 20, 2021) Intramedullary Endometriosis of the Conus Medullaris. Cureus 13(4): e14581. doi:10.7759/cureus.14581

Endometriosis of the Eyelid, an Extraordinary Extra-abdominal Location Highlighting the Spectrum of Disease

Ocular surface changes, including squamous metaplasia, may be observed in the conjunctiva of patients with endometriosis. Symptoms include bleeding of the eye. Evaluation of the ocular surface by impression cytology in patients with endometriosis.

Graefes Arch Clin Exp Ophthalmol. 2020

Postprocedural disorders of genitourinary system

GA34.5 Ovarian remnant syndrome
Chronic pelvic pain in a patient after bilateral salpingooophorectomy for severe endometriosis or PID, caused by residual ovarian cortical tissue left in situ after difficult dissection. Symptoms may include lateralizing pelvic pain, often cyclic and associated with genitourinary or gastrointestinal symptoms. Signs may include a tender mass in the lateral region of the pelvis.

GC70 Postoperative adhesions of vagina
A condition caused by or subsequent to any vaginal surgery or intervention. This condition is characterised by fibrous bands of scar tissue between the intravaginal tissues (intravaginal adhesions). This condition may also present with pelvic pain and dyspareunia.

GC71 Prolapse of vaginal vault after hysterectomy
A condition of the vagina, caused by or subsequent to hysterectomy. This condition is characterised by descensus of the vaginal vault that may also lead to weakening of the vaginal walls.

GC72 Postprocedural urethral stricture
Urethral stricture caused by catheterization, transurethral manipulations (e.g. transurethral resections), urethral instillations, or irradiation exposure

GC73 Postprocedural pelvic peritoneal adhesions
A condition caused by or subsequent to any pelvic intervention leading to damage and inflammation of the peritoneum. This condition is characterised by fibrous bands of scar tissue and abnormal connection between pelvic organs or tissues. This condition may also present with pelvic pain or bowel obstruction. Exclusions: Endometriosis

GC74 Malfunction or complication of external stoma of urinary tract
A condition caused by a surgically created opening connecting the urinary tract to the external environment. This condition is characterised by dysfunction or decreased function of the incision.
Associated with
> Surgical or other medical procedures associated with injury or harm in diagnostic or therapeutic use
> Surgical or other medical devices, implants or grafts associated with injury or harm in therapeutic use

GC75 Malfunction of the afferent segment of a continent urinary pouch
A condition characterised by the dysfunction or lack of function of a surgically created urine reservoir within the body, specifically along the path by which urine enters the pouch.

GC76 Malfunction of the efferent segment of a continent urinary pouch
A condition characterised by the dysfunction or lack of function of a surgically created urine reservoir within the body, specifically along the path by which urine exits the pouch.

GC77 Postprocedural nonmenstrual uterine bleeding

GC78 Postprocedural acute female pelvic inflammatory disease

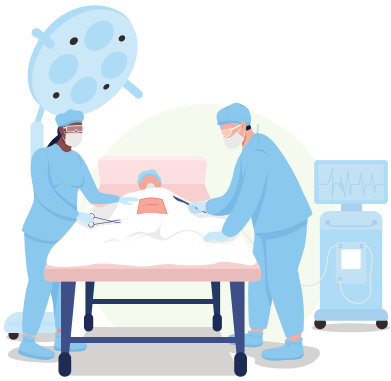
GC7B Postinterventional ischemia or infarction of kidney
This refers to a restriction in blood supply to tissues of the kidney due to a health care intervention causing a shortage of oxygen and glucose needed for cellular metabolism resulting in the death of kidney tissue cells.
Postprocedural disorders of digestive system

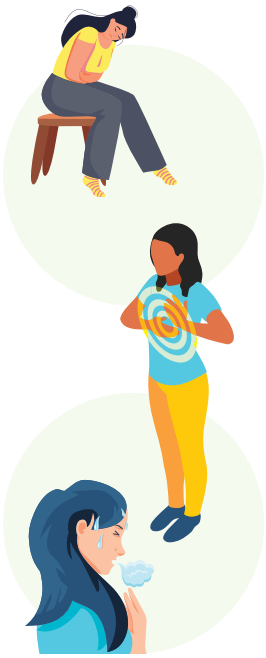
Postprocedural disorders of digestive system

DE10 Vomiting following gastrointestinal surgery

Postprocedural disorders of respiratory system

CB61 Chronic pulmonary insufficiency following surgery



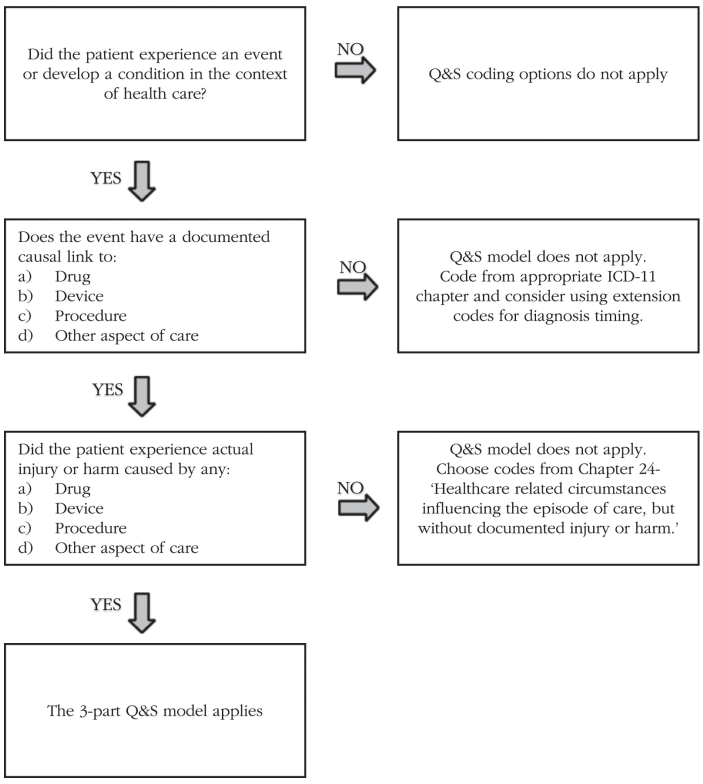


Causes of healthcare Related harm	Code for mode/mechanism	Code description
Surgical or other medical procedure	PL11	Mode of injury or harm associated with a surgical or other medical procedure
(any of codes PK80-PK8Z)	PL11.0	Cut, puncture or tear, as mode of injury or harm
	PL11.1	Burn arising during procedure, as mode of injury or harm
	PL11.2	Embolisation, as mode of injury or harm
	PL11.20	Air embolism, as mode of injury
	PL11.3	Foreign body accidentally left in body, as mode of injury or harm
	PL11.4	Failure of sterile precautions, as mode of injury or harm
	PL11.5	Procedure undertaken at wrong site or wrong side, as mode of injury or harm
	PL11.6	Pressure, as mode of injury or harm
Surgical or other medical device, implant or graft	PL12	Mode of injury or harm associated with a surgical or other medical device, implant or graft
(any of codes PK90-PK9C)	PL12.0	Structural device failure, as mode of injury or harm
	PL12.1	Functional device failure, as mode of injury or harm
	PL12.2	Perforation or protrusion by device, as mode of injury or harm
	PL12.3	Obstruction of device, as mode of injury or harm
	PL12.4	Dislodgement, misconnection or de-attachment, as mode of injury or harm
	PL12.5	Operator error, as mode of injury or harm
	PL12.6	Combination or interaction of operator error and device failure, as mode of injury or harm
Drug, medicament or biological substance	PL13	Mode of injury or harm associated with exposure to a drug, medicament or biological substance
(Code PL00)	PL13.0	Overdose of substance, as mode of injury or harm
	PL13.1	Underdosing, as mode of injury or harm
	PL13.2	Drug-related injury or harm in the context of correct administration or dosage, as mode of injury or harm
	PL13.3	Incorrect substance, as mode of injury or harm
	PL13.5	Incorrect administration of drug or medicament, as mode of injury
	PL13.50	Incorrect route of drug or medicament, as mode of injury
	PL13.51	Incorrect rate of drug or medicament, as mode of injury
	PL13.52	Incorrect timing of drug or medicament, as mode of injury
	PL13.53	Incorrect duration of drug or medicament, as mode of injury
	PL13.6	Medication or substance that is known to be an allergen, as mode of injury or harm
	PL13.7	Medication or substance that is known to be contraindicated for the patient, as mode of injury or harm
	PL13.8	Expired or deteriorated medication or substance, as mode of injury or harm
	PL13.9	Drug or substance interactions, as mode of injury or harm
	PL13.A	Inappropriate stoppage or discontinuation of drug, as mode of injury or harm
Other healthcare-related causes	PL14	Mode of injury or harm associated with other healthcare-related causes
(Code PL10)	PL14.0	Non-administration of necessary drug
	PL14.1	Non provision of necessary procedure
	PL14.2	Problem associated with physical transfer of patient
	PL14.3	Mismatched blood used in transfusion
	PL14.4	Other problem associated with transfusion
	PL14.5	Problem associated with physical restraints
	PL14.6	Problem associated with isolation protocol
	PL14.7	Problem associated with clinical documentation
	PL14.8	Problem associated with clinical software
	PL14.9	Incorrect diagnosis
	PL14.A	Delayed diagnosis
	PL14.B	Delayed treatment
	PL14.C	Patient received diagnostic test or treatment intended for another patient
	PL14.D	Problem associated with transitions of care, hand offs, or handovers
	PL14.E	Fall in healthcare

Quality and safety of health care exemplifies the potential of clustering. Consider a person admitted to hospital for a surgical procedure who experiences a complication of care. ICD-11-MMS allows for coding of the disease for which surgery was undertaken (that would be the subject of one cluster) and of the complication. A code cluster on the latter can record the harm sustained (e.g., marked nausea and vomiting after surgery), the medication involved (perhaps a particular anesthetic agent), and how the problem came about (e.g., dose too high or too low, or administered at the wrong time). Extension codes can also record whether a condition had been recognized as present when the episode of care began.

Decision algorithm for when to use the ICD-11 3-part model for healthcare harms

Using the decision-tree of the 3-part model helps identify and code harm or patient safety event more accurately. The 3-part model also helps add information about the circumstances which may have contributed to the injury. The decision tree helps gather the proper information and simplifies the decision points for coders. It is vital to distinguish between which medical event can be classified as harm and which cannot be classified as harm. Information for cause and mode can be grouped as healthcare-related harm and used for quality improvement purposes [4]. Future harms may be avoided if the actions which led to the injury or harm are documented and studied.



Achieving reliable pain change scores for individuals in the postoperative phase: carefully choose sampling density, test length, and administration mode

Despite tremendous efforts to increase the reliability of pain measures and other self-report instruments, improving or even evaluating the reliability of change scores has been largely neglected.

(1) that near perfect reliability can be achieved if measures from all days over the whole study period, obtained with all pain interference or pain behavior items, were used to estimate the observed change,
(2) that various combinations of the number of items and the number of measurement occasions could achieve acceptable reliability, and
(3) that computer adaptive testings were superior to short forms in achieving sufficient reliability. We conclude that the specific strategy for assessing individual postoperative change in pain experience must be selected carefully.

Surgery Timing

Immediate

Minutes

Surgery: respiratory failure, lung collapse, heart failure

Urgent

Hours

Surgery: bowel/urinary obstruction, diaphragm paralysis

Expedited

Days

Surgery: lesions with the potential to bleed or obstruct

Elective

Planned

Surgery: remove endometriosis lesions and adhesions

7 types of surgery account for 80% of all hospital admissions

- Partial colectomy
- Small-bowel resection
- Gall bladder removal
- Peptic ulcer disease
- Abdominal adhesions
- Appendectomy
- Laparotomy

Obbarius, Alexandera,b,; Schneider, Stefana; Junghaenel, Doerte U.a; Stone, Arthur A.a,c. Achieving reliable pain change scores for individuals in the postoperative phase: carefully choose sampling density, test length, and administration mode. PAIN: January 2022 - Volume 163 - Issue 1 - p 170-179 doi: 10.1097/j.pain.0000000000002328*

Endometriosis

ICD-11

Signs, Symptoms and Clinical Findings

Symptoms, signs or clinical findings

Reproductive
MD82 Intra-abdominal or pelvic swelling, mass or lump
GA12 Dyspareunia (Painful Intercourse)

Urinary System
MF50.0 Frequent micturition
MF50.2 Urinary incontinence
MF50.7 Dysuria (Pain)
MF50.4 Haematuria

Digestive system or abdomen
MD81 Abdominal or pelvic pain
MD82 Intra-abdominal or pelvic swelling, mass or lump

Upper gastrointestinal tract
MD90.0 Nausea
MD90.1 Vomiting

Lower gastrointestinal tract or abdomen
ME01 Abdominal distension
ME05 Change in bowel habit
• ME05.0 Constipation
• ME05.1 Diarrhoea
ME24.A3 Haematochezia
ME24.A4 Melaena
ME24.A6 Positive occult blood in stool

Thoracic
MD11.5 Dyspnoea (Shortness of Breath)
MD30.0 Chest pain on breathing
MC81.0 Tachycardia
MC81.2 Heart Palpitations
MD22 Haemoptysis (Coughing up blood)
CB26 Haemothorax
CB27 Pleural effusion

Diaphragm > Phrenic Nerve
MD20 Epistaxis (Nose Bleeds)
AB70.2 Otalgia (Earache)
8A06.21 Chronic Hiccups

Musculoskeletal
ME81 Musculoskeletal chest pain
ME84.2 Low back pain
ME84.3 Sciatica Nerve
ME86.D Symptom or complaint of the shoulder
ME86.C Symptom or complaint of the neck

Female pelvic pain

GA34 Female pelvic pain associated with genital organs or menstrual cycle
A symptom affecting females, characterised by pain in the pelvic region associated with any of the genital organs or the menstrual cycle.
• GA34.0 Pain related to vulva, vagina or pelvic floor
• GA34.00 Vulval pain
• GA34.01 Perineal pain
• GA34.02 Vulvodynia

GA34.1 Vaginal laxity

GA34.2 Female pelvic pain
A symptom affecting females, caused by gynaecological and physiological aspects associated with the menstrual cycle such as dysmenorrhoea or mittelschmertz. This symptom is characterised by recurrent pain in the pelvis, anterior abdominal wall, lower back, or buttocks, associated with a specific moment or period of time.
• GA34.20 Cyclic pelvic pain
• GA34.21 Noncyclic pelvic pain

GA34.3 Dysmenorrhoea
A condition of the genital system caused by endometriosis, adenomyosis, ovarian cysts, or may be idiopathic. This condition is characterised by cyclic pelvic pain preceding or accompanying menstruation that interferes with daily activities, lower, umbilical, or suprapubic abdominal pain, such as sharp, throbbing, burning, or shooting pains that may extend to the thighs and lower back.

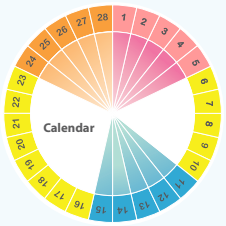
GA20 Menstrual cycle bleeding disorders

GA20.0 Amenorrhoea
  GA20.00 Primary amenorrhoea
  GA20.01 Secondary amenorrhoea
GA20.1 Abnormal frequency of uterine bleeding
GA20.2 Ovulation bleeding
  GA20.20 Intermenstrual bleeding
GA20.3 Abnormal regularity of uterine bleeding
GA20.4 Abnormal duration of uterine bleeding
GA20.5 Abnormal volume of uterine bleeding
  GA20.50 Heavy menstrual bleeding
GA20.51 Light menstrual bleeding
GA21 Nonmenstrual bleeding disorders
GA22 Excessive menstruation with irregular cycle
GA23 Anovulatory bleeding

Traditional Medicine (TCM)-Supplementary Chapter
The International Classification of Traditional Medicine Treatments range from acupuncture, herbal medicine, Tai Qi and medical massage. Traditional medicine can provide support to patients who suffer from chronic pain.

Menstruation cycle disorders

SB80 Advanced menstruation disorder
SB81 Delayed menstruation disorder
SB82 Irregular menstruation disorders
SB90 Menorrhagia disorder
SB91 Decreased menstruation disorder
SB92 Prolonged menstruation disorder
SB93 Metrorrhagia disorder
SB94 Amenorrhea disorder
SB95 Menopausal disorder
SB96 Dysmenorrhea disorder
SC22 Infertility Disorder



CH:7 Sleep-wake disorders

Circadian rhythm sleep-wake disorders

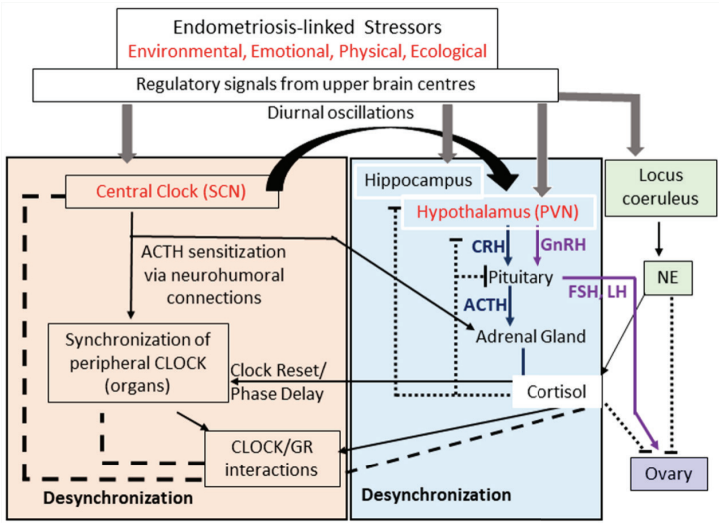
Circadian rhythm sleep-wake disorders are disturbances of the sleep-wake cycle (typically manifest as insomnia, excessive sleepiness, or both) due to alterations of the circadian time-keeping system, its entrainment mechanisms, or a misalignment of the endogenous circadian rhythm and the external environment. Sleep logs and, if possible, actigraphy for a minimum of one week should be utilized to define the specific sleep-wake schedule disturbance.

7A62 Irregular sleep-wake rhythm disorder

Irregular sleep-wake rhythm disorder is characterised by absence of a clearly-defined cycle of sleep and wake. Sleep becomes distributed in multiple episodes of variable duration throughout the 24-hour period. Patients typically complain of insomnia and/or excessive daytime sleepiness as a result of the condition. The symptoms should have persisted for at least several months and result in significant distress or mental, physical, social, occupational or academic impairment.

7A23 Hypersomnia due to a medical condition

Hypersomnia due to a medical condition is characterised by excessive nocturnal sleep, daytime sleepiness, or excessive napping of at least several months duration that is attributable to a coexisting medical or neurological disorder and is sufficiently severe to require an independent focus of clinical attention.



Circadian Rhythm

Women with endometriosis are often under stress due to the associated pain, infertility, inflammation-related and other comorbidities including cancer. Additionally, these women are also under stress due to taboos, myths, inter-personal troubles surrounding infertility and pain of the disease as well as due to frequent incidences of missed diagnosis and treatment recurrence. Often these women suffer from frustration and loss of valuable time in the prime phase of life. All these complexities integral to endometriosis posit a hyperstructure of integrative stress physiology with overt differentials in effective allostatic state in women.

Ghosh D, Filaretova L, Bharti J, Roy KK, Sharma JB, Sengupta J. Pathophysiological Basis of Endometriosis-Linked Stress Associated with Pain and Infertility: A Conceptual Review. Reproductive Medicine. 2020; 1(1):32-61. https://doi.org/10.3390/reprodmed1010004

Overall Symptoms

MG22 Fatigue

A feeling of exhaustion, lethargy, or decreased energy, usually experienced as a weakening or depletion of one's physical or mental resource and characterised by a decreased capacity for work and reduced efficiency in responding to stimuli. Fatigue is normal following a period of exertion, mental or physical, but sometimes may occur in the absence of such exertion as a symptom of health conditions.

DA96.02 Malabsorption or intolerance of specific nutrients

Food intolerance is a term used for difficulty in digesting a food because of widely for varied physiological responses associated with a particular food, or compound found. Food intolerance should not be mistaken for food allergy, which is primarily involving the immune reaction against the food.

GB23.5 Mastodynia

The symptom of breast pain. This symptom may be classified as cyclic or non-cyclical depending on the clinical patterns

Premenstrual Symptoms

MF33 Premenstrual symptom - PMS

A symptom of premenstrual syndrome affecting females that is idiopathic. This symptom is characterised by cyclic emotional, physical, or behavioural symptoms such as mood alterations, psychological changes, fluid retention, neurologic changes, gastrointestinal changes, pelvic heaviness, or dermatological changes affecting women in the luteal phase of the menstrual cycle that interfere with an individual's lifestyle.

GA34.40 Premenstrual tension syndrome - PMT Menstrual Migraine

A syndrome affecting females that is frequently idiopathic. This syndrome is characterised by certain environmental, metabolic, or behavioural factors that occur during the luteal phase of the menstrual cycle, and leads to cyclic emotional, physical, or behavioural symptoms that interfere with an individual's lifestyle. Confirmation is by documentation of specific cyclic symptoms associated with the luteal and menstrual phases of the cycle (from a prospective symptom diary), and evidence of socioeconomic dysfunction.

GA34.41 Premenstrual dysphoric disorder - PMDD

During a majority of menstrual cycles within the past year, a pattern of mood symptoms (depressed mood, irritability), somatic symptoms (lethargy, joint pain, overeating), or cognitive symptoms (concentration difficulties, forgetfulness) that begin several days before the onset of menses, start to improve within a few days after the onset of menses, and then become minimal or absent within approximately 1 week following the onset of menses. The temporal relationship of the symptoms and luteal and menstrual phases of the cycle should ideally be confirmed by a prospective symptom diary over at least two symptomatic menstrual cycles. The symptoms are severe enough to cause significant distress or significant impairment in personal, family, social, educational, occupational or other important areas of functioning and do not represent the exacerbation of a mental disorder.

Anxiety and Depression

In ICD-11, anxiety disorders that manifest across the lifespan are brought together under a new grouping, and are partly distinguished by their focus of apprehension. The focus of apprehension is the stimulus or situation that triggers the fear or anxiety. The qualifier 'with prominent anxiety symptoms', introduced in the ICD-11, is of special clinical interest. The presence of a significant anxiety component in a depressive episode is associated with a higher suicide risk, a longer duration of illness and a greater likelihood of non-response to treatment.

In the ICD-11, a depressive episode is defined by the concurrent presence of at least five out of a list of ten symptoms, which must occur most of the day, nearly every day, for at least 2 weeks. One of these symptoms must be depressed mood or markedly diminished interest or pleasure in activities. The mood disturbance must result in significant functional impairment and not be a manifestation of another health condition, or due to the effects of a substance or medication. The ten symptoms are depressed mood, markedly diminished interest or pleasure in activities, reduced ability to concentrate and sustain attention or marked indecisiveness, beliefs of low self-worth or excessive or inappropriate guilt, hopelessness about the future, recurrent thoughts of death or suicidal ideation or evidence of attempted suicide, significantly disrupted sleep or excessive sleep, significant changes in appetite or weight, psychomotor agitation or retardation, and reduced energy or fatigue. The list includes one symptom (hopelessness). The ICD-11 states that a depressive episode is differentiated from a normal reaction to adverse life events (e.g. divorce, job loss) "by the severity, range and duration of symptoms".

The acknowledgment of stress as an external source of mental disorders is still relatively new in psychiatric nosology despite recognition that almost all mental disorders, to a greater or lesser degree, are shaped by it. The ICD-11 includes a new grouping of 'disorders specifically associated with stress' that identifies disorders in which external stress is a necessary and prominent causal factor. Depressive disorders are characterised by depressive mood (e.g., sad, irritable, empty) or loss of pleasure accompanied by other cognitive, behavioural, or neurovegetative symptoms that significantly affect the individual's ability to function. A depressive disorder should not be diagnosed in individuals who have ever experienced a manic, mixed or hypomanic episode, which would indicate the presence of a bipolar disorder.

Disorders Specifically Associated with Stress

Disorders specifically associated with stress are directly related to exposure to a stressful or traumatic event, or a series of such events or adverse experiences. For each of the disorders in this grouping, an identifiable stressor is a necessary, though not sufficient, causal factor.

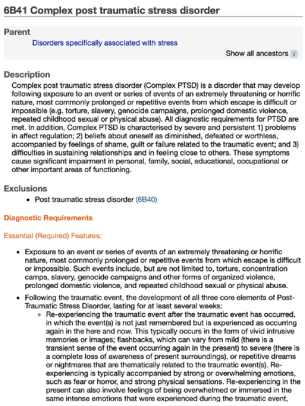
Overall Symptoms

Mental or behavioural symptoms,signs or clinical findings
MB24.3 Anxiety
MB22.3 Hopelessness
MB23.H Panic attack
MB23.R Suicide attempt
Coded Elsewhere: Premenstrual dysphoric disorder (GA34.41)

Disorder

6B42 Prolonged grief disorder
6B43 Adjustment disorder
QE84 Acute stress reaction

6B41 Complex post traumatic stress disorder (New)



6B41 Complex post traumatic stress disorder

Parent
Disorders specifically associated with stress
Show all ancestors

Description
Complex post traumatic stress disorder (Complex PTSD) is a disorder that may develop following exposure to an event or series of events of an extremely threatening or horrific nature, most commonly prolonged or repetitive events from which escape is difficult or impossible (e.g. torture, slavery, genocide campaigns, prolonged domestic violence, repeated childhood sexual or physical abuse). All diagnostic requirements for PTSD are met. In addition, Complex PTSD is characterised by severe and persistent 1) problems in affect regulation; 2) beliefs about oneself as diminished, defeated or worthless, accompanied by feelings of shame, guilt or failure related to the traumatic event; and 3) difficulties in sustaining relationships and in feeling close to others. These symptoms cause significant impairment in personal, family, social, educational, occupational or other important areas of functioning.

Exclusions
- Post traumatic stress disorder (6B40)

Diagnostic Requirements

Essential (Required) Features:

- Exposure to an event or series of events of an extremely threatening or horrific nature, most commonly prolonged or repetitive events from which escape is difficult or impossible. Such events include, but are not limited to, torture, concentration camps, slavery, genocide campaigns and other forms of organized violence, prolonged domestic violence, and repeated childhood sexual or physical abuse.
- Following the traumatic event, the development of all three core elements of Post-Traumatic Stress Disorder, lasting for at least several weeks:
  - Re-experiencing the traumatic event after the traumatic event has occurred, in which the event(s) is not just remembered but is experienced as occurring again in the here and now. This typically occurs in the form of vivid intrusive memories or images; flashbacks, which can vary from mild (there is a transient sense of the event occurring again in the present) to severe (there is a complete loss of awareness of present surroundings), or repetitive dreams or nightmares that are thematically related to the traumatic event(s). Re-experiencing is typically accompanied by strong or overwhelming emotions, such as fear or horror, and strong physical sensations. Re-experiencing in the present can also involve feelings of being overwhelmed or immersed in the same intense emotions that were experienced during the traumatic event.

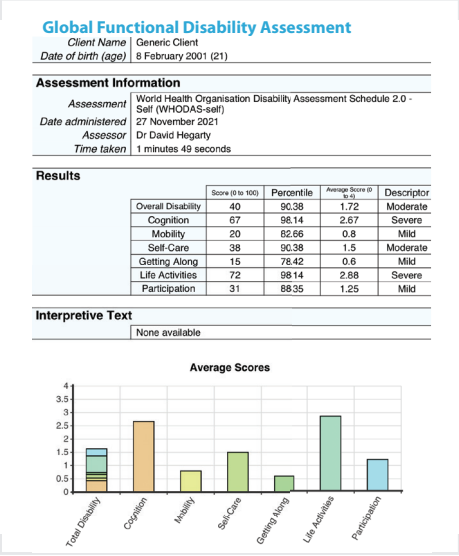
Caregiver Burnout

QF27 Difficulty or need for assistance at home and no other household member able to render care

Endometriosis and the WHO Functional Assessment
International Classification of Functioning, Disability and Health (ICF)

It integrates an individual's level of functioning in major life domains and directly corresponds with ICF's "activity and participation" dimensions. WHODAS 2.0 was developed through a collaborative international approach with the aim of developing a single generic instrument for assessing health status and disability across different cultures and settings. In ICD-11, links with ICF have been created in terms of aligning the concepts of disease and functioning and facilitating the joint use. Conceptual alignment between ICD-11 and ICF has taken place in several areas. Signs and symptoms in the ICD are aligned with body functions in the ICF, and 'factors influencing health status' in the ICD align with contextual.

A short, simple and easy to administer (5 to 20 minutes)
Applicable in both clinical and general population settings.
A tool to produce standardized disability levels and profiles.
Applicable across cultures, in all adult populations.



Global Functional Disability Assessment

Client Name	Generic Client
Date of birth (age)	8 February 2001 (21)

Assessment Information

Assessment	World Health Organisation Disability Assessment Schedule 2.0 - Self (WHODAS-self)
Date administered	27 November 2021
Assessor	Dr David Hegarty
Time taken	1 minutes 49 seconds

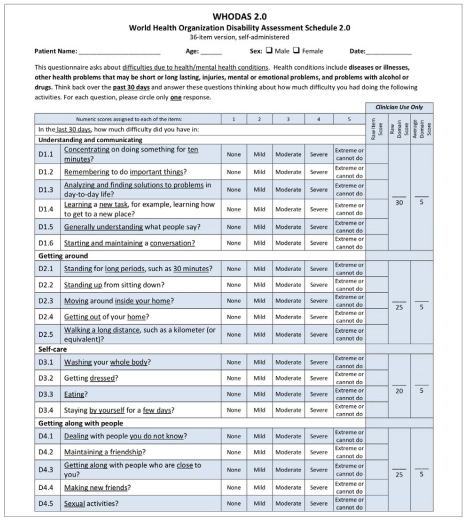
Results

	Score (0 to 100)	Percentile	Average Score (0 to 6)	Descriptor
Overall Disability	40	90.38	1.72	Moderate
Cognition	67	98.14	2.67	Severe
Mobility	20	82.66	0.8	Mild
Self-Care	38	90.38	1.5	Moderate
Getting Along	15	78.42	0.6	Mild
Life Activities	72	98.14	2.88	Severe
Participation	31	88.35	1.25	Mild

Interpretive Text

None available

Average Scores



WHODAS 2.0
World Health Organization Disability Assessment Schedule 2.0
36-item version, self-administered

Patient Name: _____ Age: _____ Sex: ☐ Male ☐ Female Date: _____

This questionnaire asks about difficulties due to health/mental health conditions. Health conditions include **diseases or illnesses, other health problems that may be short or long lasting, injuries, mental or emotional problems, and problems with alcohol or drugs.** Think back over the **past 30 days** and answer these questions thinking about how much difficulty you had doing the following activities. For each question, please circle only **one** response.

Numeric scores assigned to each of the items:		1	2	3	4	5	Clinician Use Only: Raw Item Score	Domain Score	Average Domain Score
In the last 30 days, how much difficulty did you have in:									
Understanding and communicating									
D1.1	Concentrating on doing something for ten minutes?	None	Mild	Moderate	Severe	Extreme or cannot do			
D1.2	Remembering to do important things?	None	Mild	Moderate	Severe	Extreme or cannot do			
D1.3	Analyzing and finding solutions to problems in day-to-day life?	None	Mild	Moderate	Severe	Extreme or cannot do			
D1.4	Learning a new task, for example, learning how to get to a new place?	None	Mild	Moderate	Severe	Extreme or cannot do		30	5
D1.5	Generally understanding what people say?	None	Mild	Moderate	Severe	Extreme or cannot do			
D1.6	Starting and maintaining a conversation?	None	Mild	Moderate	Severe	Extreme or cannot do			
Getting around									
D2.1	Standing for long periods, such as 30 minutes?	None	Mild	Moderate	Severe	Extreme or cannot do			
D2.2	Standing up from sitting down?	None	Mild	Moderate	Severe	Extreme or cannot do			
D2.3	Moving around inside your home?	None	Mild	Moderate	Severe	Extreme or cannot do		25	5
D2.4	Getting out of your home?	None	Mild	Moderate	Severe	Extreme or cannot do			
D2.5	Walking a long distance, such as a kilometer (or equivalent)?	None	Mild	Moderate	Severe	Extreme or cannot do			
Self-care									
D3.1	Washing your whole body?	None	Mild	Moderate	Severe	Extreme or cannot do			
D3.2	Getting dressed?	None	Mild	Moderate	Severe	Extreme or cannot do			
D3.3	Eating?	None	Mild	Moderate	Severe	Extreme or cannot do		20	5
D3.4	Staying by yourself for a few days?	None	Mild	Moderate	Severe	Extreme or cannot do			
Getting along with people									
D4.1	Dealing with people you do not know?	None	Mild	Moderate	Severe	Extreme or cannot do			
D4.2	Maintaining a friendship?	None	Mild	Moderate	Severe	Extreme or cannot do			
D4.3	Getting along with people who are close to you?	None	Mild	Moderate	Severe	Extreme or cannot do		25	5
D4.4	Making new friends?	None	Mild	Moderate	Severe	Extreme or cannot do			
D4.5	Sexual activities?	None	Mild	Moderate	Severe	Extreme or cannot do			

Severity Level

NYHA Functional Classification: Class I-IV
XS3A NYHA Class I - No limitation of physical activity
XS6B NYHA Class II - Slight limitation of physical activity
XS9T NYHA Class III - Marked limitation of physical activity
XS9F NYHA Class IV - Unable to carry on any physical activity without

Level of functioning

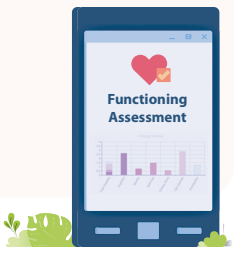
0 - None (no problem)
1 - Mild
2 - Moderate
3 - Severe
4 - Extreme or cannot do

1 - Cognition – understanding & communicating
2 - Mobility – moving & getting around
3 - Self-care – hygiene, dressing, eating & staying alone
4 - Getting along – interacting with other people
5 - Life activities – domestic tasks, leisure, work & school
6 - Participation – joining in community activities

Mobility
VD10 Maintaining a standing position
VD11 Changing body position - standing
VD12 Moving around within the home
VD13 Moving around outside the home
VD14 Walking

Life activities
VD40 Taking care of household responsibilities
VD41 Doing most important household tasks
VD42 Doing housework
VD43 Remunerative employment
VD43.0 Difficulties in daily work or school
VD43.1 Doing most important work or school task
VD43.2 Getting all needed work or school work done
VD43.3 Getting remunerative work or school work done quickly

Participation and impact of health problems
VD50 Recreation and leisure
VD51 Problems by barriers
VD52 Human rights
VD53 Time spent on health condition
VD54 Emotional effect of health condition
VD55 Health drain on financial resources
VD56 Health problems causing family problems
VD57 Problems in relaxation or pleasure



Associated Illnesses

GA34.02 Vulvodynia

DD91.0 Irritable bowel syndrome

GC00.3 Interstitial cystitis

8E49 Postviral fatigue syndrome
Inclusions: Chronic fatigue syndrome

MG30.01 Chronic widespread pain

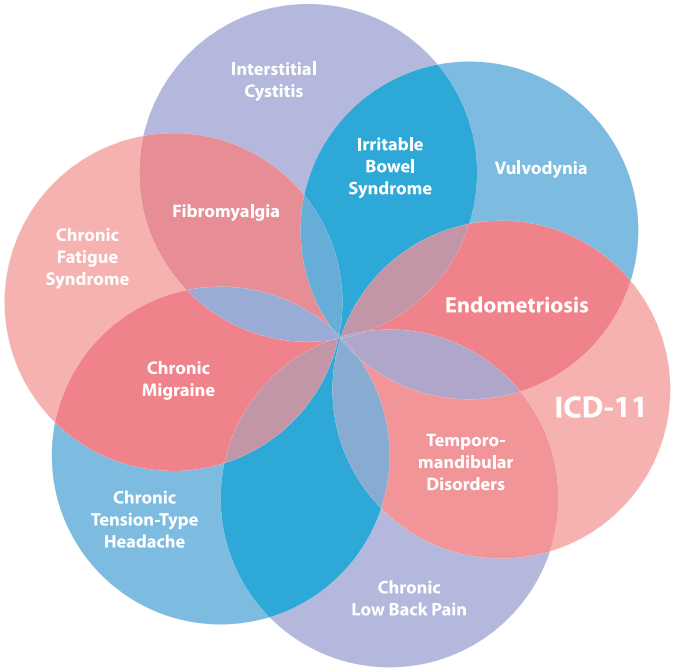
Inclusions: Fibromyalgia syndrome

8A80.2 Chronic migraine

8A81 Tension-type headache

MG30.02 Chronic primary musculoskeletal pain

Chronic primary low back pain



Generalized Sensory Sensitivity
+ Increased sensitivity to external stimuli across multiple sensory modalities
+ Increased sensitivity to internal symptoms and sensations (ie, somatic awareness)
+ Hyperalgesia/allodynia in multiple body regions

SPACE
+ S - Sleep disturbance
+ P - Pain that is widespread
+ A - Affect - negative
+ C - Cognitive dysfunction
+ E - Energy depletion/fatigue

Management of Chronic Overlapping Pain Conditions

Mounting evidence shows that millions of people, particularly women, suffer simultaneously from multiple pain conditions that share similar disease mechanisms – mainly of the neurological, endocrine, and immune systems – which are frequently associated with sleep, mood, fatigue, and cognitive disorders. The clinical state of overlap of these conditions – recently termed by the NIH as Chronic Overlapping Pain Conditions – is gaining increased recognition and for good reason. Ample data demonstrate a number of deleterious effects as an individual's number of COPCs increases, including: worsening of localized and systemic pain symptoms, decreased treatment effectiveness, reduced health and psychosocial outcomes, increased levels of disability, increased personal and societal costs, and markedly diminished quality of life.

The Number of Patients with COPCs is Multiplying

It has become clear that our current healthcare system has to change in order to improve care and reduce costs for patients. This step begins with promoting an understanding of the pathophysiological complexity of COPCs. Evidence suggests that COPCs are not just an extension of acute pain but a complex multisystem illness. Genetic predisposition and environmental exposures combine to increase the risk of developing and maintaining COPCs through abnormal pain amplification and emotional distress, moderated by factors from multiple body systems.

Not All Practitioners Are Communicating

Due to the inadequate number of pain management specialists trained to address the millions with chronic pain, most individuals are under the care of multiple specialists who may not be aware of the interconnection of these conditions, nor their association with nervous system abnormalities.

It Cannot Be Stated Enough: Always Assess the Whole Patient

Patients with COPCs may have any number and type of conditions, which require a targeted individualized approach. For example, a patient with fibromyalgia, interstitial cystitis, anxiety, and cognitive impairment may require a different assessment and treatment plan than a patient with IBS, endometriosis, vulvodynia, depression, and a sleep disorder. As such, the biopsychosocial model offers the most heuristic approach to COPCs.26 Multimodal, interdisciplinary treatment, based on this model, is vital to addressing the complexities faced by patients with COPCs. Elements of such a plan should include taking a detailed medical history and conducting a physical exam to clarify pathophysiology, if possible, and assessing the critical pain domains and non-pain domains, such as sleep, mood, cognition, and fatigue. Finally, assessment of the pain's impact on physical, social, and sexual function should be discussed with the patient. Physical and occupational therapy is often utilized to maximize and maintain one's functional ability, without increasing pain severity, and to help patients perform activities of daily living.

Veasley C. The Management of Chronic Overlapping Pain Conditions. Pract Pain Manag. 2019;19(2).

Endometriosis

ICD-11

Infertility

Endometriosis and Infertility

Infertility affects millions of people of reproductive age worldwide and has an impact on their families and communities. In the female reproductive system, infertility may be caused by a range of abnormalities of the ovaries, uterus, fallopian tubes, and the endocrine system, among others. Fertility care encompasses the prevention, diagnosis and treatment of infertility. Equal and equitable access to fertility care remains a challenge in most countries; particularly in low and middle-income countries. Infertility is a disease of the male or female reproductive system defined by the failure to achieve a pregnancy after 12 months. Estimates suggest that between 48 million couples and 186 million individuals live with infertility globally. Primary infertility is when a pregnancy has never been achieved by a person, and secondary infertility is when at least one prior pregnancy has been achieved.

Infertility may be caused by:

- Tubal disorders such as blocked fallopian tubes, which are in turn caused by complications of unsafe abortion, postpartum sepsis or abdominal/pelvic surgery
- Uterine disorders which could be inflammatory in nature as Endometriosis or benign in nature as fibroids
- Ovary disorders, such as polycystic ovarian syndrome and other follicular disorders; disorders of the endocrine system causing imbalances of reproductive hormones.

GA31 Female infertility

GA31.00 Primary female infertility of uterine origin
Female infertility caused by uterine abnormalities on the level of the endometrium or myometrium, with more detailed description classified elsewhere, i.e. under genitourinary infections, STDs and noninflammatory benign gynaecological disease

GA31.01 Primary female infertility of tubal origin
Female infertility caused by dysfunction of one or both fallopian tubes, usually related to pelvic adhesions or occurring after pelvic surgery, with or without hydrosalpinx

GA31.1 Secondary female infertility
Infertility in a woman who has had at least one clinical pregnancy

GA32 Complications associated with medically assisted production
GA33 Recurrent pregnancy loss

GB04 Male infertility

GB04.0 Azoospermia
Any condition of the genital system affecting males, caused by obstruction of the reproductive tract, abnormal hormone levels, testicular failure, or inadequate production of spermatozoa. These conditions are characterised by the absence of a measurable level of sperm cells in semen, and very low levels of fertility. Confirmation is by the absence of spermatozoa in the sediment of a centrifuged sample of ejaculate.

Overall Symptoms

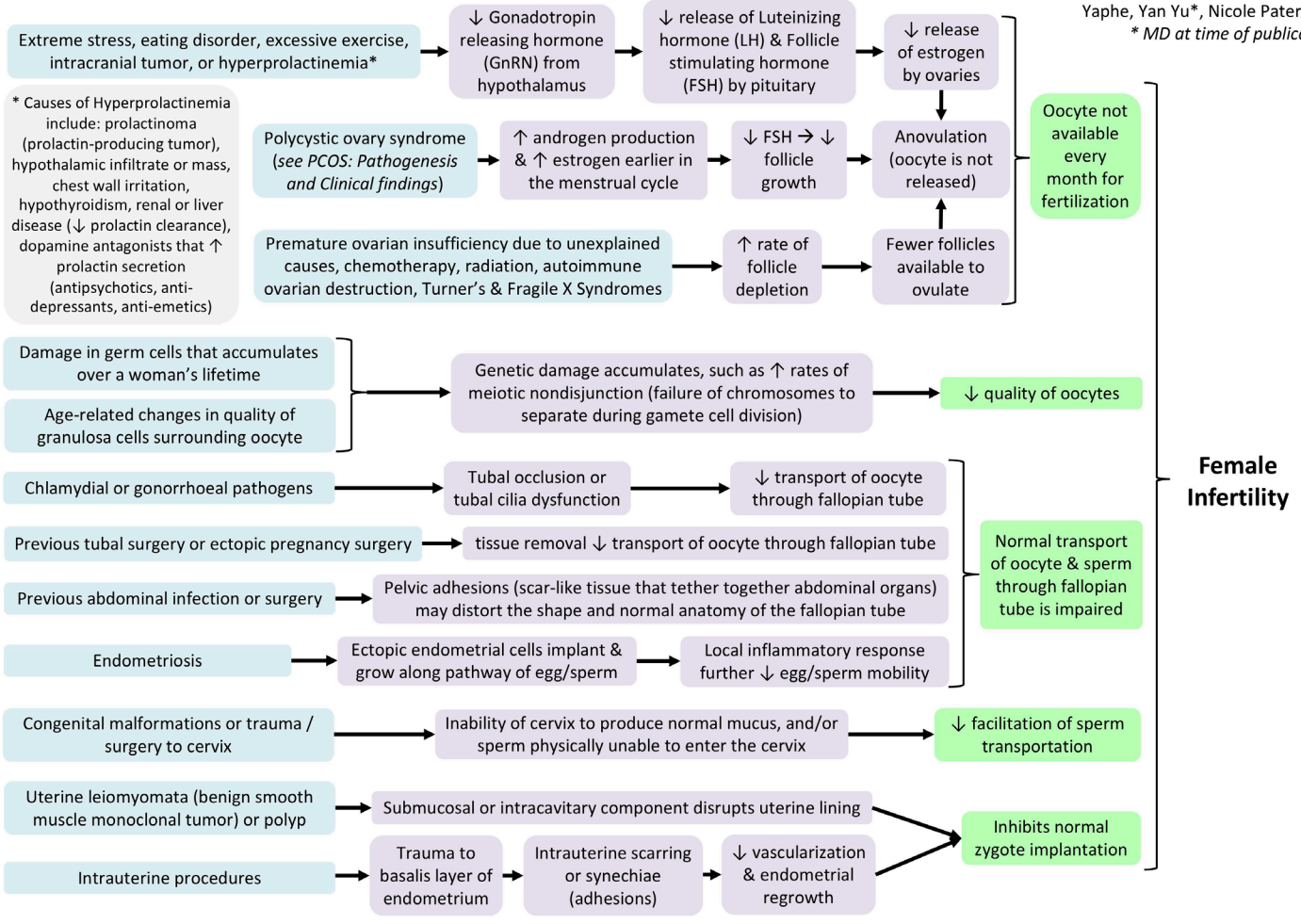
Disorders of the gonadal hormone system
5A80 Ovarian dysfunction
5A80.0 Clinical hyperandrogenism
5A80.1 Polycystic ovary syndrome
5A80.2 Polycystic ovary
5A80.3 Anovulation
5A80.4 Oligo-ovulation

5A80.5 Diminished ovarian reserve
Condition characterised by ovaries with lower number of oocytes than expected for female chronologic age, marked by biochemical abnormalities (increased serum FSH levels, decreased serum AMH levels) and/ or ultrasound findings (low antral follicle count) associated with ovarian ageing, reduced response to ovarian stimulation, and female infertility.

5D44 Postprocedural ovarian failure
A condition in women characterised by amenorrhea, caused by or subsequent to any intervention. This condition may also present with hot flashes, night sweats, irritability, poor concentration, decreased sex drive, pain during sex, vaginal dryness.

Pathogenesis of Female Infertility

Author: Simonne Horwitz
Reviewers: Claire Lothian, Hannah Yaphe, Yan Yu*, Nicole Paterson*
** MD at time of publication*



Legend: Pathophysiology | Mechanism | Sign/Symptom/Lab Finding | Complications

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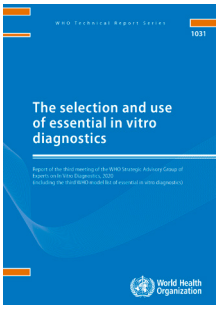
Diagnosing and Managing Infertility: Disease condition and impact on patients

Menstrual disorders. Estimates of the prevalence of menstrual disorders range from 5% to ~36%; occurrence depends on age, nutritional status and country of residence. PCOS, which is a subset of menstrual irregularity, is thought to be the most common endocrine disorder found in women of reproductive age and impacts all races and ethnicities. In unspecified populations, PCOS has a reported incidence rate of 3–10%, although more precise incidence is unknown due to underdiagnosis.



Ovarian reserve. The number of ovarian follicles present in the ovaries (oocytes) is established at birth and declines with time throughout a woman's lifetime without regeneration. Ovarian reserve testing can inform women of their reproductive lifespan. Confirming the presence of viable oocytes and the potential to ovulate is also useful for female cancer patients of reproductive age who are being treated with gonadotoxic therapy. Other methods, including AMH and antral follicular count, already exist to evaluate ovarian reserve in subfertile women , but measuring FSH levels at predetermined times of a menstrual cycle (typically day 3) remains an important test. Single FSH measures are not predictive of the perimenopausal state or the timing of menopause, but elevated FSH levels can confirm menopausal status, particularly in women who have had hysterectomies (with ovaries intact) and in whom the absence of menses cannot be used as a reliable indicator of ovarian function.

Menstrual disorders. Irregular menses, particularly amenorrhoea and oligomenorrhoea, generally indicate a defect at some point in the hypothalamicpituitary-ovarian-uterine axis. Menstrual disorders. FSH levels can be used in the evaluation of irregular menstrual bleeding by helping to distinguish ovulatory dysfunction from uterine abnormalities as the cause. FSH levels are used in evaluating the etiology of irregular menstrual bleeding. Elevated FSH levels indicate ovarian dysfunction or failure, while normal or low levels suggest pituitary or hypothalamic failure

Polycystic ovary syndrome (PCOS) causes irregular menstrual cycles, polycystic ovaries and hirsutism (1); it may also include infertility, insulin-resistance, impaired glucose tolerance (type 2 diabetes) and dyslipidaemia. It is associated with negative psychosocial impacts, and the premature pubertal growth spurt and accelerated bone maturation can also result in reduced adult height. Confirmation that irregular menstrual bleeding is caused by hypothalamicpituitary-ovarian (HPO) dysfunction allows corrective treatment with hormonal intervention and carries a high degree of success in regulating cycles. Appropriate hormonal replacement will aid in preventing the sequelae of estrogen deficiency. An elevated ratio of LH to FSH (greater than 3) is often used with history and physica exam to support a diagnosis of PCOS. Appropriate diagnosis of PCOS allows hormonal treatments that can regulate menstrual cycles, induce ovulation when indicated, decrease androgenic effects and also reduce the risks of metabolic abnormalities such as diabetes and metabolic syndrome, which frequently occur with PCOS. Multiple diagnostic criteria have been adopted for PCOS, but the common denominator appears to be oligoovulation and androgen excess.

Public health relevance

Estimates suggest that up to 186 million women globally are infertile. Although differing methods and definitions have been used to derive infertility burden, a recent review estimated the global prevalence of infertility to be 9%. As many as 70 million couples would benefit from medical intervention to achieve pregnancy. The selection and use of essential in vitro diagnostics trends over the past 20 years. The economic and social impact of infertility is significant, particularly for women, who will often suffer from social isolation, discrimination, disinheritance, depression, abuse, divorce and possible abandonment in old age. Infertility as a common cause of childlessness can also have a broader negative economic impact on families, particularly in LMICs, where children contribute to family incomes and older parents depend on their children for support. Paradoxically, nations with the highest overall fertility are also the ones with the greatest prevalence of infertility and these often include LMICs. Given the economic, resource, cultural and religious constraints in these countries, infertility services among them vary significantly. Assays that measure serum FSH levels are, however, relatively non-invasive (requiring only a blood draw or finger stick), inexpensive and accessible from laboratories throughout the world.

Estradiol

Serum estrogen level to the EDL as an IVD to assess reproductive function in women, to include menstrual irregularities and menopausal status, and to evaluate infertility and guide its treatment.

Follicle-stimulating hormone

Luteinizing hormone: serum LH levels to the EDL as an IVD to aid in the diagnosis of diseases caused by malfunction of the HPG axis; and to aid the clinical evaluation of infertility (both female and male), menstrual irregularities, pituitary disorders, precocious or delayed puberty, and ovarian/testicular dysfunction.

Progesterone

Serum progesterone levels to the EDL as an IVD to confirm evidence of ovulation and assess luteal phase function during fertility investigations.

Prolactin

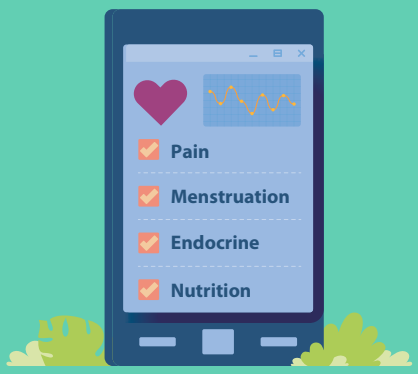
The main function of PRL lies in the development of mammary glands, milk synthesis and maintenance of milk secretion during pregnancy and lactation. Serum prolactin levels rise rapidly during pregnancy with increase in the size and number of lactotrophs. During lactation, suckling induces rapid secretion of PRL via a neuroendocrine reflex pathway. In the absence of pregnancy, hyperprolactinaemia (elevated levels of PRL) may present with symptoms of HH, including menstrual disturbance and infertility or visual symptoms from a pituitary mass effect by a prolactinoma, the most common pituitary tumour.

Prolactinoma is a benign tumour of the pituitary gland.Symptoms include infertility, galactorrhoea (milk leaking from nipples), amenorrhoea or oligomenorrhoea, loss of libido, vaginal dryness, acne, hirsutism as well as visual or neurological symptoms caused by the mass of the tumour itself. Treatment is primarily medical (bromocriptine or cabergoline as first-line agents); but a surgical approach may be needed in large tumours that compress other brain structures and do not respond to the pharmacological approach. There are many other causes of functional hyperprolactinaemia, including stress, medicines, pregnancy and compression of the pituitary stalk by other tumours. These (usually) mild elevations of PRL may be symptomatic or asymptomatic and do not usually require pharmacological treatment.

Endometriosis

ICD-11

Pain Classification



ICD-11 Provides Comprehensive Coverage of Clinically Relevant Painful Disorders

International Association for the Study of Pain (IASP) differentiates between diseases in ICD11 (endometriosis, secondary dysmenorrhea with endometriosis) and chronic pelvic pain syndromes, and specifically defines "endometriosis-associated pain syndrome." Endometriosis is defined as persistent or recurrent pelvic pain in individuals where symptoms persist after adequate treatment, and is associated with cognitive, behavioral, sexual or emotional consequences. Pain can exceed levels expected based on endometriotic lesions visualized at laparoscopy, individuals often experience symptoms of lower urinary tract, sexual and bowel dysfunction. An improved and systematic classification of chronic visceral pain must acknowledge that, once the pain becomes chronic, it should be recognized as a health condition in its own right and should receive adequate treatment. If the original medical condition resolves, yet the chronic pain persists, the chronic secondary pain diagnosis remains appropriate.

Manifestation codes: Chronic Pain

Chronic secondary visceral pain is chronic pain secondary to an underlying condition originating from internal organs of the head or neck region or of the thoracic, abdominal or pelvic regions. It can be caused by persistent inflammation, vascular mechanisms or mechanical factors.

Diagnostic criteria

Conditions A to D are fulfilled:

A. Chronic pain (persistent or recurrent for longer than 3 months) is present and characterized by both of the following:

A.1 The distinct anatomical location is compatible with typical referral pain patterns from specific internal organs.

A.2 The history is suggestive of relevant dysfunction/disease of one or more internal organs.

B. At least one confirmatory test demonstrates an anatomical location compatible with a specific referred pain pattern.

C. At least one confirmatory test demonstrates the relevant dysfunction/disease.

D. The pain is not better accounted for by another diagnosis of chronic pain.

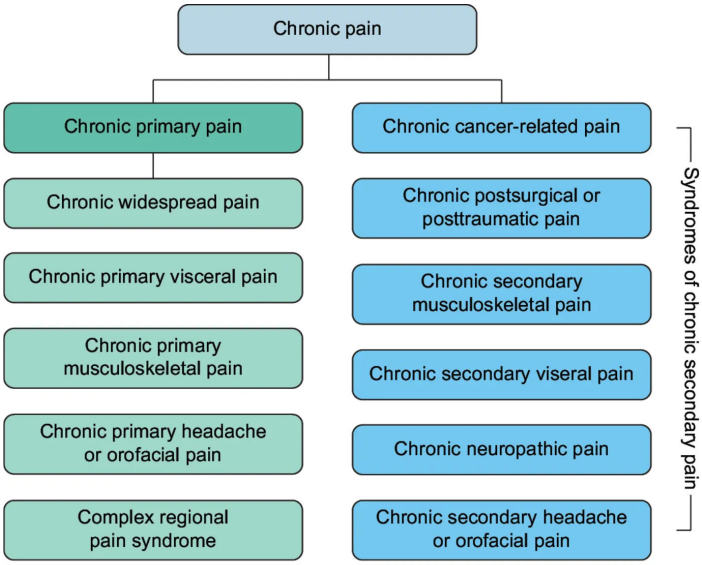


Figure 1. Chronic pain in the ICD-11. The classification distinguishes between conditions of *Chronic primary pain* and syndromes of known etiology or established pathophysiology that are associated with chronic (secondary) pain.

MG30.40 Chronic visceral pain from mechanical factors

Parent
MG30.4 Chronic secondary visceral pain
Show all ancestors

Description
Chronic visceral pain from mechanical factors is chronic pain deriving from a) the obstruction of hollow viscera as a consequence of internal migrating obstacles (e.g., stones) or stenosis, with dilation above the obstacle/stenosis or b) from the traction of ligaments and vessels of internal organs or the external compression of internal organs.

MG30.41 Chronic visceral pain from vascular mechanisms

Parent
MG30.4 Chronic secondary visceral pain
Show all ancestors

Description
Chronic visceral pain from vascular mechanisms is chronic visceral pain due to alterations of arterial and/or venous blood vessels to/from viscera of the head/neck region, thoracic, abdominal and pelvic cavities or pain conditions of the vascular system producing pain in other locations.

MG30.42 Chronic visceral pain from persistent inflammation

Parent
MG30.4 Chronic secondary visceral pain
Show all ancestors

Description
Chronic visceral pain from persistent inflammation is chronic pain due to longlasting inflammation of internal organs of the head/neck region and of the thoracic, abdominal, or pelvic cavities.

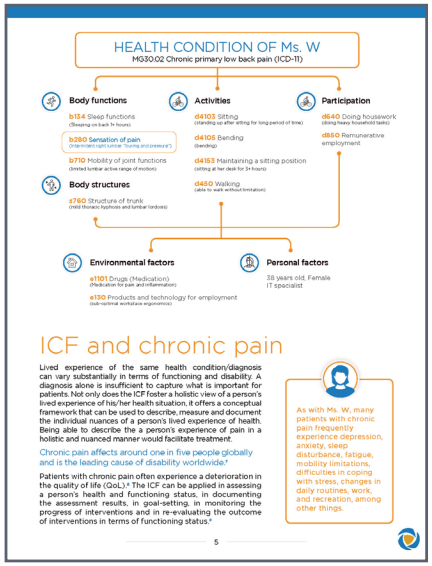
Primary care

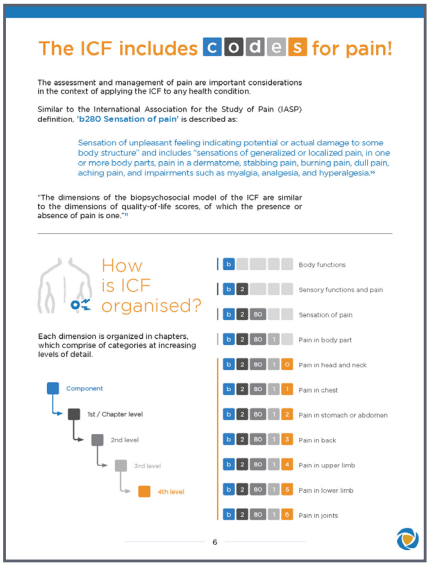
Chronic pain is a novel concept originating in the insight that diseases or long-term conditions associated with chronic pain should be acknowledged in their own right, even if a clear understanding of the underlying etiology or pathophysiology is missing. It marks a deliberate move away from the practice of labeling unexplained pain a somatic symptom disorder. A diagnosis of somatic symptom disorder implies that the pain is caused by a behavioral, that is, mental condition. However, it is not appropriate to diagnose individuals with a mental disorder solely because an alternative medical cause cannot be established.

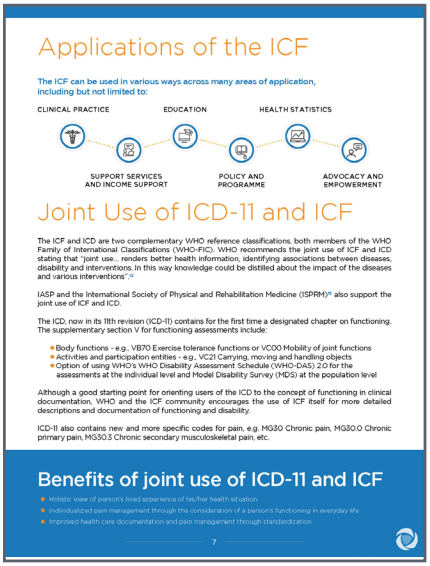
The visceral etiology of the pain should be highly probable; if it is vague, consider using codes in the section of chronic primary pain. The pain is perceived in the somatic tissues of the body wall (skin, subcutis, muscle) in areas that receive the same sensory innervation as the internal organ at the origin of the symptom (referred visceral pain). In these areas, secondary hyperalgesia (increased sensitivity to painful stimuli in areas other than the primary site of the nociceptive input) often occurs. The intensity of the symptom may bear no relationship with the extent of the internal damage/noxious visceral stimulation.

Barke A, Korwisi B, Jakob R, Konstanjsek N, Rief W, Treede RD. Classification of chronic pain for the International Classification of Diseases (ICD-11): results of the 2017 international World Health Organization field testing. Pain. 2022 Feb 1;163(2):e310-e318. doi: 10.1097/j.pain.0000000000002287. PMID: 33863861; PMCID: PMC8756346.

Scholz J. Finally, A Systematic Classification of Pain (the ICD-11). Pract Pain Manag. 2019;19(3).







The WHO International classification of Functioning, Disability and Health (ICF)

- SOCIETAL IMPACT OF PAIN (SIP)

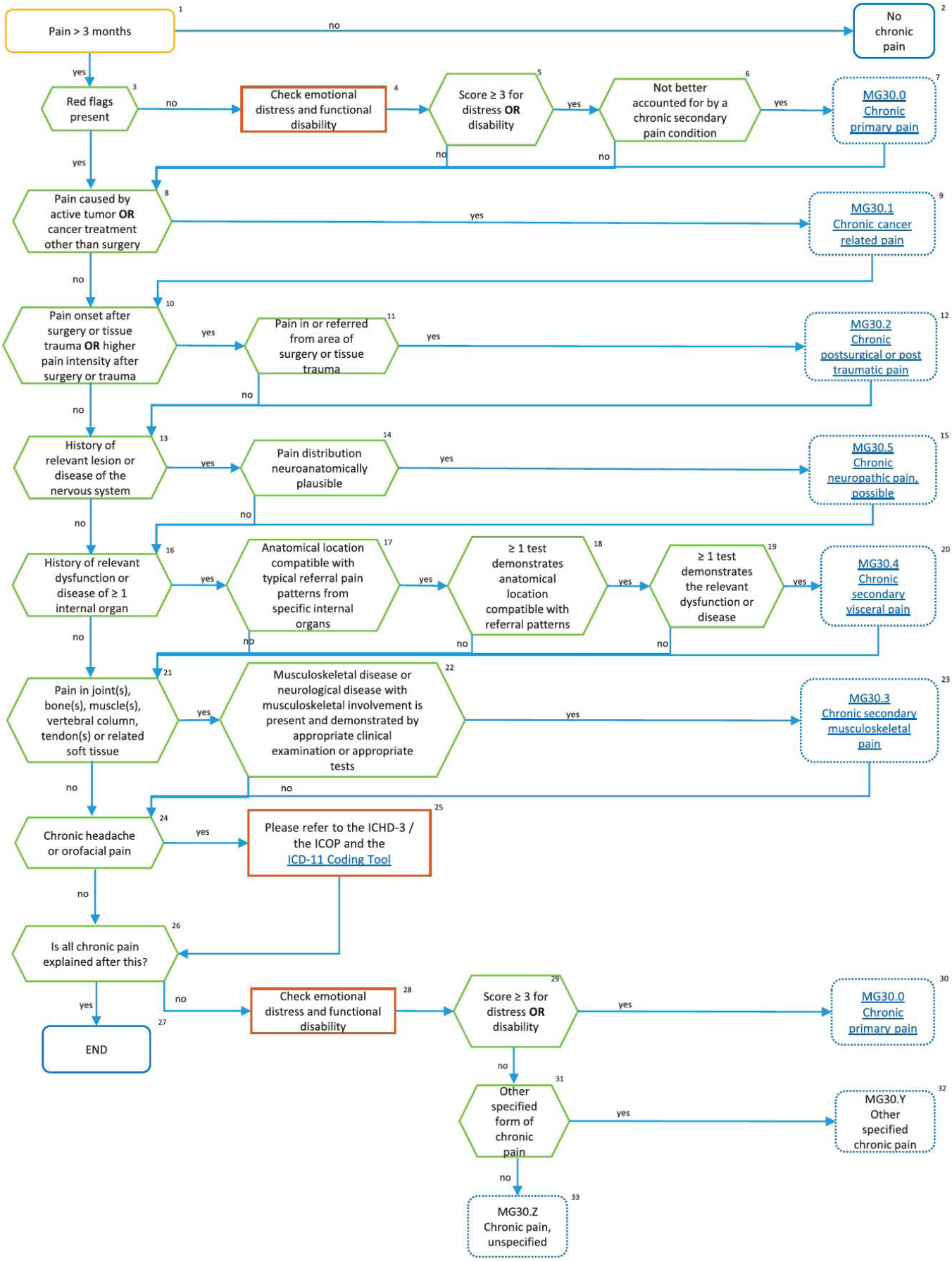
Pain is one of the most significant causes of disability and suffering worldwide. Unfortunately, this fact is not often addressed in health policies.

The problems which health care systems are facing when it comes to managing pain are diverse. One of the most significant is the lack of a 'health system quality indicator' for pain. Health system quality indicators are used to gather data and establish the relative quality of care offered between hospitals or even between countries. Measuring and managing the impact that pain has on the individual, to his/her relatives and social life, as well as on society will support the overall functioning of our health care systems by minimising the chance of pain conditions becoming chronic, and reducing long-term expenditures. One of the challenges is to allocate budget and resources for pain management. The issue of whether chronic pain can be considered a diagnostic entity, or even a condition "in its own right", can lead to consternation. The first step in tackling this issue is to define common ground regarding the documentation of chronic pain for clinical, budget and policy purposes. An international classification that takes pain into account is the WHO's International Classification of Functioning, Disability and Health (ICF). Along with the 11th International Classification of Diseases (ICD-11), the ICF provides a framework for documenting health at an individual and population level. For future policy development, the combined use of the ICF and ICD to document pain will be a big step forward. Systematic documentation by ICF and ICD will provide a data base for policy decisions on reimbursement, resource allocation and education.

Do you want to know more about ICF?

You find the ICF at the WHO website here:
https://www.who.int/classifications/icf/en/

An ICF e-Learning Tool is available under:
https://www.icf-elearning.com/


1
Pain > 3 months
no
2
No chronic pain
yes
3
Red flags present
no
4
Check emotional distress and functional disability
5
Score ≥ 3 for distress OR disability
yes
6
Not better accounted for by a chronic secondary pain condition
yes
7
MG30.0 Chronic primary pain
no
no
yes
8
Pain caused by active tumor OR cancer treatment other than surgery
yes
9
MG30.1 Chronic cancer related pain
no
10
Pain onset after surgery or tissue trauma OR higher pain intensity after surgery or trauma
yes
11
Pain in or referred from area of surgery or tissue trauma
yes
12
MG30.2 Chronic postsurgical or post traumatic pain
no
no
13
History of relevant lesion or disease of the nervous system
yes
14
Pain distribution neuroanatomically plausible
yes
15
MG30.5 Chronic neuropathic pain, possible
no
no
16
History of relevant dysfunction or disease of ≥ 1 internal organ
yes
17
Anatomical location compatible with typical referral pain patterns from specific internal organs
yes
18
≥ 1 test demonstrates anatomical location compatible with referral patterns
yes
19
≥ 1 test demonstrates the relevant dysfunction or disease
yes
20
MG30.4 Chronic secondary visceral pain
no
no
no
21
Pain in joint(s), bone(s), muscle(s), vertebral column, tendon(s) or related soft tissue
yes
22
Musculoskeletal disease or neurological disease with musculoskeletal involvement is present and demonstrated by appropriate clinical examination or appropriate tests
yes
23
MG30.3 Chronic secondary musculoskeletal pain
no
no
24
Chronic headache or orofacial pain
yes
25
Please refer to the ICHD-3 / the ICOP and the ICD-11 Coding Tool
no
26
Is all chronic pain explained after this?
yes
27
END
no
28
Check emotional distress and functional disability
29
Score ≥ 3 for distress OR disability
yes
30
MG30.0 Chronic primary pain
no
31
Other specified form of chronic pain
yes
32
MG30.Y Other specified chronic pain
no
33
MG30.Z Chronic pain, unspecified

IASP classification of chronic pain for ICD-11: chronic postsurgical

Chronic pain after tissue trauma is frequent and may have a lasting impact on the functioning and quality of life of the affected person. Despite this, chronic postsurgical and posttraumatic pain is underrecognised and, consequently, undertreated. It is not represented in the current International Classification of Diseases (ICD-10). This article describes the new classification of chronic postsurgical and posttraumatic pain for ICD-11. Chronic postsurgical or posttraumatic pain is defined as chronic pain that develops or increases in intensity after a surgical procedure or a tissue injury and persists beyond the healing process, ie, at least 3 months after the surgery or tissue trauma. In the classification, it is distinguished between tissue trauma arising from a controlled procedure in the delivery of health care (surgery) and forms of uncontrolled accidental damage (other traumas). In both sections, the most frequent conditions are included. This provides diagnostic codes for chronic pain conditions that persist after the initial tissue trauma has healed and that require specific treatment and management. It is expected that the representation of chronic postsurgical and posttraumatic pain in ICD-11 furthers identification, diagnosis, and treatment of these pain states. Even more importantly, it will make the diagnosis of chronic posttraumatic or postsurgical pain statistically visible and, it is hoped, stimulate research into these pain syndromes.

MG30.2 Chronic postsurgical or post traumatic pain

Parent

MG30 Chronic pain

Show all ancestors

Description

Chronic postsurgical or post traumatic pain is pain developing or increasing in intensity after a surgical procedure or a tissue injury (involving any trauma including burns) and persisting beyond the healing process, i.e. at least 3 months after surgery or tissue trauma. The pain is either localized to the surgical field or area of injury, projected to the innervation territory of a nerve situated in this area, or referred to a dermatome (after surgery/injury to deep somatic or visceral tissues). Other causes of pain including infection, malignancy etc. need to be excluded as well as pain continuing from a pre-existing pain problem.

Coded Elsewhere

- Complex regional pain syndrome (MG30.04)

Coding Note

The postsurgical or posttraumatic aetiology of the pain should be highly probable; if it is vague, consider using codes in the section of chronic primary pain.

Postcoordination

Add detail to **Chronic postsurgical or post traumatic pain**

Has causing condition *(code also)*

Search

Associated with *(use additional code, if desired .)*

XS7G	Psychosocial factors present
XS8B	No psychosocial factors present

Has severity *(use additional code, if desired .)*

XS5B	No pain
XS5D	Mild pain
XS9Q	Moderate pain
XS2E	Severe pain

Has alternative severity1 *(use additional code, if desired .)*

XS1J	No distress
XS3R	Mild distress
XS7C	Moderate distress
XS7N	Severe distress

Has alternative severity2 *(use additional code, if desired .)*

XS71	No pain-related interference
XS5R	Mild pain-related interference
XS2L	Moderate pain-related interference
XS2U	Severe pain-related interference

Temporal pattern and onset *(use additional code, if desired .)*

XT5G	Intermittent
XT6Z	Persistent
XT5T	Persistent with overlaid attacks

Schug, Stephan A.a; Lavand'homme, Patriciab; Barke, Antoniac; Korwisi, Beatricec; Rief, Winfriedc; Treede, Rolf-Detlefd,; The IASP Taskforce for the Classification of Chronic Pain. The IASP classification of chronic pain for ICD-11: chronic postsurgical or posttraumatic pain. PAIN: January 2019 - Volume 160 - Issue 1 - p 45-52 doi: 10.1097/j.pain.0000000000001413*

Endometriosis (EM) and adenomyosis (AM) are common conditions with pain.

The pathophysiology of pain comprises sensory and somatoform pain mechanisms. Over time, these may aggravate and lead to individual complex disease patterns if not diagnosed and treated. Despite the known facts, several years often pass between the onset of symptoms and diagnosis. It recurs after the surgical removal of EM lesions in high numbers and leads to long-term treatment needs in 50% of affected women. There is a clear correlation between the duration, the intensity of the complaints, and the extent of the EM and AM manifestations. In general, all lesions can cause a variety of symptoms. The combination of cyclic lower abdominal pain/dysmenorrhea and dyspareunia is typical. Depending on where the lesions are located, somatic (peritoneum, pelvic wall) or visceral (uterus, bladder, or intestine) pain occurs.

These two pain characteristics differ.

Somatic pain is rather sharp and point-shaped and due to the high density of sensory nerve fibers in the parietal peritoneum, it can be located quite specifically by the person in pain.

Visceral pain, on the other hand, is dull and spasm-like. Visceral organs interact with each other, and bladder-induced pain can be hardly distinguished from uterine-induced pain. In severe pain, reactions such as nausea, vomiting, collapse tendency, and cyclic menstrual-associated diarrhea are common complaints in patients. Peritoneal lesions show a hyperinnervation of sensory nerve fibers but a loss of sympathetic nerve fibers.

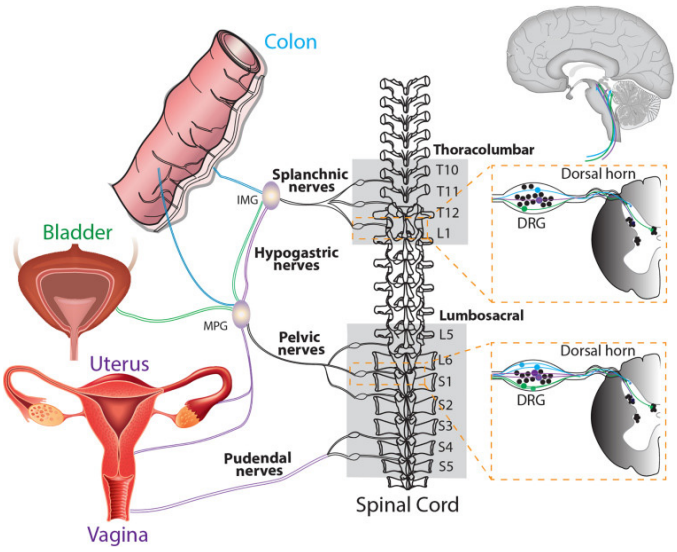
It has been demonstrated that the expression of nerve growth factor (NGF) in the peritoneum of women with EM is elevated in comparison to the peritoneum of women without EM. A further complicating factor is adhesion-related pain, which may have both somatic and visceral qualities. Due to chronic pain, patients may develop reactive depression and somatoform pain disorders, which make the clinical picture appear even more complex.

Pathophysiological pathways and clinical consequences. The underlying biological key concepts of EM include hormonal imbalance, activation of stem cells, changes on genetic and epigenetic levels, tissue injury and repair mechanisms, hyper-peristalsis, epithelial-mesenchymal transition, and fibroblast to myofibroblast transition. In consequence, the formation of adhesions, fibrosis, inflammation, and local invasion arise. This coexistence of different pathways and their interactions triggers the clinical outcomes that affect multiple organ systems. EM patients present with complaints that include pain, infertility and sterility, complications in pregnancy, and even malignant transformation of preexisting lesions as ovarian cancer.

Development of Central Sensitization with Spinal Hyperalgesia

Physiologically, pain is a warning signal. If severe dysmenorrhea (menstrual pain that leads to the need for bedrest or incapacity to go to school or to work) remains untreated, it will recur monthly. The pain is initially perceived cyclically, which subsides as the release of the inflammatory and pain mediators decreases. If this pain occurs repeatedly, however, the body's warning signals take effect, and it is classified as threatening. The modulation at the spinal level does not regulate it down but rather increases it. The release of neurotransmitters is altered (glutamate upregulation), and several modulating mechanisms are set in motion: the nociceptive field is expanded and dysuria and/or dyschezia may occur.

These processes lead to spinal hyperalgesia marked by a lowered pain threshold and the perception of pain, even with slight stimuli such as touch. Increasing pain frightens the person experiencing it and makes pain processing more difficult. Severe cramps, accompanied by vegetative reactions, lead the patient to adopt a relieving posture, which is used to seek pain relief. Reactively, this leads to a reflex contraction of the pelvic floor muscles and eventually to pelvic floor dysfunction. If these tensions persist, dyspareunia intensifies. Fear of pain during intercourse can strongly influence the ability to relax and a disorder manifests itself. Functional MRI assessments demonstrated the first morphologica adjustments of the brain after a pain latency of two years. Patients suffering from chronic pain have an increased risk of developing complex chronic pain syndromes with bladder dysfunction, irritable bowel syndrome, and vulvodynia.17



Gruber, Teresa Mira, and Sylvia Mechsner. "Pathogenesis of Endometriosis: The Origin of Pain and Subfertility." Cells vol. 10,6 1381. 3 Jun. 2021, doi:10.3390/cells10061381
Maddern, J., Grundy, L., Castro, J., & Brierley, S. M. (2020). Pain in Endometriosis. Frontiers in cellular neuroscience, 14, 590823. https://doi.org/10.3389/fncel.2020.590823
Shrikhande AA. The Consideration of Endometriosis in Women with Persistent Gastrointestinal Symptoms and a Novel Neuromusculoskeletal Treatment Approach. Arch Gastroenterol Res. 2020; 1(3): 66-72.

Pelvic floor dysfunction is a common condition with Endometriosis

GA34.0Y Pelvic floor dysfunction

Pelvic floor tension myalgia

GC40.4Z Pelvic floor muscle disruption

XA2J71 Muscles of the pelvis and perineum
XA2E07 Bulbospongiosus muscle
XA5FZ1 Cremaster muscle
XA8HG2 Dartos muscle
XA2LG6 Deep transverse perinei muscle
XA3YC6 Iliococcygeus muscle
XA73H8 Ischiocavernosus muscle
XA9T66 Levator ani-coccygeus muscle
XA3HP4 Pubococcygeus muscle
XA7MM8 Puborectalis muscle
XA4RK4 Pubovaginalis muscle
XA3ML6 Sphincter ani muscle
XA8FT0 Sphincter urethrae muscle
XA56U7 Superficial transverse perinei muscle

GC40 Pelvic organ prolapse

GC40.0 Prolapse of anterior vaginal wall
GC40.1 Prolapse of posterior vaginal wall
GC40.2 Prolapse of the vaginal apex
GC40.3 Uterovaginal prolapse
GC40.4 Pelvic floor muscle disruption
GC40.5 Urinary incontinence associated with pelvic organ prolapse
GC40.6 Functional bladder disorders associated with pelvic organ prolapse

DD92.2 Pelvic floor dyssynergia
Functional defaecation disorders are characterised by paradoxical contraction or inadequate relaxation of the pelvic floor muscles during attempted defaecation (dyssynergic defaecation) or inadequate propulsive forces during attempted defaecation (inadequate defaecatory propulsion). The patients must satisfy diagnostic criteria for functional constipation.=

Endometriosis and Dyssynergia

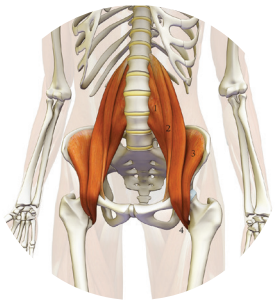
Endometriosis can cause gastro-intestinal symptoms via several mechanisms stimulating a hypertonic pelvic floor, cross-sensitization, peripheral, and central sensitization. Endometriosis can directly innervate pelvic nerves, particularly the pudendal nerve. This contributes to pudendal neuralgia symptoms of anorectal pain and pain with bowel movements. Innervation of the pudendal nerve also contributes to increased bowel frequency. The presence of endometriosis can cause a secondary chronic guarding of pelvic floor musculature. This chronic guarding state leads to nonrelaxing pelvic floor dysfunction and myofascial trigger points. The pelvic floor muscles in nonrelaxing pelvic floor dysfunction are short, spastic, weaker and poorly coordinated.19

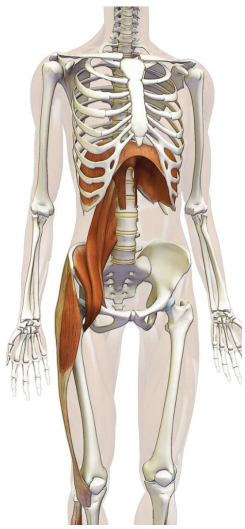
Endometriosis and Abdomino-phrenic Dyssynergia

The abdominal muscles relax when they should be contracting and the respiratory diaphragm contracts when it should relax during digestion. Normally what should occur is the abdominal muscles increase in tone and the respiratory diaphragm relaxes as the colon or intestines begin filling. In patients with abdomino-phrenic dyssynergia the dysfunction leads to abdominal distention, bloating, constipation, and pain Functional gastrointestinal disorders.

Pain in Endometriosis

The roles of inflammation, neurogenic inflammation, neuroangiogenesis, peripheral sensitization and central sensitization. As endometriosis patients are also known to have co-morbidities such as irritable bowel syndrome and overactive bladder syndrome, we highlight how common nerve pathways innervating the colon, bladder and female reproductive tract can contribute to co-morbidity via cross-organ sensitization. There's evidence for an overall heterogeneity in endometriosis, rather than a ' one size fits all' approach. This strongly suggests a personalized treatment approach based on etiology and symptomatology. Shifting the paradigm of lesion specific and cyclical inflammatory pain will continue to open up further areas to expand treatment opportunities.





Maddern J, Grundy L, Castro J, Brierley SM. Pain in Endometriosis. Front Cell Neurosci. 2020 Oct 6;14:590823. doi: 10.3389/fncel.2020.590823. PMID: 33132854; PMCID: PMC7573391.

Endometriosis

ICD-11

Imaging Dianostics

Endometriosis can affect almost any organ or structure, although most endometriotic implants are located in the pelvic cavity. Pelvic endometriosis has a somewhat predictable and repetitive distribution pattern. Imaging mapping is at the core of clinical practice and allows a comprehensive evaluation for patient counseling and preoperative planning. The pelvic cavity, abdominal wall, small bowel, appendix, and inguinal area can be evaluated with transvaginal ultrasonography (US) after bowel preparation, high-resolution US with a linear transducer, and magnetic resonance (MR) imaging. The pelvic cavity is the most common location for endometriotic implants, which usually affect the retrocervical space, ovaries, vagina, rectosigmoid colon, bladder dome, and round ligaments. The most common atypical locations are the gastrointestinal tract, urinary tract, lung, umbilicus, inguinal area, breast, and pelvic nerves, as well as abdominal surgical scars. Gastrointestinal lesions are the most common extragenital manifestation, and the diaphragm is the most frequent extrapelvic site. Endometrioma, adhesions and deep nodular forms of disease often require ultrasonography or magnetic resonance imaging (MRI) to detect. Histologic verification, usually following surgical/laparoscopic visualization, can be useful in confirming diagnosis, particularly for the most common superficial lesions. The need for histologic/laparoscopic confirmation should not prevent the commencement of empirical medical treatment.

Bowel Endometriosis
Rectum & sigmoid colon account for 90% of bowel endometriosis
Terminal ileum is the most common location of small bowel involvement

Urinary Endometriosis
• **Extrinsic** – abuts the ureter resulting in tethering, angular deviation, and compression
75-80% of cases of ureteral involvement
• **Intrinsic** – invades the ureter resulting in luminal narrowing and hydroureteronephrosis
20-25% of cases of ureteral involvement

XY9R Diagnosis confirmed by imaging

Clinical Findings
MG00 Clinical findings on diagnostic imaging of breast
MG01Clinical findings on diagnostic imaging of urinary organs
Exclusions: hypertrophy of kidney (GB90)

MF3Y Other specified symptoms, signs or clinical findings involving the female genital system
• Abnormal findings on diagnostic imaging of uterus

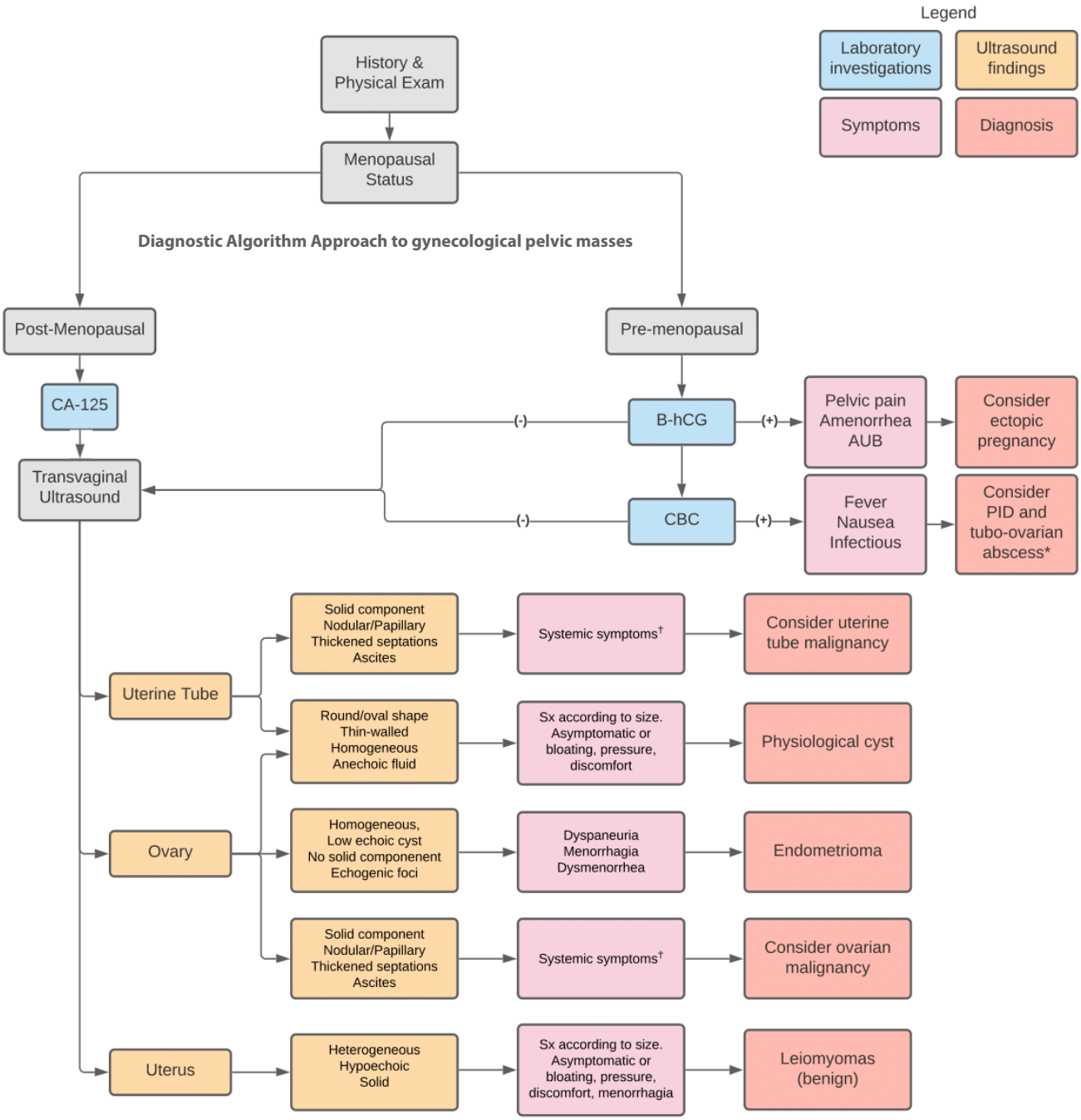
ME21 Clinical findings on diagnostic imaging of liver or biliary tract
ME22 Clinical findings on diagnostic imaging of digestive tract
ME2Y Other specified clinical findings in the digestive system
• Abnormal diagnostic imaging of retroperitoneum

MD41 Clinical findings on diagnostic imaging of lung
MC90 Clinical findings on diagnostic imaging of heart or coronary circulation
ME92.Y Other specified clinical findings on diagnostic imaging of other parts of musculoskeletal system
ME92.Z Clinical findings on diagnostic imaging of other parts of musculoskeletal system, unspecified
MB71.Y Other specified clinical findings on diagnostic imaging of central nervous system
MB71.Z Clinical findings on diagnostic imaging of central nervous system, unspecified

QA0B Preprocedural examination
Encounter for radiological and imaging examinations as part of preprocedural examination.

PK8Y Diagnostic imaging procedures associated with injury or harm

MD82 Intra-abdoominal or pelvic swelling, mass or lump



This basic algorithm represents the usual management of a patient who presents with a gynecological mass. Including the patient's history and basic laboratory investigations, it is centered on the ultrasound findings which is the modality of choice in the evaluation of a pelvic mass. Common symptoms of specific conditions are indicated but it is crucial to remember that most pelvic masses are asymptomatic.

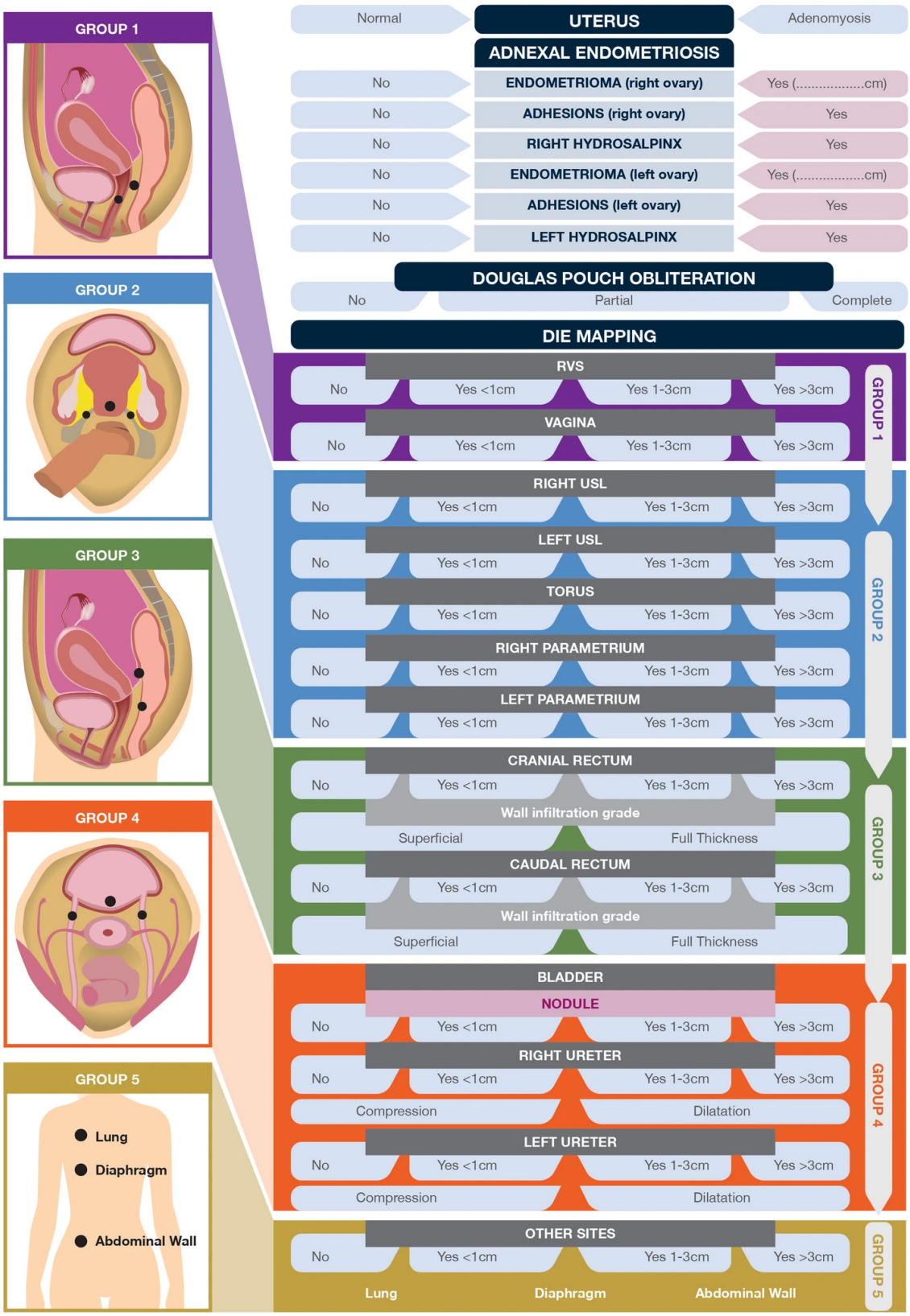
*Although they are more prevalent in premenopausal women, pelvic inflammatory disease and tubo-ovarian abscesses can also present rarely in post-menopausal women.

†Adnexal malignancies can also be asymptomatic or present with symptoms associated with their size, notably bloating, pressure, discomfort and urinary symtpoms.

AUB: **Abnormal uterine bleeding**
B-hCG: **Beta-human chorionic gonadotropin**
CA-125: **Cancer antigen 125**
CBC: **Complete blood count (Note: in this flowchart, it is said to be positive if it shows signs of infection, e.g. elevated white blood cell count)**
PID: **Pelvic inflammatory disease**
Sx: **Symptom**

Dubé L-R. Approach to Gynecological Adnexal Masses. MJM [Internet]. 2021Jul.20 [cited 2021Dec.19];20(1). Available from: https://mjm.mcgill.ca/article/view/340

Role of preoperative ultrasound mapping in the surgicalmanagement of deep infiltrating endometriosis.
Endometriosis Preoperative Evaluation Proforma (E-PEP). The proforma is filled out and marked according to ultrasound and laparoscopy findings. The site of deep infiltrating endometriosis can be also sketched in the schematic diagrams on the left corresponding to each group.



El-Maadawy, S.M., Alaaeldin, N. & Nagy, C.B. Role of preoperative ultrasound mapping in the surgical management of deep infiltrating endometriosis: a prospective observational study. Egypt J Radiol Nucl Med 52, 159 (2021). https://doi.org/10.1186/s43055-021-00526-w

Table 1 Structured MRI reporting

Anterior compartment				
	Lesion size	**Location**	**Distance from UVJ**	**Hydronephrosis**
Bladder	If present the size in minimum 2 dimensions	Intrinsic/extrinsic	Involved/not involved	Present/absent
Ureters	If present the size in minimum 2 dimensions	Intrinsic/extrinsic	In mm/cm	Present/absent
Vesicouterine space	If present the size in minimum 2 dimensions			
Vesicovaginal space	If present the size in minimum 2 dimensions			
Prevesical space	If present the size in minimum 2 dimensions			

Middle compartment				
Ovaries	Size of ovaries	Presence of follicles	Endometriomas: present/absent Size in three planes	Presence/absence of adhesions Relation to adjoining structures
Fallopian tubes	If dilated then size	Dilated/nondilated	Hydrosalpinx/hematosalpinx: present/absent	Presence/absence of adhesions Relation to adjoining structures
Ligaments	If thickened then length of involvement			Presence/absence of adhesions Relation to adjoining structures
Uterus	Size of uterus Anteverted/ retroverted Endometrial thickness Junctional zone thickness		Lesion: present/absent Size, location and depth	Presence/absence of adhesions Relation to adjoining structures
Cervix			Lesion: present/absent Size, location and depth	
Vagina			Lesion: present/absent Size, location and depth	

Posterior compartment			
	Involved/ not involved	***Size***	***Adjoining structures***
Rectocervical space	Yes/no	If present the size in minimum 2 dimensions	Adhesions, structures involved
Anterior rectal wall	Yes/no	If present the size in minimum 2 dimensions	Circumferential/focal, adhesions, structures involved Muscular layer: invasion present/absent Distance from anal verge
Uterosacral ligament	Yes/no	Length of involvement	Nodularity/diffuse involvement Adhesions, structures involved
Rectovaginal space/ septum	Yes/no	If present the size in minimum 2 dimensions	Adhesions, structures involved

Other locations	
Sigmoid	If present then describe length, size, depth of invasion, and location
Appendix	If present describe size and location
Abdominal wall	If present then describe size and location
Nerves	If involved then describe size and location

Abbreviation: UVJ, ureterovesical junction.

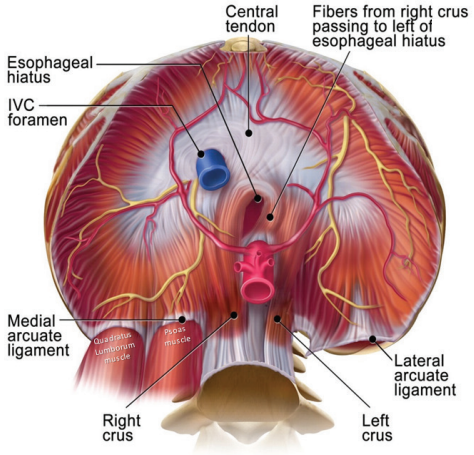
Sud S, Buxi TBS, Sheth S, Ghuman SS. Endometriosis and Its Myriad Presentations: Magnetic Resonance Imaging-Based Pictorial Review. Indian J Radiol Imaging. 2021 Jan;31(1):193-202. doi: 10.1055/s-0041-1729670. Epub 2021 May 23. PMID: 34316127; PMCID: PMC8299511.

Abdominal Wall
The abdominal wall is one of the most frequent extrapelvic locations of endometriosis. Endometriotic implants are usually embedded in the subcutaneous fatty layer and the muscles of the abdominal wall near or at the site of surgical scars. Abdominal endometriosis is often misdiagnosed and is commonly confused with abscess, lipoma, hematoma, sebaceous cyst, stitch granuloma, and desmoid tumors, which results in diagnostic delay. The condition is frequently associated with a gynecologic procedure such as cesarean delivery, episiotomy, amniocentesis, laparoscopy, tubal ligation, or hysterectomy, but it can be found in nongynecologic surgical scars such as those from appendectomy or umbilical hernioplasty.

Umbilicus is the typical US finding is a nodular formation that occupies the umbilical scar, with ground-glass echogenicity, irregular margins, and no papillary structures with a detectable blood flow. MR imaging is very useful to define the size, extension, and hemorrhagic content of cysts. It is also a valuable method to exclude concomitant abdominal disease. Inguinal Canal is characterized by the presence of endometrial stroma and glands in the extraperitoneal portion of the round ligament, the inguinal lymph nodes, the subcutaneous adipose tissue, or even the sac wall of inguinal or femoral hernias. The prevalence of inguinal endometriosis on the right side is 90%–94% as compared to the left side. Endometriosis of the round ligament is associated with groin hernias (usually inguinal) in about 40% of cases, which increases the diagnostic difficulty. The presumptive diagnosis is most often confused with incarcerated hernia, lymphadenopathy, neuroma, abscess, lymphoma, lipoma, hematoma, sarcoma, or subcutaneous cysts.

Bowel / Digestive Tract
Although the rectosigmoid colon is the most common location, endometriotic implants can also be found in the small bowel, especially in the terminal ileum. Enteric endometriosis characteristically manifests as a mural nodule that affects the serosa, muscularis propria, and submucosa. The mucosa is usually intact. MR imaging allows concomitant evaluation of the bowel, urinary tract, and pelvic nerves, along with other commonly involved sites such as the retrocervical space, vagina, and ovaries. Transvaginal US is an excellent imaging modality to investigate bowel endometriosis, especially that affecting the rectosigmoid colon. The same protocol can be used to diagnose ileocecal lesions. The nodules demonstrate the same imaging manifestations as rectosigmoid lesions, with hypoechoic nodules attached to the bowel wall and deeply infiltrating the muscularis propria.

Appendix
Appendiceal endometriosis can also be associated with intussusception into the cecum. Lesions preferentially affect the body and tip of the appendix. Diagnostic imaging of appendiceal endometriosis is difficult and requires dedicated protocols. Transvaginal US can be used to readily identify a nodular thickening of the appendix, but investigation of the right iliac fossa with a high-resolution linear transducer is mandatory.
MR imaging can also be useful, especially when used with enterography, but the method may have a limited performance on the right side of the colon, especially for small lesions, because of peristaltic artifacts and bowel content.



Thoracic Cavity
MR imaging is an excellent imaging modality with high accuracy for identification of diaphragmatic and pericardial implants, and it is superior to thin-section CT. Cystic areas and contrast enhancement are also common findings. Intraoperative findings include red lesions and endometriotic implants frequently associated with multiple diaphragmatic holes, fenestrations, perforations, and pores of different sizes, usually located at the central tendon. The catamenial nature of the symptoms (occurring between 24 hours before and 72 hours after the onset of menstruation) may help suggest the diagnosis, but imaging by specialists is fundamental to evaluation.

Pelvic Nerves
Neural entrapment is a possible occurrence and has been described in different pelvic nerves, such as the sciatic, obturator, femoral, and pudendal nerves and the inferior hypogastric and lumbosacral plexus. Catamenial sciatica may be associated with signs of other nerve trunk involvement (ie, pudendal or inferior hypogastric plexus). Over time, the sciatic pain may become permanent. Symptomatic obturator nerve endometriosis is a rare occurrence. The obturator nerve and its branches supply the muscle and skin of the medial thigh. Aggressive infiltration of the retroperitoneal space by paracervical endometriotic lesions can cause obturator infiltration. Patients may present with thigh adduction weakness or difficulty ambulating. The pelvic floor is another possible route for extension of endometriotic lesions, mainly from a retrocervical lesion with parametrium and paracolpium infiltration. The levator ani muscle may be compromised, along with the rectovaginal fascia.

Comprehensive neurologic and radiologic evaluation is mandatory to rule out lumbar disk disease, spondylotic nerve root compression, primary neural tumor, and metastasis. Early diagnosis of endometriosis infiltrating the nerve is important to prevent irreversible damage to the nerve and corresponding muscle. Results of electrophysiologic studies can help in positive diagnosis of peripheral nerve damage and can help localize the disease to the nerve trunk or nerve root involved, but they do not indicate the mechanism of the damage.*

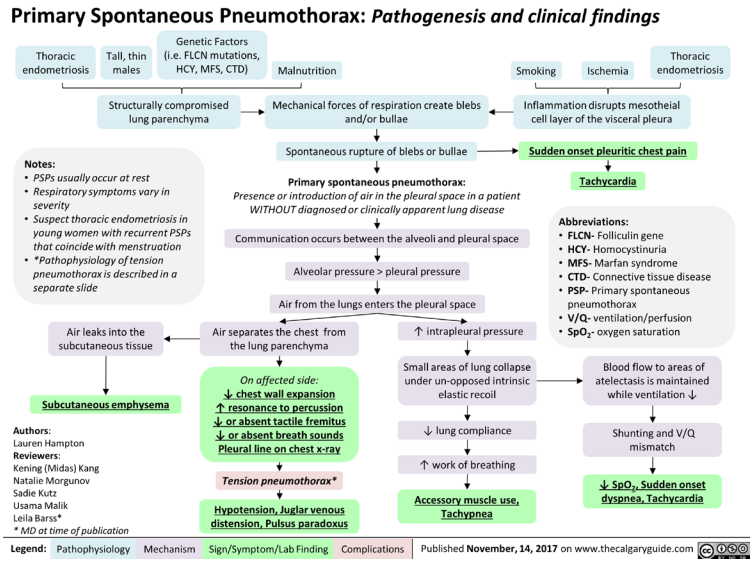
•

Thoracic Endometriosis

Thoracic endometriosis is defined as the presence of functional ectopic endometrial tissue inside the thoracic cavity. The finding of endometrial implants in the airways, pleura, pericardium, and lung parenchyma is called thoracic endometriosis syndrome. TES is the most frequent extrapelvic type of endometriosis and encompasses four clinical manifestations: catamenial pneumothorax, catamenial hemothorax, catamenial hemoptysis, and lung nodules. Pleural endometriosis manifests as catamenial pneumothorax, pneumomediastinum, hemothorax, and chest pain, and the pulmonary form manifests as catamenial hemoptysis and pulmonary nodules. Catamenial pneumothorax is the most common clinical manifestation 73% followed by catamenial hemothorax 14%, hemoptysis 7%, and lung nodules 6%.

Catamenial pneumothorax is characterized by repeated episodes of pneumothorax that are synchronized with the menstrual cycle. A pneumothorax occurring from 24 hours before to 72 hours after the onset of menstruation is described as catamenial. It is observed in 20%–30% of women with spontaneous pneumothorax. In most cases, pneumothoraces are typically right sided and small to moderate in size. A possible explanation for the right-sided predominance is the preferential clockwise flow of the peritoneal fluid circulation: there is more extensive diaphragmatic lymphatic drainage on the right side, and the anatomic barrier formed by the round and hepatic falciform ligaments predisposes right subdiaphragmatic deposition of endometrial implants.

A review of cases of catamenial pneumothorax reported lesions in the right chest in 91.7% of patients, in the left chest in 4.8% of patients, and in both sides in 3.5% of patients, findings that indicate a right-sided predominance. Symptoms of TES are typically catamenial, and chest pain is the most common clinical manifestation (90%), followed by dyspnea (31%), hemoptysis (7%), and scapular pain and cough (rare). About 30%–60% of patients are infertile. The CA-125 concentration is significantly higher in women with TES compared to those without TES.



Diaphragm and Lung Ultrasound

Lung ultrasound is an important diagnostic tool in the everyday clinical practice of specialists. Lung ultrasound facilitates a rapid and efficient diagnosis or suspicion of specific pulmonary diseases. Consequently, the utilization of lung ultrasound expedites decisions regarding the introduction of an appropriate therapy, or the extension of the diagnostic process as compared to the classical diagnostic procedures. Lung ultrasound is recommended in the assessment of pneumothorax, pleural effusion, pulmonary embolism and diaphragm function assessment. The use of lung ultrasound is a good diagnostic strategy for determining the causes of dyspnea, for the differential diagnosis and pleuritic chest pain.

The use of lung ultrasound (LUS) has been growing rapidly as a method for the diagnosis of respiratory diseases in the intensive care unit (ICU), operating room (OR), and emergency department (ER) due to its lack of radiation, high accuracy, repeatability, portability, and noninvasiveness. Although lung-protective strategies are widely used in thoracic surgery, postoperative atelectasis can still occur. Both lung ultrasound (LUS) and diaphragmatic excursion assessments are accurate and noninvasive for bedside imaging and examination. It has been deemed necessary to use LUS in the postoperative period to enhance recovery after thoracic surgery if needed.

Key Points

• US of the lungs is increasingly being used clinically and is simple to learn, perform, and interpret.
• Lung US is predominantly artifact-based as opposed to most US examinations, which allow direct visualization of the target region of interest. At lung US, the A-line artifact is seen in air-filled lung, the B-line artifact is seen in conditions such as pulmonary edema and/or fibrosis, and consolidation and effusion are directly visualized.

Video-assisted Thoracic Surgery

Although protective strategies are widely used in thoracic surgery, postoperative lung collapse and diaphragm paralysis can still occur. Ultrasound assessments are accurate and noninvasive. Critical care providers have adopted the bedside lung US in emergency (BLUE) protocol. This protocol can be performed in less than 3 minutes at the bedside. Lung US also has a well-established role in guiding interventional procedures, including thoracentesis and biopsy, and has been shown to improve outcomes in these procedures by reducing complications (eg, pneumothorax).

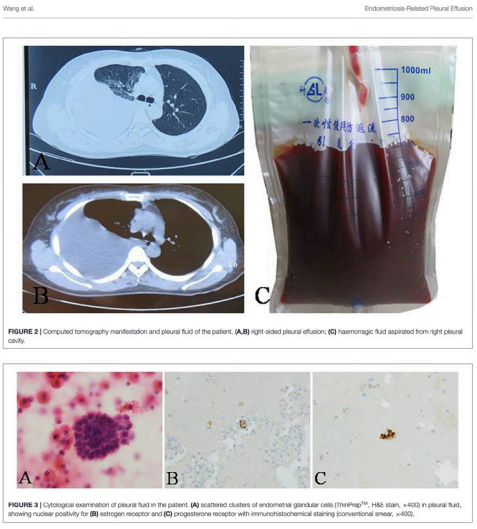
Topbas Selcuki, N. F., Yilmaz, S., Kaya, C., Usta, T., Kale, A., & Oral, E. (2021). Thoracic Endometriosis: A Review Comparing 480 Patients Based on Catamenial and Noncatamenial Symptoms. Journal of minimally invasive gynecology, S1553-4650(21)00384-8. Advance online publication. https://doi.org/10.1016/j.jmig.2021.08.005
Buda N, Kosiak W, Wełnicki M, et al. Recommendations for Lung Ultrasound in Internal Medicine. Diagnostics (Basel). 2020;10(8):597. Published 2020 Aug 16. doi:10.3390/ diagnostics10080597
Xie, C., Sun, N., Sun, K., Ming, Y., You, Y., Yu, L., Huang, J., & Yan, M. (2020). Lung ultrasound and diaphragmatic excursion assessment for evaluating perioperative atelectasis and aeration loss during video-assisted thoracic surgery: a feasibility study. Annals Of Palliative Medicine, 9(4), 1506-1517. doi:10.21037/apm-19-595b
Lung ultrasound and diaphragmatic excursion assessment for evaluating perioperative atelectasis and aeration loss during video-assisted thoracic surgery

Endometriosis-related pleural effusion (PE)
Chest pain is the most common symptoms (90%) while dyspnea (31%), haemoptysis (7%), and cough (rare) are less common (2). This discrepancy can be explained by different pathological entities in the two study cohorts. Although the symptoms of TES often developed within 24–72 h of the onset of menstruation, the temporal association between symptoms and menses was not apparent in patients with endometriosis-related PE. Less than half patients presented catamenial symptoms. This may be caused by insidiousness and persistence of symptoms due to accumulation of bloody pleural effusion in thoracic cavity after menstruation.

About 80% of the patients with endometriosis-related PE had concomitant pelvic endometriosis and were infertile or nulliparous. Less than one fourth patients had history of pelvic surgery. In contrast, it has been reported that patients with lung parenchymal endometriosis tended not to have pelvic disease (only a 10% association) but to have a significantly higher incidence of previous vaginal delivery or gynecological operative procedures than patients with pleural endometriosis. These findings imply that specific mechanisms maybe involved in the development of various types of TES. In the endometriosis- related PE, transdiaphagmatic pass of endometrium tissue and local metaplasia of coelomic epithelium have been thought as possible reasons. In parenchymal type thoracic endometriosis, haematogenous expansion of endometrium tissue and microembolization after surgical operations may hold the responsibility.

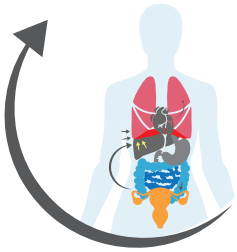
Specific mechanisms maybe involved in the development of various types of TES
In the endometriosis-related PE, transdiaphagmatic pass of endometrium tissue and local metaplasia of coelomic epithelium have been thought as possible reasons. In parenchymal type thoracic endometriosis, haematogenous expansion of endometrium tissue and microembolization after surgical operations may hold the responsibility. Patients with lung parenchymal endometriosis tended not to have pelvic disease (only a 10% association) but to have a significantly higher incidence of previous vaginal delivery or gynecological operative procedures than patients with pleural endometriosis.

Surgery-based therapy has a longer time to recurrence compared with hormonal therapy. Physicians should be familiar with the clinical features of this potentially treatable cause of spontaneous hemothorax. The cytologic diagnosis of endometriosis-related PE can be made if the examination is done in a right clinical setting with good clinical-pathological communications, avoiding unnecessary diagnostic surgical procedures for both patients and surgeons.



Specific mechanisms involved in the development of various types of Thoracic Endometrisis Syndrome

Endometriosis pleural effusions: transdiaphagmatic pass of endometrium tissue and local metaplasia of coelomic epithelium. **1**



Pulmonary Parenchymal endometriosis: haematogenous expansion of endometrium tissue and microembolization after surgical operations. **2**

Symptoms:
- **Pneumothorax**
- **Pleural Effusion**
- **Atelectasis**
- **Pulmonary Embolism**
- **Diaphragm Dysfunction**
- **Dyspnea**
- **Pleuritic chest pain**

Symptoms usually occur at rest

Ultrasound can detect

Aligns to cycle diary

Cytology = Pleural effusions

Wang P, Meng Z, Li Y and Xu Z (2021) Endometriosis-Related Pleural Effusion: A Case Report and a PRISMA-Compliant Systematic Review. Front. Med. 8:631048. doi: 10.3389/fmed.2021.631048

Thoracic Endometriosis

Diaphragmatic Function

The dangling diaphragm sign was first described by Desser in 2010 as the visualization of the free edges of the torn diaphragm as comma-shaped structures, which curl inward, toward the center of the abdomen. It is usually associated with a segmental diaphragmatic defect and diaphragm thickening. Fluoroscopy is the primary radiologic means of evaluating diaphragmatic motion, though MRI and ultrasound also are capable of this function. Ultrasound of the thorax can be used to assist with the diagnosis of diaphragm paralysis and pneumothorax.

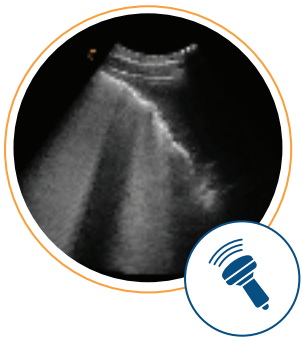
Lung Ultrasound Score

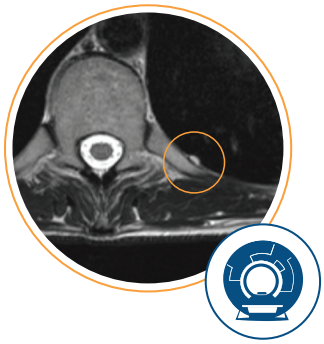
The B mode of ultrasound can show the diaphragm as a thick echogenic line.

The M mode can show the movement of the paralyzed diaphragm and can show no motion or a paradoxical movement with quiet breathing, voluntary sniffing, or deep breathing.

MRI

An MRI may be considered to diagnose the etiology of the diaphragm weakness accurately.





When analyzing the obtained ultrasound image, first of all, answer the following questions:

(a) Was the pleural line visible on the entire lung fields during the examination?
(b) is lung sliding present?
(c) is the pleural line correct?
(d) are there any pathological artifacts?
(e) f pathological artifacts are found, their location should be determined (according to the anatomical topography of the chest)
(f) if any subpleural consolidations are found, provide their location, dimensions, shape, echogenicity, and the degree of separation from the environment. If technically possible, an assessment of the vascularization (doppler) is also advisable.

Diaphragm

Ultrasonography can assess the characteristics of diaphragmatic movement, such as amplitude, force and velocity of contraction, special patterns of motion, and changes in diaphragmatic thickness during inspiration.

Heart

The number of B-lines correlates with an abnormal echocardiogram; hence the detection of B-lines is an indication for performing echocardiography, irrespective of the possible etiology of B-lines.

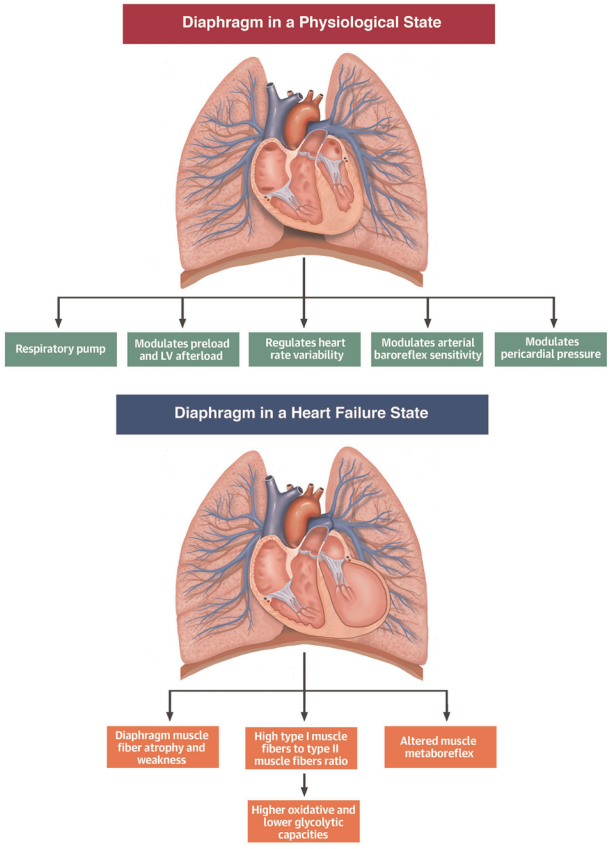
Invasive procedures

Diaphragmatic Function in Cardiovascular Disease:

Epiphrenic endometrial implants have erosive properties with subsequent development of diaphragmatic defects causing recurrent pneumothorax. These findings have to be taken into consideration for the management of this relatively rare entity, which is ideally approached in an interdisciplinary setting.

The diaphragm plays a key role in modulating cardiovascular hemodynamics. Heart failure is associated with diaphragmatic dysfunction.

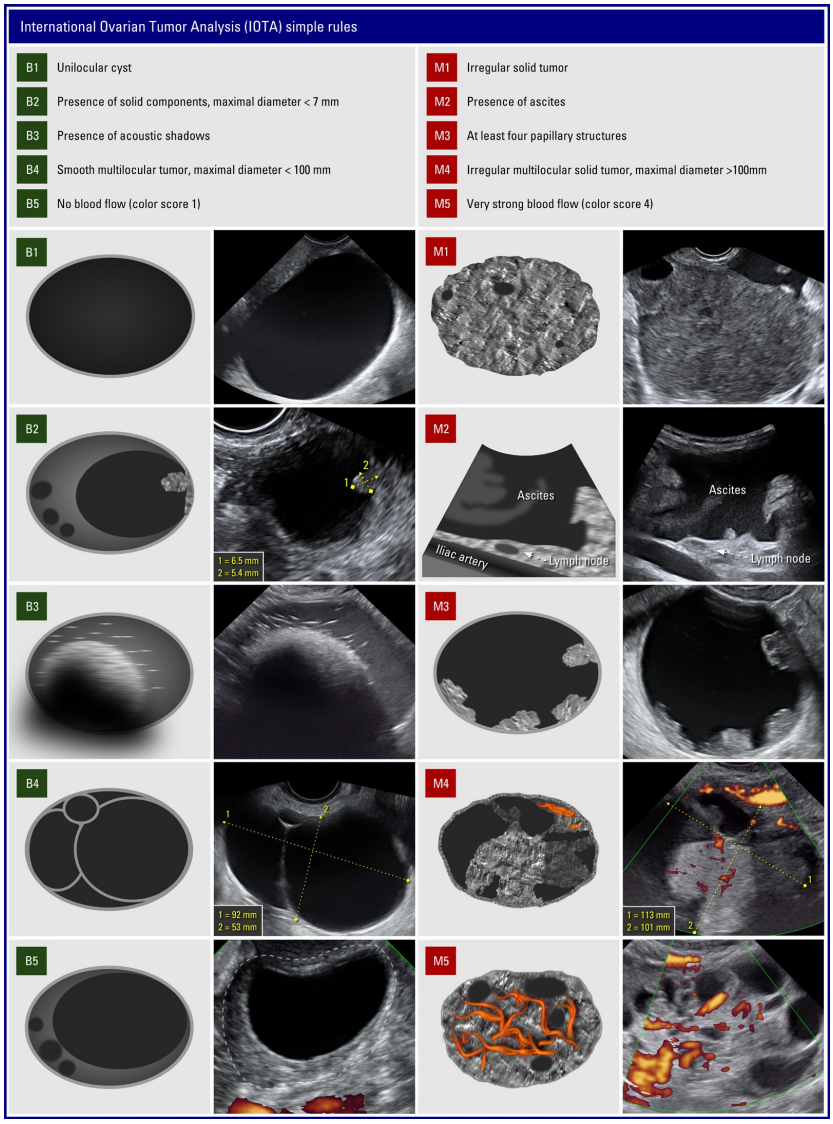
CENTRAL ILLUSTRATION: Diaphragm as a Therapeutic Target in Cardiovascular Disease



Salah HM, et al. J Am Coll Cardiol. 2022;80(17):1647-1659.

International Ovarian Tumor Analysis (IOTA) – Simple rules

The IOTA group developed a model of simple rules to help distinguish benign and malignant masses on sonography. The simple rules are comprised of 5 features that are suggestive of a malignant mass (M-features) and 5 features that are suggestive of a benign mass (B-features).



Understanding malignant transformation of endometriosis: imaging features with pathologic correlation.

Transformation of benign endometriosis to endometriosis associated ovarian carcinoma (EAOC) is rare; however, women with endometriosis can present 20 years earlier than ovarian cancer. Presenting symptoms are often vague and the radiologist's role in recognizing EAOC is critical for early detection and treatment. Malignancy most often occurs in ovarian endometriomas with less common sites involving the rectovaginal septum, rectosigmoid colon, and abdominal wall scars. Magnetic resonance (MR) relaxometry provides a noninvasive tool to discriminate between ovarian endometrioma (OE) and endometriosis-associated ovarian cancer (EAOC). The R2 predictive index is useful and valuable to the detection of the malignant transformation of endometrioma. Presenting symptoms are often vague and the radiologist's role in recognizing EAOC is critical for early detection and treatment. Multiple factors contribute to the malignant transformation of endometriosis including genetic alterations, hormonal influences, oxidative stress, and inflammation. Malignancy most often occurs in ovarian endometriomas with less common sites involving the rectovaginal septum, rectosigmoid colon, and abdominal wall scars.

International Ovarian Tumor Analysis (IOTA) – Simple rules: https://www.iotagroup.org/education/educational-material
Kawahara, N., Miyake, R., Yamanaka, S., & Kobayashi, H. (2021). A Novel Predictive Tool for Discriminating Endometriosis Associated Ovarian Cancer from Ovarian Endometrioma: The R2 Predictive Index. Cancers, 13(15), 3829. https://doi. org/10.3390/cancers13153829. Understanding malignant transformation of endometriosis: imaging features with pathologic correlation. Abdominal Radiology 2020

Endometriosis

ICD-11

Associated Tumours

ICD-O

The 2020 Blue Book includes several new 'stand-alone' chapters like Endometriosis to avoid repetition at different sites. The WHO Blue Books are regarded as the gold standard for the diagnosis of tumours and comprises a unique synthesis of histopathological diagnosis with digital and molecular pathology. These authoritative and concise reference books provide indispensable international standards for anyone involved in the care of patients with cancer or in cancer research, underpinning individual patient treatment as well as research into all aspects of cancer causation, prevention, therapy, and education.

Gynaecological Pathology: WHO 2020 and Beyond

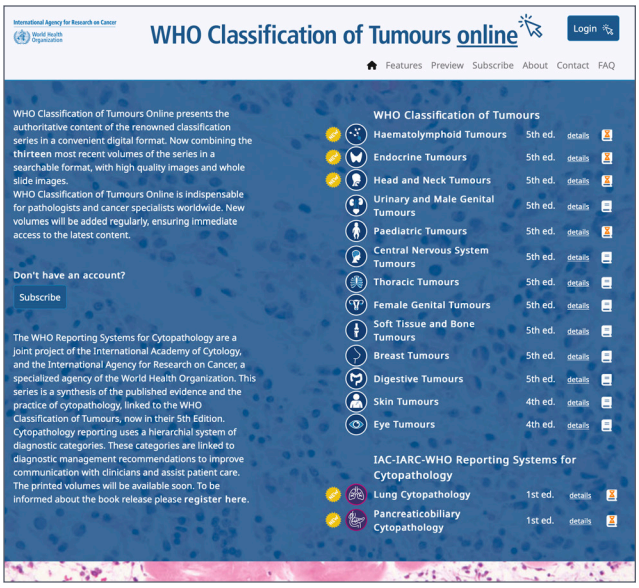
Endometriosis is an extremely common condition and, in most cases, establishing a histological diagnosis is straightforward, although a variety of benign alterations may result in problems with interpretation. Types include the contentious issue of atypical endometriosis, stromal endometriosis, polypoid endometriosis, and the association of endometriosis with florid mesothelial hyperplasia. The propensity of endometriosis to undergo neoplastic transformation especially to endometrioid and clear cell carcinoma is well known. Selected issues relating to the various neoplasms that can arise in endometriosis, with a particular concentration on unusual variants of endometrioid carcinoma that result in a disproportionately high number of issues in referral practice. The propensity of ovarian endometrioid carcinomas to show an unexpected ('aberrant') immunophenotype with positive staining with 'intestinal' markers and negative staining with Mullerian markers. Uncommon tumour types that may arise in endometriosis: seromucinous neoplasms, mesonephric-like carcinomas, and somatically derived yolk sac tumours.

Endometriosis Associated Tumours

Ovarian epithelial tumors may arise within endometriosis. These include low-grade endometrioid carcinomas, clear cell carcinomas, borderline and low-grade serous carcinomas, and mucinous carcinomas. These tumors are evolve slowly from lower-grade precursor conditions (endometriotic cysts, cystadenomas, etc) and are classified as type I tumors. The peritoneum, including the omentum and pelvic and abdominal viscera, is the most common site for dissemination of ovarian and fallopian tube cancers. This includes the diaphragmatic and liver surfaces. Pleural involvement is also seen. Other extraperitoneal or extrapleural sites are relatively uncommon, but can occur.36

Vagina Endometriosis

Endometriosis is defined as the abnormal presence of endometrial tissue, most often on the ovaries, fallopian tubes, around the ureters, and more rarely in extrapelvic locations, such as bowel, rectum, and bladder. It can rarely be presenting as vaginal mass and vaginal endometriosis is difficult to diagnosis. Vaginal cancer constitutes 1–2% of all gynecologic malignancies. The second most common subtype is adenocarcinoma, accounting for 15% of all primary vaginal cancer. Most adenocarcinoma cases correlate with benign endometriosis.



tumourclassification.iarc.who.int

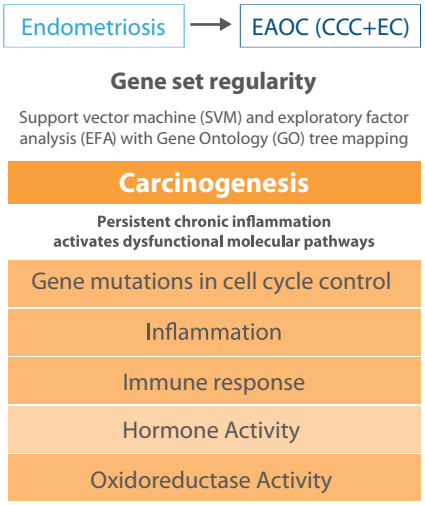
What Is New on Ovarian Carcinoma: Integrated Morphologic and Molecular Analysis Following the New 2020 World Health Organization Classification of Female Genital Tumors.

- Endometrioid and clear cell carcinomas are frequently associated with endometriosis. WHO classification integrates modern diagnostic criteria with immuno-molecular algorithms for better definitions and high diagnostic reproducibility of the different main histotypes.
- Endometriotic lesions, in particular ovary endometrioma present a 2–3-fold increased risk of transformation in clear cell or endometrioid ovarian carcinomas.
- Endometrioid and clear cell carcinoma arise from endometriosis: ectopic endometrium.
- There are multiple histopathologic subtypes for endometrial cancer including endometrioid carcinoma, serous adenocarcinoma, mucinous adenocarcinoma, clear cell adenocarcinoma, neuroendocrine tumor, malignant mixed Müllerian tumor, undifferentiated carcinoma, and mixed carcinoma.
- There are multiple histopathologic subtypes for endometrial cancer including endometrioid carcinoma, serous adenocarcinoma, mucinous adenocarcinoma, clear cell adenocarcinoma, neuroendocrine tumor, malignant mixed Müllerian tumor, undifferentiated carcinoma, and mixed carcinoma.
- The components of mixed carcinoma suggest that the common mutations reflect a field-effect The slightest increase in the risk of malignant transformation of this preventable pathology should raise awareness during obstetrical and gynecological interventions.

Singh, N. and Gilks, C.B. (2020), The changing landscape of gynaecological pathology: WHO 2020 and beyond. Histopathology, 76: 2-5. https://doi.org/10.1111/his.14035
McCluggage W. G. (2020). Endometriosis-related pathology: a discussion of selected uncommon benign, premalignant and malignant lesions. Histopathology, 76(1), 76–92. https:// doi.org/10.1111/his.13970
De Leo, A., Santini, D., Ceccarelli, C., Santandrea, G., Palicelli, A., Acquaviva, G., Chiarucci, F., Rosini, F., Ravegnini, G., Pession, A., Turchetti, D., Zamagni, C., Perrone, A. M., De Iaco, P., Tallini, G., & de Biase, D. (2021). What Is New on Ovarian Carcinoma: Integrated Morphologic and Molecular Analysis Following the New 2020 World Health Organization Classification of Female Genital Tumors. Diagnostics (Basel, Switzerland), 11(4), 697. https://doi.org/10.3390/diagnostics11040697

Complete excision of endometriosis lesions is needed because the remnant lesion might include the concealed malignancy.

Endometrioid and clear cell carcinoma arise from endometriosis: ectopic endometrium. The components of mixed carcinoma suggest that the common mutations reflect a field-effect. The slightest increase in the risk of malignant transformation of this preventable pathology should raise awareness during obstetrical and gynecological interventions.



How Does Endometriosis Lead to Ovarian Cancer?

The Molecular Mechanism of Endometriosis-Associated Ovarian Cancer Development Cancer-associated gene mutations are identified in both endometriosis and normal endometrium. Multiregional sequencing demonstrates that epithelial cells with cancerassociated mutations such as oncogenic PIK3CA and KRAS mutations clonally expand in ovarian endometriosis without cancer. Single-endometrial gland sequencing found that each gland carries distinct cancer-associated gene mutations, demonstrating the heterogeneity of the genomic architecture of the uterine endometrial epithelium. These findings support endometriosis derives from menstrual dissemination of endometrial tissue into the peritoneal cavity at the genomic level. Driver gene mutations have been identified at the genetic level in benign endometriosis, which is the origin of endometriosisassociated ovarian cancer, as well as in the normal endometrium, which is the origin of endometriosis.

The recent progress and therapy in endometriosis-associated ovarian cancer

Ovarian cancer, originating in the ovaries or its adnexal organs, with the ability to invade or spread to other parts of the body, is one of the most common gynecologic cancers. Endometriosis-associated ovarian cancers (EAOCs) including endometrioid and clear cell ovarian carcinoma are subgroups of epithelial ovarian carcinomas (EOCs). The precise pathogenesis and carcinogenesis of EOC is not well understood till now. EOCs have been classified into five major subgroups based on histology that differ in origination, pathogenesis, molecular alterations, risk factors, and prognosis.

Epidermal growth factor receptor (ERBB) and Phosphoinositide 3-kinases (PI3K)-related pathways are important in the carcinogenesis of type I EOCs, including clear cell, endometrioid, and mucinous ovarian carcinoma. Dysfunctional molecular pathways, such as deregulated oxidoreductase activity, metabolism, hormone activity, inflammatory response, innate immune response, and cell–cell signaling, play key roles in the malignant transformation of EAOCs. Nine genes related to inflammasome complex and inflammasome related pathway were identified, indicating the importance of inflammation/immunity in EAOC transformation.

Core deregulated functions, including genetic mutations involved in cell cycle control, inflammation, immune response, hormone activity, and oxidoreductase activity, forming the principle members of EAOC pathogenesis, contribute to the carcinogenesis of EAOC from ES via a crossover interaction with each other. In the microenvironment of ovarian ES, specific damage-associated molecular patterns (DAMPs) could cause inflammasome complex to prime active caspase of proinflammatory events via proinflammatory cytokines, leading to inflammation. Subsequently, persistent chronic inflammation activates inflammasome-related genes and oncogene over-expression, inducing carcinogenesis of EAOC. Therefore, dysregulated inflammasomes have played a crucial role in malignant transformation and cancer progression from ES to EAOC.

Yachida, N.; Yoshihara, K.; Yamaguchi, M.; Suda, K.; Tamura, R.; Enomoto, T. How Does Endometriosis Lead to Ovarian Cancer? The Molecular Mechanism of Endometriosis-Associated Ovarian Cancer Development. Cancers 2021, 13, 1439. https://doi.org/10.3390/cancers13061439

Su, Kuo-Mina; Wang, Peng-Huib,c; Yu, Mu-Hsiena; Chang, Chia-Mingb,c,; Chang, Cheng-Changa,*. The recent progress and therapy in endometriosis-associated ovarian cancer. Journal of the Chinese Medical Association 83(3):p 227-232, March 2020. | DOI: 10.1097/JCMA.0000000000000262*

	High-Grade Serous Carcinoma	Low-Grade Serous Carcinoma	Endometrioid Carcinoma	Clear Cell Carcinoma	Mucinous Carcinoma
Percentage of all ovarian carcinomas	70%	<5%	10%	6–10%	3–4%
Site of origin	Fallopian tube	Endosalpingiosis/ Fallopian tube	Endometriosis	Endometriosis	Teratoma/ Unknown
Precursor lesion	Serous tubal intraepithelial carcinoma (STIC)	Serous borderline tumor	Atypical endometriosis; endometrioid borderline tumor	Atypical endometriosis; clear cell borderline tumor	Mucinous borderline tumor
Hereditary cancer syndrome	BRCA1/2-associated hereditary breast and ovarian cancer syndrome (HBOC)	-	Lynch syndrome	Lynch syndrome	-
Molecular alterations	*TP53* *BRCA1/2* HRD Chromosomal instability Copy-number alterations	*KRAS* *NRAS* *BRAF* *HER2*	*CTNNB1* *PIK3CA* *PTEN* *KRAS* *ARID1A* *MSI* *POLE* *TP53*	*ARID1A* *PIK3CA* *PTEN* *MSI*	*CDKN2A* copy-number loss *KRAS* *HER2* amplification *TP53*
Potential molecular targeted therapies	PARP inhibitors; Immune checkpoint inhibitors	MEK inhibitor	mTOR inhibitors; Immune checkpoint inhibitors	Tyrosine kinase inhibitor; Immune checkpoint inhibitors	Trastuzumab

Ovarian Carcinoma: Integrated Morphologic and Molecular Analysis

Ovarian carcinomas represent a heterogeneous group of neoplasms consisting of separate entities with distinct risk factors, precursor lesions, pathogenesis, patterns of spread, molecular profiles, clinical course. The 2020 World Health Organization classification of tumors of the female genital tract divides ovarian carcinomas into at least five main and distinct types of ovarian carcinomas: high-grade serous carcinoma, low-grade serous carcinoma, endometrioid carcinoma, clear cell carcinoma, and mucinous carcinoma. The most important novelty of the fifth edition of the WHO classification of female genital tumors concerns the integration of modern diagnostic criteria with immunomolecular algorithms for a better definition and highly diagnostic reproducibility of the different main histotypes. Most Endometrioid carcinoma (EC) are found at an early stage (FIGO stage I or II) at diagnosis. The tumors are bilateral in 20% of cases and are associated in 15–20% of cases with a synchronous endometrial carcinoma. Most of ECs are frequently associated with endometriosis or contain areas of endometrioid adenofibroma and endometrioid borderline tumor. Atypical endometriosis represents the precursor lesion of about 40% of ECs. Furthermore, the finding of a direct transition from atypical ovarian endometriosis to carcinoma is substantiated by the finding of common molecular alterations in both tumor and adjacent endometriosis. Endometrioid and clear cell carcinomas are frequently associated with endometriosis. Endometrioid tumors are characterized by -catenin alterations, microsatellite instability, and PTEN and POLE mutations, while ARID1A mutations occur in both endometrioid and clear cell carcinomas.

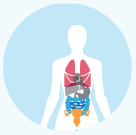
Tallini, G., & de Biase, D. (2021). What Is New on Ovarian Carcinoma: Integrated Morphologic and Molecular Analysis Following the New 2020 World Health Organization Classification of Female

The multistep process of vaginal cancer arising from deep infiltrating endometriosis.

Malignant transformation of endometriosis in extraovarian sites remains rare and facilitates excess estrogen accumulation through several mechanisms: oxidative stress, inflammation, hyperestrogenism, and specific molecular alterations. Hyperestrogenism is associated with the malignant transformation of endometriosis, and the microenvironment provided by endometriosis facilitates excess estrogen accumulation through several mechanisms. Hyperestrogenism can be caused by ovarian tumors, genetic conditions such as aromatase excess syndrome, or overconsumption of exogenous sources of estrogen, including medications used in hormone replacement therapy and hormonal contraception. High levels of estrogen can develop naturally, but too much estrogen can also result from taking certain medications. Hyperestrogenism may occur as a result of excessive estrogen secretion in the body or administration of estrogen-containing medications, such as diethylstilbestrol. Normally, aromatase is absent in a eutopic endometrial tissue, but in an endometriotic tissue, it is present in high levels. This enzyme catalyzes the conversion of androstenedione and testosterone into estrone and estradiol, respectively. Its presence in endometriotic tissue leads to the constitutive expression of estradiol, and excess estradiol can result in cellular proliferation by inducing cytokine production. In addition, estradiol stimulates prostaglandin E2 production, which promotes tumor growth and triggers aromatase activity, resulting in a positive feedback loop in favor of continuous estrogen formation in endometriosis.

Kim, J.H., Song, S.H., Kim, G. et al. The multistep process of vaginal cancer arising from deep infiltrating endometriosis: a case report. BMC Women's Health 21, 271 (2021). https://doi. org/10.1186/s12905-021-01410-5

Malignancies Associated with Extraovarian Endometriosis



78% ovaries
22% extraovarian

60–70% of cases of urinary tract endometriosis had a history of pelvic surgery.

- **Intestine**
- Abdominal scar
- Vagina and vulva
- Peritoneum
- Deep endometriosis
- Urinary tract
- Uterine cervix

Rare
Diaphragm
Inguina
Liver
Omentum
Umbilicus
Chest wall
Sciatic nerve

Endometrioid carcinoma is the dominant histological type in extraovarian sites. **70%**

Clear cell carcinoma represents the largest number of abdominal scars. **24%**

6% Various other types of malignancy : MEC, mixed epithelial carcinoma, endometrioid stromal sarcoma, adenosarcoma, and carcinosarcoma

Physicians should be careful about estrogen monotherapy after hysterectomy and long-term hormone replacement therapy in patients with a history of endometriosis.

Case: Clear Cell Carcinoma Arising from Ovarian and Thoracic Endometriosis

In 2022, it is estimated that there will be 19,880 new cases of ovarian cancer diagnosed in the US, and despite advances of treatment, an estimated 12,810 women will die of this disease. Ovarian clear cell carcinomas (CCC) account for 5-10% of epithelial ovarian cancers and are at times thought to arise from malignant transformation of a benign precursor lesion such as endometriosis. The time course from the presence of benign endometriosis to CCC in our patient suggests that the transformation may have occurred simultaneously in the chest and ovaries. In addition, the presence of CCC limited to the locations of her prior endometriotic implants without infiltration in areas where there had not been endometriosis present previously further supports that CCC arising from endometriosis behaves differently than other epithelial ovarian tumors. Endometriotic lesions being precursors for EAOCs, and the postulation that these lesions carry prooncogenic mutations, have an important implication for the treatment of CCC arising from endometriosis. It can then be concluded that when one endometriotic implant is found to be malignant, removal of all endometriotic implants may be necessary to prevent future development of clear cell cancer at other sites. Foregoing systemic lymphadenectomy may be considered especially if this may lead to increased perioperative morbidity.

Adenomyosis Associated Tumours:

Gynecologist should be aware that an increased ovarian cancer incidence also exists in women with adenomyosis. Hyperplastic changes with or without atypia are not unusual in adenomyosis, and can often be detected in the corresponding eutopic endometrium. However, malignant transformation of adenomyosis is a rare event occurring mostly in postmenopausal women. Endometrioid carcinoma is the most common histological type of malignant transformation of adenomyosis, but serous carcinoma, clear cell carcinoma, and poorly differentiated carcinoma may also be seen. Pathologic findings that suggest malignant transformation of adenomyosis include the presence of cancerous tissue and ectopic endometrial tissue in the same lesion, diagnosis of adenomyosis, transformation evidence between benign and malignant gland structures, and exclusion of other sources of tumor invasion or metastasis. In addition to epithelial cells, stromal cells in adenomyosis can also undergo neoplastic transformation to form intramural adenosarcoma, but this is exceedingly rare.39 Assessing myometrial invasion may be difficult. Depth of invasion should be measured from the endomyometrial junction to the deepest point of invasion, which may not be easy because the endomyometrial junction in normal conditions is often irregular. In these cases, it is always helpful to look for compressed, nonneoplastic endometrial glands at the nearby endomyometrial junction or even at the base of the tumor. Carcinoma involving adenomyosis foci should not be interpreted as invasive carcinoma. However, the distinction between invasive carcinoma and carcinoma involving adenomyosis may be difficult, because in some cases invasive carcinoma may not elicit stromal response. In the absence of adenomyosis uninvolved by tumor in other sections of the specimen, a diagnosis of adenomyosis involved by adenocarcinoma should be made with caution. CD10 staining is not helpful in this differential diagnosis because stromal cells surrounding foci of invasive carcinoma are also frequently CD10 positive. There are no rules for determining how to measure the depth of invasion in the rare cases where myoinvasive carcinoma is only encountered in foci of adenomyosis involved by carcinoma. In such cases, it is advised that the distance from the adenomyotic focus to the deepest area of invasion be measured. Therefore, if there is a tumor with a 2-mm focus of myoinvasion from a focus of adenomyosis in the deep myometrium, it is still considered as having <50% myometrial invasion (FIGO stage IA). In EEC with a MELF (microcystic, elongated and fragmented) pattern of invasion, desmoplasia alone should not be a criteria to measure the depth of invasion. Depth of invasion should be measured as the deepest extent with malignant cells present. LVI should not be used in measuring depth of myometrial invasion; only carcinoma infiltrating the myometrium is to be measured.

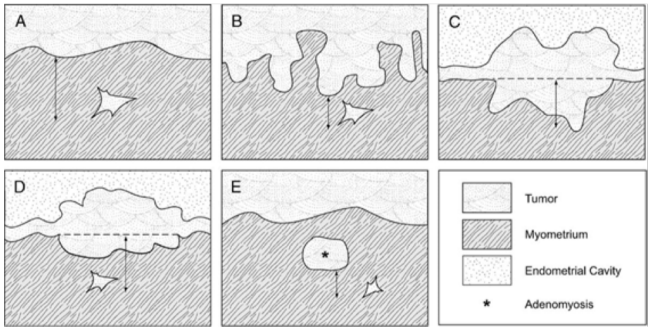


Figure 1. Schematic of measurement of depth of invasion in (A) tumor with a regular interface; (B) tumor with an irregular endomyometrial interface; (C) and (D) tumor with an exophytic growth; (E) tumor arising from adenomyosis. From Ali A, Black D, Soslow RA. Difficulties in assessing the depth of myometrial invasion in endometrial carcinoma. Int J Gynecol Pathol. 2007;26:115-123. Copyright © 2007, Wolters Kluwer Health. Reproduced with permission.

Inoue, N.; Hirakawa, T.; Mitsushita, J.; Kitahara, Y.; Iwase, A., Malignancies Associated with Extraovarian Endometriosis: A Literature Review. Endocrines 2021, 2, 251–265. https://doi. org/10.3390/endocrines2030024
Wang, D., Yang, Q., Wang, H. et al. Malignant transformation of hepatic endometriosis: a case report and literature review. BMC Women's Health 21, 249 (2021). https://doi.org/10.1186/ s12905-021-01366-6
Mendoza Stanteen, S., Pak, T., Chen, H., Carlson, M., & Lee, J. (2022). Clear Cell Carcinoma Arising from Ovarian and Thoracic Endometriosis: A Case Report and Review of Literature. Case reports in obstetrics and gynecology, 2022, 7624305. https://doi.org/10.1155/2022/7624305

The Evolution of Ovarian Carcinoma Subclassification. Cancers 2022
Endometrioid (EC) and clear cell carcinoma (CCC) arise from endometriosis, which is ectopic endometrium, meaning that the tissue of origin is not the ovary.

Köbel, M., & Kang, E. Y. (2022). The Evolution of Ovarian Carcinoma Subclassification. Cancers, 14(2), 416. https://doi.org/10.3390/cancers14020416

TPF3: Acts as a tumor suppressor in many tumor types; induces growth arrest or apoptosis depending on the physiological circumstances and cell type. Involved in cell cycle regulation as a trans-activator that acts to negatively regulate cell division by controlling a set of genes required for this process. One of the activated genes is an inhibitor of cyclin-dependent kinases. Regulates the circadian clock by repressing CLOCK-ARNTL/BMAL1-mediated transcriptional activation of PER2

proteinatlas.org: TPF3

Endometriosis-associated mesenchymal stem cells support ovarian clear cell carcinoma through iron regulation. Ovarian clear cell carcinoma (OCCC) is a deadly and treatment-resistant cancer which arises within the unique microenvironment of endometriosis. Endometriosis derived mesenchymal stem cells (enMSCs) characterized by loss of CD10 expression that specifically support OCCC growth. RNA sequencing identified alterations in iron export in CD10 negative enMSCs and reciprocal changes in metal transport in co-cultured OCCC cells. CD10 negative enMSCs exhibited elevated expression of iron export proteins hephaestin and ferroportin and donate iron. Endometriosis-associated mesenchymal stem cells support ovarian clear cell carcinoma through iron regulation. Ovarian clear cell carcinoma (OCCC) is a deadly and treatment-resistant cancer which arises within the unique microenvironment of endometriosis. Endometriosis derived mesenchymal stem cells (enMSCs) characterized by loss of CD10 expression that specifically support OCCC growth. RNA sequencing identified alterations in iron export in CD10 negative enMSCs and reciprocal changes in metal transport in co-cultured OCCC cells. CD10 negative enMSCs exhibited elevated expression of iron export proteins hephaestin and ferroportin and donate iron.

Atiya, H. I., Frisbie, L., Goldfeld, E., Orellana, T., Donnellan, N., Modugno, F., Calderon, M., Watkins, S., Zhang, R., Elishaev, E., Soong, T. R., Vlad, A., & Coffman, L. (2022). Endometriosis-Associated Mesenchymal Stem Cells Support Ovarian Clear Cell Carcinoma through Iron Regulation. Cancer research, 82(24), 4680–4693. https://doi.org/10.1158/0008-5472.CAN-22-1294

Recurrent Non-invasive Breast Tumors May Not Always Be Related to the Primary Lesion
More than 10 percent of cases of recurrent ductal carcinoma in situ (DCIS) of the breast were "de novo" tumors that occurred independently of the primary lesion and had distinct genetic alterations, according to data presented byy AACR.

- TP53 gene were detected frequently in the recurrences related to the primary lesion, but these gene variations were not common in primary DCIS cases that don't recur and those that had non-clonal (independent) recurrence.
- The most relevant breast cancer driver mutations, such as those in the TP53 or PIK3CA genes.

AACR Annual Meeting 2022 AACR Annual Meeting 2022. https://www.aacr.org/about-the-aacr/newsroom/news-releases/recurrent-non-invasive-breast-tumors-may-not-always-be-related-to-the-primary-lesion/

Frequent PIK3CA mutations in eutopic endometrium of patients with ovarian clear cell carcinoma
Eutopic endometrial glands in ovarian cancer and endometriosis show high frequency of PIK3CA and multiple hotspot mutations are often found in the same glands. Recent advances in sequencing technology have revealed the presence of numerous cancer-associated mutations in the eutopic endometrial epithelium in healthy patients. Cancer-associated mutations, including mutations in PIK3CA, are frequently found in deep infiltrating endometriosis (DIE).

Murakami, K., Kanto, A., Sakai, K. et al. Frequent PIK3CA mutations in eutopic endometrium of patients with ovarian clear cell carcinoma. Mod Pathol 34, 2071–2079 (2021). https://doi.org/10.1038/s41379-021-00861-3

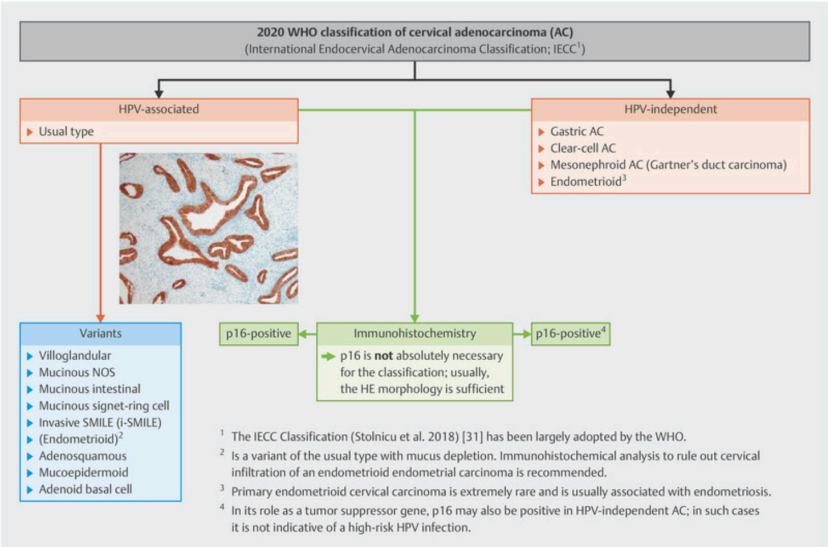
The application of risk models based on machine learning to predict endometriosis-associated ovarian cancer in patients with endometriosis

Factors predictive of endometriosis malignancy include increasing age, postmenopausal status, higher levels of carbohydrate antigen 125, larger endometriomas, and long-standing endometriosis. Chief complaints consists of dysmenorrhea, preoperative use of GnRHa, and concurrent leiomyoma or adenomyoma were negatively associated with malignant transformation of endometriosis.

- magnetic resonance relaxometry
- sensitivity of serum Smac + HE4 + CA125
- proteomic analysis of endometrial fluid
- circulating tumor DNA
- total iron levels of cyst fluid

Endometriosis-associated ovarian cancer = 1.84%

Chao X, Wang S, Lang J, Leng J, Fan Q. The application of risk models based on machine learning to predict endometriosis-associated ovarian cancer in patients with endometriosis. Acta Obstet Gynecol Scand. 2022 Dec;101(12):1440-1449. doi: 10.1111/aogs.14462. Epub 2022 Oct 9. PMID: 36210724; PMCID: PMC9812095.



Endocervical adenocarcinoma

This is a very rare primary tumor of the cervix that is said to arise in the setting of endometriosis. The WHO classification is focused on the distinction between HPV-associated and HPV-independent squamous cell carcinoma of the lower female genital organs. The incidence of endocervical adenocarcinoma, the second most common cervical cancer in the world, has been on the rise. While most cervical cancers are squamous cell carcinomas and associated with high-risk oncogenic human papillomavirus (HPV), approximately 15% of endocervical adenocarcinomas, which now represent about one quarter of all cervical cancers, are HPV-independent. Endometrioid adenocarcinoma of the cervix must display endometrioid morphology with "confirmatory endometrioid features," such as: (a) at least focally identified low-grade endometrioid glands, (b) lined by columnar cells, (c) pseudostratified nuclei, (d) no more than moderate atypia, (e) with or without squamous differentiation, (f) and/or endometriosis present, and (g) lacking HPV associated features, such as prominent mitotic figures and apoptotic bodies.

Stolnicu, Simona M.D.; Park, Kay J. M.D.; Kiyokawa, Takako M.D.; Oliva, Esther M.D.; McCluggage, W. Glenn M.D.; Soslow, Robert A. M.D. Tumor Typing of Endocervical Adenocarcinoma: Contemporary Review and Recommendations From the International Society of Gynecological Pathologists, International Journal of Gynecological Pathology: March 2021 - Volume 40 - Issue - p S75-S91 doi: 10.1097/PGP.0000000000000751

Clear cell carcinoma – clear cell adenocarcinoma of the cervix is a rare neoplasm, accounting for 3% of all cervical adenocarcinomas. This tumor is historically associated with intrauterine exposure to diethylstilbestrol (DES) or with cervical endometriosis. The decreasing costs of next generation sequencing technologies and greater acceptance of molecular and biologic findings into the pathology domain, have shifted our paradigms of classification for many gynecologic tumors.

Noorah Almadani, Emily Frances Thompson, Basile Tessier-Cloutier, Jennifer Pors, Lynn Hoang, An update of molecular pathology and shifting systems of classification in tumours of the female genital tract, Diagnostic Histopathology, Volume 26, Issue 6, 2020, Pages 278-288, ISSN 1756-2317, https://doi.org/10.1016/j.mpdhp.2020.03.007.

Ovarian seromucinous tumors

Only benign and borderline seromucinous tumors are recognized. A histogenesis of seromucinous tumors from the secondary Mullerian system or vestigial structures is favored. Seromucinous carcinoma is a subtype of endometrioid carcinoma with mucinous differentiation. There is no doubt regarding the close relationship of seromucinous ovarian tumors with ovarian endometriosis.

Idrees, R., Din, N.U., Siddique, S. et al. Ovarian seromucinous tumors: clinico-pathological features of 10 cases with a detailed review of the literature. J Ovarian Res 14, 47 (2021). https:// doi.org/10.1186/s13048-021-00796-y

Adenosarcoma

Adenosarcoma mostly involves uterus, but it can arise from other tissue such as ovaries, cervix, vagina, fallopian tubes, and pelvis particularly in a contest of endometriosis. More rarely adenosarcoma can also involve extrapelvic sites. It generally recurs locally, such as for ovarian adenosarcoma, but also with distant metastases (especially lung and liver). Since that UAS usually present as a polypoid mass within the uterine cavity, the most common clinical presentation is an abnormal uterine bleeding, observed in about 65–76%. The presence of myometrial invasion as well as the extent of disease outside the uterus determine the stage of disease.

Nigro MC, Nannini M, Rizzo A, Pantaleo. MA. Current status on treatment of uterine adenosarcoma: updated literature review. Gynecol Pelvic Med 2021;4:15.

Carcinosarcoma

UCS is now listed among endometrial carcinoma histotypes. Uterine carcinosarcomas (UCS), previously termed malignant mixed Mullerian tumors (MMMT), are a rare subtype (~5%) of uterine cancer. Their histological diagnosis is based on mixed epithelial and mesenchymal cell types within the tumor. Traditionally thought of as a class of sarcoma, molecular profiling and identification of similar risk profiles to endometrial carcinomas has led to the reclassification of UCS as carcinomas.

Beckmann, K., Selva-Nayagam, S., Olver, I., Miller, C., Buckley, E. S., Powell, K., Buranyi-Trevarton, D., Gowda, R., Roder, D., & Oehler, M. K. (2021). Carcinosarco-

Mesonephric-like Adenocarcinoma of the Female Genital Tract: From Morphologic Observations to a Well-characterized Carcinoma With Aggressive Clinical Behavior

Mesonephric-like adenocarcinoma (MLA) was introduced as a new tumor type in the endometrium and the ovary in the 2020 World Health Organization (WHO) Classification. This is a rare recently described (2016) and clinically aggressive carcinoma with a propensity for distant spread, especially to the lungs. MLA has a characteristic morphology and immunophenotype (hormone receptor negative; TTF1 and/or GATA3 positive). These neoplasms are commonly associated with KRAS and PIK3CA mutations and in the Cancer Genome Atlas (TCGA) molecular classification of endometrial carcinomas fall into the copy number low/no specific molecular profile category. Although they show significant morphological, immunophenotypic and molecular overlap with cervical mesonephric adenocarcinomas, there are other parameters which suggest a Mullerian origin and, as such, the term MLA seems apt. MLA can be added to the list of endometriosis-associated ovarian neoplasms. The outline of the series of events which lead to the first description of MLA and review the subsequent literature on this tumor type which has expanded on the morphologic features and immunophenotype, discovered the molecular underpinnings and elucidated the clinical behavior. The discovery of MLA represents an example of "new" entities still to this day being discovered through careful morphologic observations and referral of cases for specialist opinion.

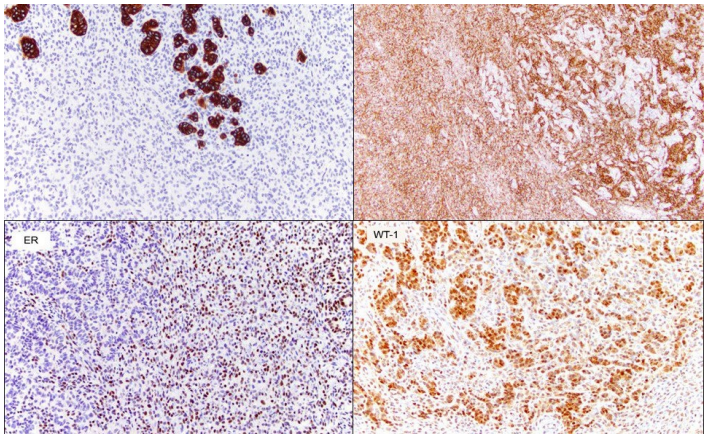
McCluggage WG. Mesonephric-like Adenocarcinoma of the Female Genital Tract: From Morphologic Observations to a Well-characterized Carcinoma With Aggressive Clinical Behavior. Adv Anat Pathol. 2022 Jul 1;29(4):208-216. doi: 10.1097/PAP.0000000000000342. Epub 2022 Apr 7. PMID: 35384888.

Stromal Endometriosis

A malignant, infiltrating mesenchymal tumour arising from the uterine corpus, cervix, vagina, and the ovary. Based on its morphologic characteristics, it is classified as either a low grade or an undifferentiated (high grade) stromal sarcoma. The low grade endometrioid stromal sarcoma is characterised by the presence of oval to spindle-shape cells that resemble the cells of the endometrial stroma, without evidence of significant atypia and pleomorphism. Numerous small vessels are also present. The undifferentiated stromal sarcoma is characterised by an aggressive clinical course, the presence of significant cellular atypia, pleomorphism, and high mitotic activity.

2E88 Benign endometrial stromal nodule
Endometrial Stromal Nodule XH8C13

2B5C Endometrial stromal sarcoma, primary site
Low-Grade Endometrial Stromal Sarcoma XH1S94
High-Grade Endometrial Stromal Sarcoma XH2CV3
Undifferentiated Uterine Sarcoma XH6HY6



Low-grade endometrial stromal sarcoma with sex cord-like elements. Pleural primary arising from endometriosis

Northwestern Pathology @NU_Pathology

Update on Endometrial Stromal Tumours of the Uterus

Endometrial stromal tumours (ESTs) are rare, uterine mesenchymal neoplasms with variegated histopathological, immunohistochemical and molecular characteristics. ESTs resemble endometrial stromal cells in the proliferative phase of the menstrual cycle. Endometrial Stromal Nodules are benign, whereas LG-ESS is a malignant neoplasm of the uterus and extra-uterine sites. The risk factors are pelvic radiation and prolonged use of tamoxifen or oestrogen. The most common findings are abnormal uterine bleeding and pelvic pain. Other symptoms of patients with LG-ESS are uterine mass and metastases to the adnexae, lymph nodes and lungs. 50% of endometrial stromal sarcomas (ESSs) occur in premenopausal women and the majority are detected at stage I of the International Federation of Gynecology and Obstetrics (FIGO).

LG-ESSs demonstrate strong expression with ER-alpha (ERα), while ER-beta (ERβ) expression is mainly negative with occasional reported cases showing weak positivity. PR expression positivity has been reported in the majority of cases (>70%), with strong positivity observed in >50% of cases and its positivity is part of the immunohistochemical confirmation of the diagnosis of LG-ESS. ESNs are clinically benign. LG-ESSs are tumours of low malignant potential, often with indolent clinical behaviour, with some cases presented with a late recurrence after hysterectomy. HGESSs are tumours of high malignant potential with more aggressive clinical outcome. With the advent of molecular techniques, the morphological classification of ESTs can be integrated with molecular findings in enhanced classification of these tumours.

Akaev, I., Yeoh, C. C., & Rahimi, S. (2021). Update on Endometrial Stromal Tumours of the Uterus. Diagnostics (Basel, Switzerland), 11(3), 429. https://doi.org/10.3390/diagnostics11030429

Endometrial stromal sarcoma arising from polypoid endometriosis.

Multifocal low-grade endometrial stromal sarcoma arising from pre-existing endometriosis in a hysterectomised patient.

Endometrial "sarcomas" complicating ovarian thecoma, polycystic ovarian disease and estrogen therapy.

Risk factors are pelvic radiation and prolonged use of tamoxifen or oestrogen.

Mixed Neuroendocrine/Non-neuroendocrine Neoplasm (MiNEN) of the Ovary Arising from Endometriosis

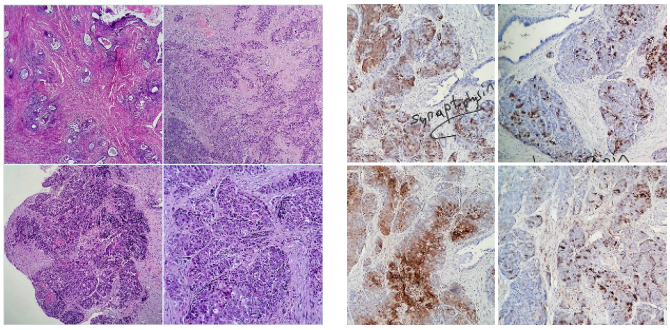
Neuroendocrine neoplasms of the ovary (Ov-NENs) are very rare and have been recently reclassified by the World Health Organization. Primary ovarian neuroendocrine neoplasms are infrequent and mainly are represented by neuroendocrine tumors. A subset of OvNECs are admixed with non-neuroendocrine carcinomas, as it occurs in female genital organs, as well (mostly endometrium and uterine cervix), and is assimilated to mixed neuroendocrine/non-neuroendocrine neoplasms (MiNENs) described in digestive and extra-digestive sites. An example is large cell OvNEC admixed with an endometrioid carcinoma of the ovary, arising in the context of ovarian endometriosis, associated with a uterine endometrial atypical hyperplasia (EAH). Findings underscore that the two neoplastic components of this Ov-MiNEN share a substantially identical molecular profile and they progress from a preexisting ovarian endometriotic lesion with a coexisting preneoplastic proliferation of the endometrium, genotypically and phenotypically related to the ovarian neoplasm. A clear molecular relationship between the endometriotic lesion and both Ov-MiNEN components emerges when immunohistochemical and genetic results are compared with morphology. The driver mutations in cancer-related genes identified in the malignant proliferation are also recognizable supporting the progression of the neoplastic clone from endometriosis cells that showed morphological signs of dysplastic transformation. A putative mechanism that links the endometrial and the ovarian lesions in these patients may be found in the retrograde flow of endometrial cells already harboring cancer-associated mutations, with selective growth advantages leading to the development of endometriosis that, in the ovarian micro- environment, finds a hormonal and inflammatory background favoring its neoplastic transformation. This represents a paradigm for the pathogenesis of high-grade neuroendocrine neoplasia in the ovary and supports the concept that NECs arise along the same pathogenetic pathways of autochthonous non- neuroendocrine carcinomas of each specific anatomical site.

Maragliano R, Libera L, Carnevali I, Pensotti V, De Vecchi G, Testa M, Amaglio C, Leoni E, Formenti G, Sessa F, Furlan D, Uccella S. Mixed Neuroendocrine/Non-neuroendocrine Neoplasm (MiNEN) of the Ovary Arising from Endometriosis: Molecular Pathology Analysis in Support of a Pathogenetic Paradigm. Endocr Pathol. 2022 Sep;33(3):400-410. doi: 10.1007/s12022-021-09689-8. Epub 2021 Aug 3. PMID: 34342838; PMCID: PMC9420090.

Neuropeptide S receptor 1 (NPSR1) activates cancer-related pathways and is widely expressed in neuroendocrine tumors

NPSR1 stimulation activates intracellular pathways relevant for cell growth. NPSR1 is expressed in neuroendocrine cells and its ligand neuropeptide S (NPS) affects cell proliferation. NPSR1 is mostly expressed in the central nervous system, but also in specific peripheral cell types, such as monocytes/macrophages and neuroendocrine cells of the gut. NPSR1 has shown genetic associations with inflammatory diseases, such as asthma, inflammatory bowel disease, and arthritis, as well as with anxiety and various stress-related phenotypes. NPSR1 is expressed in Neuroendocrine tumors - NETs, and NPS pathways are important in cancer development. NPSR1 is expressed in enteroendocrine cells of the gut. Neuroendocrine cells are distributed widely throughout the body as disseminated cells or glands. Tumors originating from neuroendocrine cells are rare. Stress responses activate the neuroendocrine and sympathetic nervous system and can impact cancer development by immune dysregulation. A highly significant gene ontology group induced by NPS is the circadian clock gene pathway. NPS affects circadian clock gene expression in the same SH-SY5Y cell line with NPSR1 overexpression. Circadian clock regulates the cell cycle, DNA damage responses, ageing and metabolism. Aberrant circadian rhythms could lead to defects in the regulation of these processes, which might result in tumorigenesis and tumor progression. The other pathways affected by NPS stimulation, namely focal adhesion, TGFB, and cytokine–cytokine interactions are highly relevant for tumor progression and metastasis.

Pulkkinen V, Ezer S, Sundman L, Hagström J, Remes S, Söderhäll C, Greco D, Haglund C, Kere J, Arola J. Neuropeptide S receptor 1 (NPSR1) activates cancer-related pathways and is widely expressed in neuroendocrine tumors. Virchows Arch. 2014 Aug;465(2):173-83. doi: 10.1007/s00428-014-1602-x. Epub 2014 Jun 12. Erratum in: Virchows Arch. 2014 Aug;465(2):251. Dario, G [corrected to Grecco, D]. PMID: 24915894; PMCID: PMC4116602.



35 lady with ovarian endometriosis tumor that developed in endometriotic foci & has prominent neuroendocrine and squamous differentiation. Daliah A/Hafeez, MD @D4L14H

Peritoneal mesothelioma

Mesothelial tumors include three pathological entities, including benign multicystic peritoneal mesothelioma (BMPM). BMPM is an uncommon neoplasm and has a high recurrence rate after surgery. BMPM consists of clear cysts that take the shape of a grape-like cluster. Clinically, BMPM resembles a tangible abdominal mass and it is challenging to be diagnosed, due to its numerous differential diagnoses. The definitive diagnosis of intraperitoneal cystic masses is usually challenging. Therefore, BMPM -although very rare- should always be thought of when dealing with an intraperitoneal cystic mass. Benign multicystic peritoneal mesothelioma (BMPM) is a benign cystic tumor arising from the peritoneal mesothelium (lining of the abdominal wall). It commonly occurs in young to middle-aged women who have a prior history of abdominal surgery, endometriosis, or pelvic inflammatory disease. The first symptoms usually include abdominal or pelvic pain, tenderness, and rarely, constipation and/or urinary hesitancy.

2C51 Malignant neoplasms of peritoneum

Exclusions: Malignant neoplasms of retroperitoneum (2C50)

2C51.0 Adenocarcinomas of peritoneum
2C51.1 Cystic, mucinous or serous carcinoma of peritoneum
2C51.2 Mesotheliomas of peritoneum
A benign or malignant mesothelial neoplasm that arises from the peritoneum.

Cancer: Known Causes and Prevention

IARC Monographs on the Identification of Carcinogenic Hazards to Humans

Corpus uteri (endometrium)
Human immunodeficiency virus
Human papillomavirus
Nutrition Disorder / Obesity
Estrogen menopausal therapy
Estrogen–progestogen menopausal therapy
Tamoxifen

Uterine cervix
Human immunodeficiency virus
Human papillomavirus
Diethylstilbestrol (exposure in utero)
Estrogen–progestogen contraceptives

Vagina
Diethylstilbestrol (exposure in utero)
Human papillomavirus

Vulva
Human papillomavirus type 16

Ovary
Nutrition Disorder / Obesity
Asbestos
Estrogen menopausal therapy

Kidney
Nutrition Disorder / Obesity
Trichloroethylene
X-radiation, gamma-radiation

Renal pelvis and ureter
Aristolochic acid
Phenacetin

ALL TYPES: Tetrachlorodibenzo-para-dioxin
Dioxins can cause cancer, reproductive and developmental problems, damage to the immune system, and can interfere with hormones.

Smoking

Colon
Alcoholic beverages
Nutrition Disorder / Obesity
Regular physical activity
Processed meat
X-radiation, gamma-radiation

Liver
Nutrition Disorder / Obesity
Aflatoxins
Alcoholic beverages
Estrogen–progestogen contraceptives

Breast
Alcoholic beverages
Nutrition Disorder / Obesity (postmenopausal)
Diethylstilbestrol
Estrogen–progestogen contraceptives
Estrogen–progestogen menopausal therapy
X-radiation, gamma-radiation

Urinary bladder
Aluminium production
4-Aminobiphenyl
Arsenic
Benzidine
Chlornaphazine
Cyclophosphamide
Magenta production
2-Naphthylamine
Opium consumption
Occupational Painter
Rubber manufacturing industry
Schistosoma haematobium
ortho-Toluidine
X-radiation, gamma-radiation

The Cancer Atlas

Associations of reproductive and hormonal risk factors with the ten most common cancers among women worldwide

	Breast	Endometrium	Ovary	Cervix uteri	Liver	Thyroid	NHL	Colon & rectum	Lung, bronchus & trachea	Stomach
High endogenous estradiol levels (vs. low)	●●●●	○○○○	○					○○○		
Older age at menarche (vs. youngest)	●	●	○		○○○○	✕		✕	✕	
Ever hormonal oral contraceptive use (vs. never)	○	●●	●●●●	●●●	✕	✕	○	○		✕
Parous (vs. nulliparous)	●	●	●●	●●	✕	✕			✕	✕
Older age at first birth (vs. younger)	●●●	●●	✕	●●	✕	○○				✕
Breastfeeding for long duration (vs. no breastfeeding)	●	✕	●●		✕	○			○	✕
Late age at menopause (vs. early)	●	○	○○		✕	✕		○	○	○○
Current use of estrogen alone menopausal hormone therapy (vs. never)	○	●●●●	○		○○○	✕	○○	○		
Current use of combination menopausal hormone therapy (vs. never)	●●●	●●	○		○○	✕	✕	○○○	○	○○
Removal of any reproductive organs (vs. retention)	○		●●●●		○○○○	○○		✕		✕

Increased Risk Association
●●●●: > 1.95
●●●: 1.57 – 1.95
●●: 1.26 – 1.56
●: 1:05 – 1.25

No Risk Association
✕ Strong Evidence
✕ Moderate Evidence

Decreased Risk Association
●: 0.80 – 0.95
●●: 0.64 – 0.81
●●●: 0.51 – 0.63
●●●●: < 0.51

Evidence Strength
● Strong Evidence
○ Moderate Evidence

Endometriosis

ICD-11

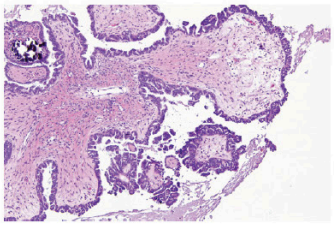
Lab Code

MF64 Abnormal immunological findings in specimens from female genital organs
MF66 Abnormal cytological findings in specimens from female genital organs
MF67 Abnormal histological findings in specimens from female genital organs
MF68 Abnormal chromosomal findings in specimens from female genital organs
MF60 Abnormal level of enzymes in specimens from female genital organs
MF61 Abnormal level of hormones in specimens from female genital organs
MF62 Abnormal level of drugs, medicaments and biological substances in specimens from female genital organs
MF63 Abnormal level of substances chiefly nonmedicinal as to source in specimens from female genital organs

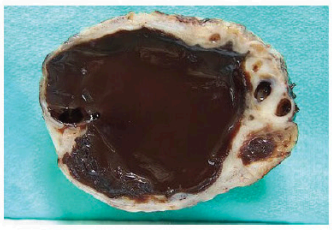
Various Types of Endometriosis

Endometriotic cyst

Esther Adler
@DrEstherAdler



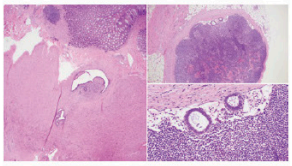
Haneen Al.Maghrabi
@Haneen_Maghrabi



Colon Endometriosis

41 year old female with colonic mass. Diffuse colonic involvement by endometriosis. Look at the lymph node sinuses.

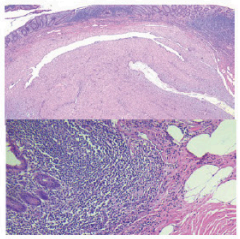
Richard Anderson
@Richardlpdpath



Appendix Endometriosis

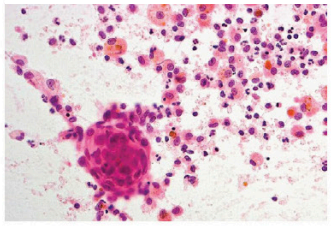
Endometriosis with extensive decidual stromal effect in a 28 year old pregnant female presented with appendicitis like symptoms.

Lina Elsayed
@linaali105



Peritoneal fluid cytology Endometriosis

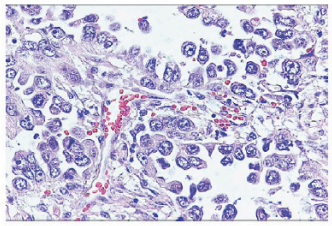
Kalyani Bambal
@kriyer68



Clear cell adenocarcinoma of the vagina.

Classically related to in utero exposure to diethylstilbestrol (DES) or often associated with endometriosis.

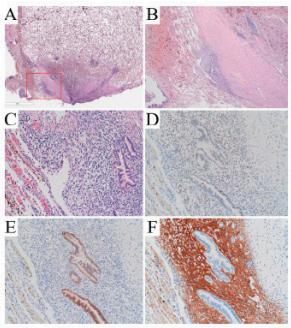
Texas Soc of Pathol
@TexPathol



Pulmonary Endometriosis

Hematogenous Metastasis
20 year old was admitted for repeated hemoptysis with her menstrual cycle.

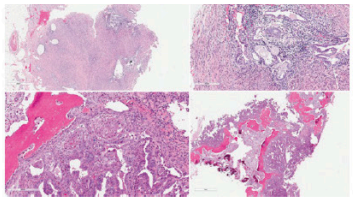
Pathobotology
@pathobotology



Ureterectomy for obstructing mass

Endometriosis involving the ureter: transforming into carcinoma. Tumor inducing an ossification response

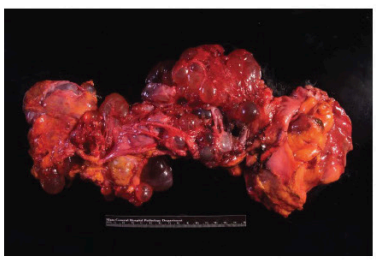
Matthew Wasco
@Gleason4plus5



Peritoneal inclusion cysts

40 year old with history of endometriosis, presenting with lower abdominal pain and distension.

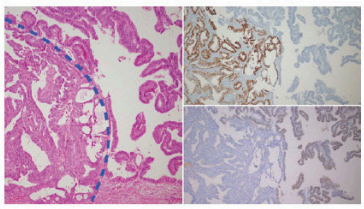
MGH Pathology
@MGHPathology



Mesonephric-like adenocarcinoma of the ovary

51 year old patient presented pelvic pain and a MRI scan revealed a mass (20cm) in the left ovary and endometriosis in the bilateral ovaries.

Mehmet Kefeli
@MehmetKefeli



Involved in the development of endometriosis/adenomyosis

Ectopic endometrial glands	**: CK7+, CK20-**
Adjacent blood vessels	**: CD34+**
Estrogen/progesterone hormone receptors	**: ER+, PR+**
Inflammatory cells	**: CD3+, CD20+, CD68+, Tryptase+**
Rate of inflammatory cells	**: Ki67+**
Oncoproteins	**: BCL2+, PTEN+, p53+**

PAX8

BCL2: controls the mitochondrial membrane permeability

Clear Cell

• **ARID1A**: During neural development a switch from a stem/progenitor to a postmitotic chromatin remodeling mechanism occurs as neurons exit the cell cycle and become committed to their adult state. The transition from proliferating neural stem/progenitor cells to postmitotic neurons requires a switch in subunit composition of the npBAF and nBAF complexes
• **PIK3CA**
• **PTEN**: A negative regulator of insulin signaling and glucose metabolism in adipose tissue
• **MSI**: A role in the proliferation and maintenance of stem cells in the central nervous system

Endometriod

• **CTNNB1** Involved in the CDK2/PTPN6/CTNNB1/CEACAM1 pathway of insulin internalization. Promotes neurogenesis by maintaining sympathetic neuroblasts within the cell cycle
• **PIK3CA**
• **PTEN**
• **KRAS** Bone marrow - mRNA splicing & cell cycle
• **ARID1A**
• **MSI**
• **POLE** Bone marrow - mRNA splicing & cell cycle, Involved in DNA synthesis during DNA repair POLK, has a role in excision repair (NER) synthesis following UV irradiation
• **TP53**

Most relevant breast cancer driver mutations: TP53 or PIK3CA (AACR) Cancer-associated mutations, including mutations in PIK3CA, are frequently found in deep infiltrating endometriosis (DIE). PIK3CA : Glyphosate pathway. EDCs hurt various aspects of women's health, particularly fertility, endometriosis, endometrial and breast cancer. A strong association between cases of ovarian germ cell tumours (OGCT) and endometriosis has been proven. The inactivation of ARID1A alone is not sufficient to cause tumour development. In fact, by imitating the estrogen molecule, they can activate the endometrial receptors, stimulating the proliferation and transformation of hormone-sensitive tissues in a tumour sense and making lifestyle increasingly crucial in preventing cancer, especially the endometrium.

Harmful effects of estrogens or progestogens
Diethylstilbestrol
Harmful effects of antigonadotrophins, antiestrogens, antiandrogens
Tamoxifen

HRT

Neuroendocrine tumors

Mixed Neuroendocrine/Non-neuroendocrine Neoplasm (MiNEN) of the Ovary Arising from Endometriosis

PIK3CA, CTNNB1, TP53, RB1, ARID1A, and P16

• Upon calcium influx, RB1 is dephosphorylated by calcineurin, which leads to release of the repressor complex.
• P16 is a cyclin-dependent kinase inhibitor that acts on CDK4/6 kinases to prevent phosphorylation of retinoblastoma (Rb) family proteins and promotes G1 cell cycle arrest, leading to senescence. ARF promotes senescence through the p53 tumor suppression pathway.

• Synaptophsin: an integral membrane protein localized to synaptic vesicles
• CD56: a member of the immunoglobulin superfamily. Tissue enhanced (brain, heart muscle)

Circadian rhythms

ESR1 Estrogen. Tissue enhanced (cervix, endometrium, fallopian tube). Play a role in growth, metabolism, sexual development, gestation. The receptor encoded by this gene plays a key role in breast cancer, endometrial cancer, and osteoporosis.

PGR Progesterone. Tissue enriched (cervix, endometrium, fallopian tube, smooth muscle). Involved in the regulation of eukaryotic gene expression and affect cellular proliferation and differentiation in target tissues.

TP53 Prognostic marker in endometrial cancer. Regulates the circadian clock by repressing CLOCK-ARNTL/BMAL1-mediated transcriptional activation of PER2. Acts as a tumor suppressor in many tumor types; induces growth arrest or apoptosis depending on the physiological circumstances and cell type. Involved in cell cycle regulation as a trans-activator that acts to negatively regulate cell division by controlling a set of genes required for this process. One of the activated genes is an inhibitor of cyclin-dependent kinases. Regulates the circadian clock by repressing CLOCK-ARNTL/BMAL1-mediated transcriptional activation of PER2

PER2 Period circadian regulator 2. Circadian rhythms allow an organism to achieve temporal homeostasis with its environment at the molecular level by regulating gene expression to create a peak of protein expression.

NPSR1 Mitogen-activated protein kinase (MAPK) pathways, circadian activity, focal adhesion, transforming growth factor beta, and cytokine-cytokine interactions. Activates cancer-related pathways and is widely expressed in neuroendocrine tumors.

Endometriosis-associated mesenchymal stem cells support ovarian clear cell carcinoma through iron regulation

CD10 Ovarian clear cell carcinoma (OCCC) is a deadly and treatment-resistant cancer which arises within the unique microenvironment of endometriosis. Endometriosis derived mesenchymal stem cells (enMSCs) characterized by loss of CD10 expression that specifically support OCCC growth. CD10 negative enMSCs exhibited elevated expression of iron export proteins hephaestin and ferroportin and donate iron.

WT1 Metal-binding, Zinc

Mesonephric-like Adenocarcinoma

TTF1 Thyroid transcription factor

GATA3 Transcriptional activator which binds to the enhancer of the T-cell receptor alpha and delta genes. Binds to the consensus sequence 5′-AGATAG-3′. Required for the T-helper 2 (Th2) differentiation process following immune and inflammatory responses.

PAX8: A Highly Sensitive Marker for the Glands in Extragenital Endometriosis

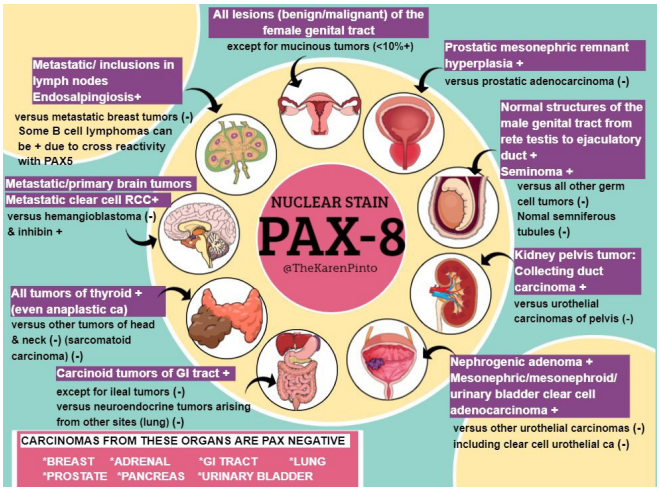
In cases of extragenital endometriosis or microscopic endometriosis lesions, pathological diagnosis can be challenging because endometriotic stroma and glands represent only a minor component of fibrotic endometriotic lesions. For better accuracy of diagnosis, the development of a sensitive and specific epithelial marker is beneficial. CD10 is helpful in detecting occult endometriosis distinguishing it from its potential mimickers. In cases of extrapelvic endometriosis, pathological diagnosis can be challenging because endometriotic stroma and glands represent only a minor component of fibrotic endometriotic lesions. For better accuracy of diagnosis, the use of a sensitive and specific epithelial marker of PAX8 is beneficial. The expression of PAX8, CD10 and PR are not affected by preoperative hormonal therapy and the positive rate of ER staining is significantly reduced by preoperative hormonal therapy. In conclusion, PAX8 is a highly sensitive epithelial marker for extragenital endometriosis. This specific expression is maintained under hormonal therapy.Histologic confirmation is not always feasible, nor is histologic examination always performed.

Arakawa, T., Fukuda, S., Hirata, T., Neriishi, K., Wang, Y., Takeuchi, A., Saeki, A., Harada, M., Hirota, Y., Matsumoto, T., Koga, K., Wada-Hiraike, O., Kurihara, M., Fujii, T., & Osuga, Y. (2019). PAX8: A Highly Sensitive Marker for the Glands in Extragenital Endometriosis. Reproductive sciences (Thousand Oaks, Calif.), 1933719119828095. Advance online publication. https://doi.org/10.1177/1933719119828095

The Importance of Stromal Endometriosis in Thoracic Endometriosis

Diagnosis of Thoracic Endometriosis is often greatly delayed leading to further complications of the disease and recurrent hospitalizations. Immunohistochemical evaluation should become mandatory and will improve diagnosis and classification of the disease. Pelvic endometriosis is an indicator of susceptibility, but not a prerequisite for TE. Diagnosis of thoracic endometriosis with immunohistochemistry Pathological and immunohistochemical features of thoracic endometriosis are not well understood. A diagnosis of thoracic endometriosis is simple when both endometrial stroma and gland are present. In cases of endometriosis with stroma only, a further classification of "aggregated pattern", in which immunohistochemistry is ER-, PR- and CD10-positive might be necessary for diagnosis. The presence of functional endometrium in the thoracic cavity may cause hemoptysis in case of bronchial location or pneumothorax in the case of pleural or diaphragmatic involvement. Even if thoracic endometriosis is suspected based on an individual's clinical background, it is difficult to identify confirmatory pathologic evidence of thoracic endometrial tissue. Classic histopathologic features of endometriosis are represented by the "triad" of endometrial glands, stroma, and hemosiderin-laden macrophages. However, the recognition of these elements is not always achieved on small tissue specimens. This "triad" was recognized in 44% of the patients, and while only stroma was present in 56% of thoracic endometriosis cases. Our analyses led us to propose a novel strategy for the diagnosis of thoracic endometriosis in women who developed pneumothorax.

Mecha E, Makunja R, Maoga JB, Mwaura AN, Riaz MA, Omwandho COA, Meinhold-Heerlein I, Konrad L. The Importance of Stromal Endometriosis in Thoracic Endometriosis. Cells. 2021 Jan 18;10(1):180. doi: 10.3390/cells10010180. PMID: 33477657; PMCID: PMC7831500.



Immunohistochemical of deep infiltrating endometriosis, lymph node endometriosis and atypical ovarian endometriosis including description of a perineural invasion

Analysis of ER, PR, Ki-67 and p53. From a histological and immunohistochemical point of view, deep infiltrating endometriosis and lymph node endometriosis appear to represent the same entity. A simple immunohistochemical panel with antibodies against ER, PR and p53 is useful in diagnosing atypical endometriosis. The marked endometriosis-associated neural changes (endometriotic neuropathy) could be one of the causes of impaired function of the affected organs after debulking surgery with macroscopic negative resection margins as well as pain symptomatology in macroscopic inapparent endometriotic lesions.

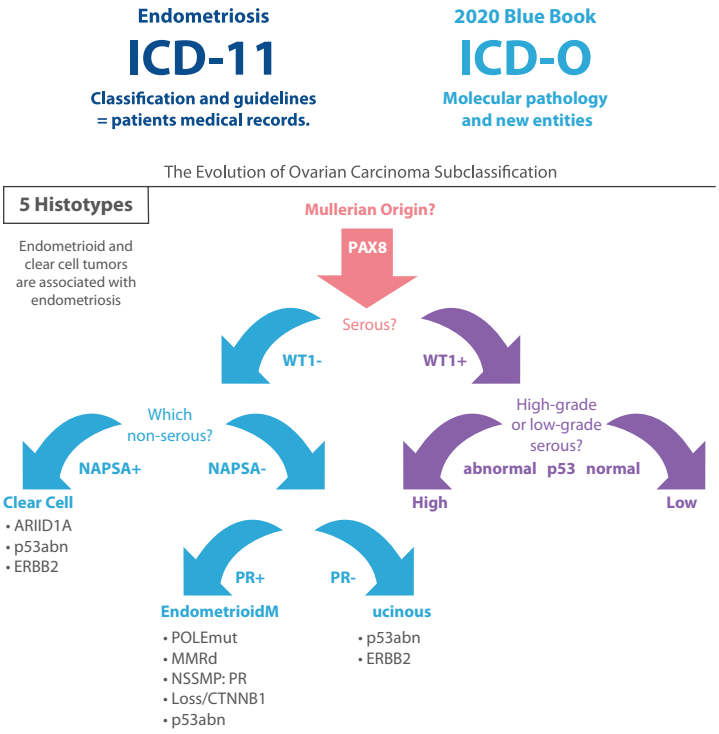
Lenz J, Chvatal R, Fiala L, Konecna P, Lenz D. Comparative immunohistochemical study of deep infiltrating endometriosis, lymph node endometriosis and atypical ovarian endometriosis including description of a perineural invasion. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub. 2021 Mar;165(1):69-79. doi: 10.5507/bp.2020.006. Epub 2020 Mar 9. PMID: 32158015.

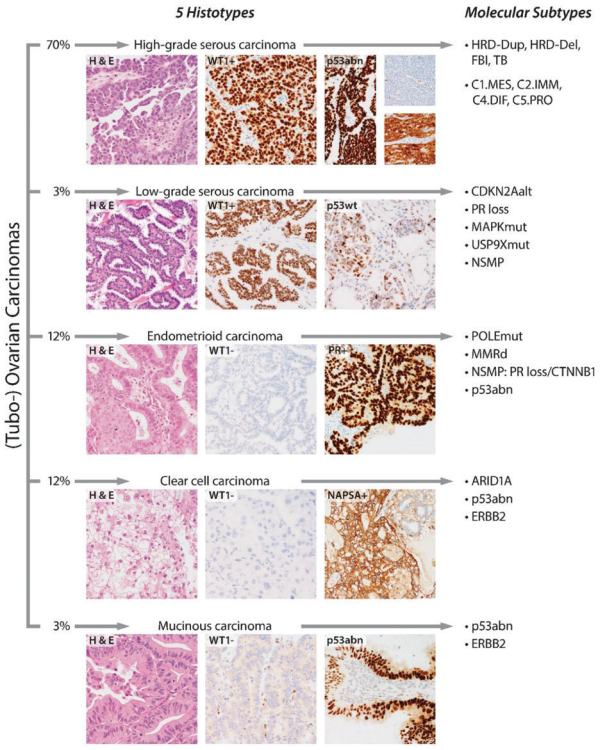
Ovarian Carcinoma: Integrated Morphologic and Molecular Analysis

Ovarian ECs have two different patterns of invasion: expansile and destructive. Expansile invasion is characterized by confluent glandular growth and has been correlated with low-stage and good prognosis. Destructive invasion shows neoplastic glands and small nests of tumor cells infiltrating the stroma associated with a marked desmoplastic reaction. The immunohistochemical profile of EC includes diffuse positivity for PAX 8, Vimentin, Estrogen (ER),
and Progesterone receptors (PR). Nuclear expression of β-catenin is present in a subset of ECs. Unlike HGSC, ECs are usually negative or only focal positive for WT1, p53, and p16. High-grade EC may show p53 mutation pattern staining.

De Leo A, Santini D, Ceccarelli C, Santandrea G, Palicelli A, Acquaviva G, Chiarucci F, Rosini F, Ravegnini G, Pession A, Turchetti D, Zamagni C, Perrone AM, De Iaco P, Tallini G, de Biase D. What Is New on Ovarian Carcinoma: Integrated Morphologic and Molecular Analysis Following the New 2020 World Health Organization Classification of Female Genital Tumors. Diagnostics (Basel). 2021 Apr 14;11(4):697. doi: 10.3390/diagnostics11040697. PMID: 33919741; PMCID: PMC8070731.

Histolo
is obtai
Atypica





Endometrial precancers

- Criteria for the diagnosis of endometrial precancers has evolved with each iteration of WHO guidelines, incorporating concepts and terminology from 4- and 2-tier systems.
- Despite refined histologic criteria, diagnosis of atypical hyperplasia/ endometrioid intraepithelial neoplasia (AH/EIN) remains a common diagnostic dilemma faced by pathologists.
- In WHO 2020, for the first time, use to biomarkers was specified as desirable.
- A panel consisting of three biomarkers– Pax2, Pten, and β-catenin–has demonstrated utility in the diagnosis of AH/EIN.
- Additional methods such as image or molecular analysis of endometrial biopsies represent future research directions in the refined diagnosis of AH/EIN with improved risk stratification.

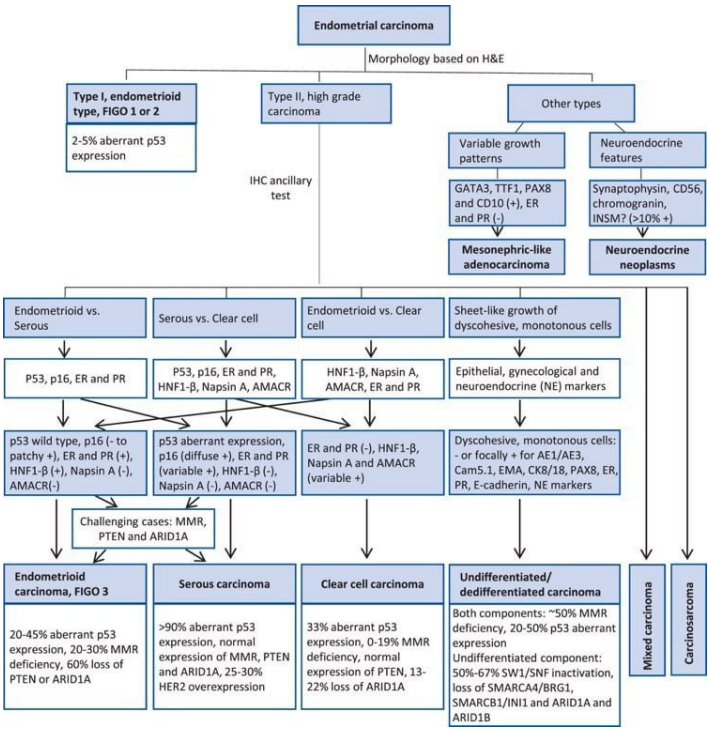
Köbel, M., & Kang, E. Y. (2022). The Evolution of Ovarian Carcinoma Subclassification. Cancers, 14(2), 416. https://doi.org/10.3390/cancers14020416

TCGA molecular classification in endometriosis-associated ovarian carcinomas: Novel data on clear cell carcinoma

Highlights

- The molecular classification of endometrial carcinoma shows prognostic value in endometriosis-associated ovarian cancers.
- The difference in patient outcome between the molecular groups was more distinct in ovarian clear cell carcinoma.
- POLE mutated and MMR deficient ovarian clear cell carcinomas were uncommon, but carried an excellent prognosis.
- The p53 abnormal group had the poorest prognosis in both histotypes, which was particularly emphasized in clear cell tumors.
- No specific molecular profile (NSMP) was the largest group in both histotypes.

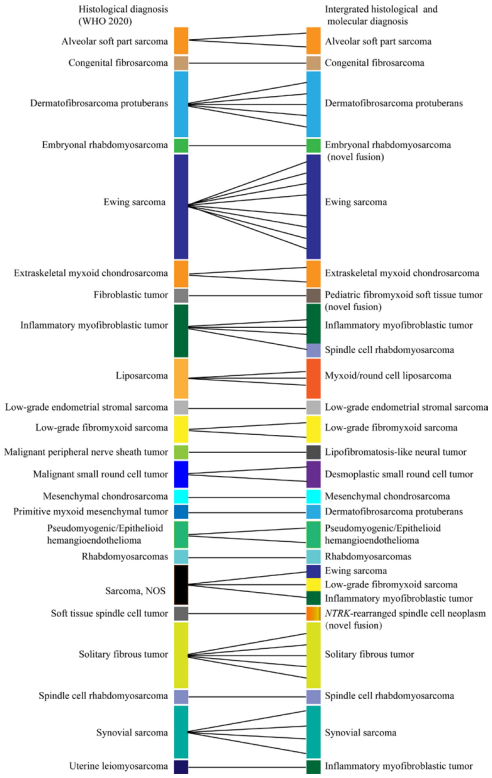
Jonna Similä-Maarala, Piret Soovares, Annukka Pasanen, Terhi Ahvenainen, Pia Vahteristo, Ralf Bützow, Heini Lassus, TCGA molecular classification in endometriosis-associated ovarian carcinomas: Novel data on clear cell carcinoma, Gynecologic Oncology, Volume 165, Issue 3, 2022, Pages 577-584, ISSN 0090-8258, https://doi.org/10.1016/j.ygyno.2022.03.016.



A Timely Update of Immunohistochemistry and Molecular Classification in the Diagnosis and Risk Assessment of Endometrial Carcinomas.

Endometrial carcinoma is the most common gynecologic malignancy in the United States and has been traditionally classified based on histology. However, the distinction of certain histologic subtypes based on morphology is not uncommonly problematic, and as such, immunohistochemical study is often needed. Advances in comprehensive tumor sequencing have provided novel molecular profiles of endometrial carcinomas. Four distinct molecular subtypes with different prognostic values have been proposed by The Cancer Genome Atlas program: polymerase epsilon ultramutated, microsatellite instability hypermutated, copy number low (microsatellite stable or no specific molecular profile), and copy number high (serouslike, p53 mutant). The utilities of commonly used immunohistochemical markers for the classification of endometrial carcinomas and the recent advancements of The Cancer Genome Atlas molecular reclassification and their potential impact on treatment strategies. The current practice of classifying endometrial cancers is predominantly based on morphology. The use of ancillary testing, including immunohistochemistry, is helpful in the identification, differential diagnosis, and classification of these cancers. New developments such as molecular subtyping have provided insightful prognostic values for endometrial carcinomas.

Wang, M., & Hui, P. (2021). A Timely Update of Immunohistochemistry and Molecular Classification in the Diagnosis and Risk Assessment of Endometrial Carcinomas. Archives of pathology & laboratory medicine, 145(11), 1367–1378. https://doi.org/10.5858/arpa.2021-0098-RA



Gene fusions are one of the most common genomic alterations in soft tissue sarcomas (STS), which contain more than 70 subtypes.

The development and clinical validation of a custom designed fusion panel for sarcoma diagnosis using RNA-based NGS (RNA-NGS) Soft tissue sarcoma is a group of highly heterogeneous tumors characterized by local invasion, invasive or destructive growth, high recurrence, and distant metastasis. Gene fusions are derived from the breakage and reconnections between chromosomes, or from intra-chromosomal rearrangements with deletions, insertions, inversions, duplications, or altered transcriptions. They represent an important class of somatic alterations and often act as drivers for tumorigenesis and progression.

Traditional methods to detect gene fusions are immunohistochemistry (IHC) and FISH. However, these technologies have a common limitation in identifying multiple fused genes simultaneously. The emergence of NGS technology and modern computational tools allows the identification of multiple fused genes in parallel. By contrast, RNA sequencing has been widely used to detect gene fusions without prior knowledge of the partner sequence or specific breakpoints in cancer cell lines, fresh frozen tissues, and FFPE samples.

Hu, W., Yuan, L., Zhang, X., Ni, Y., Hong, D., Wang, Z., Li, X., Ling, Y., Zhang, C., Deng, W., Tian, M., Ding, R., Song, C., Li, J., & Zhang, X. (2022). Development and validation of an RNA sequencing panel for gene fusions in soft tissue sarcoma. Cancer science, 113(5), 1843–1854. https://doi.org/10.1111/cas.15317

ICCR: International Collaboration on Cancer Reporting

www.iccr-cancer.org/datasets

Ovary, Fallopian Tube and Primary Peritoneal Carcinoma Clinical information

Approximately 1-2% of all ovarian carcinomas are associated with LS due to a germline mutation in one of the genes encoding the DNA mismatch repair (MMR) proteins. In approximately 60% of women with LS, a gynaecological tumour (endometrial or ovarian) will represent the sentinel cancer. Endometrioid and clear cell and endometriosis-associated carcinomas occur more frequently in LS and, therefore, immunohistochemical analysis of MMR proteins or molecular testing for microsatellite instability may be considered in these tumour types, or if there is relevant personal or family history of additional LS-related neoplasia.

Tumour site/Histological sites of tumour involvement

Sites of tumour involvement should be recorded as this is necessary for tumour staging. Although site assignment (tube versus ovary versus peritoneum) for clear cell, endometrioid, low grade serous and mucinous carcinomas is generally not problematic since almost all arise in the ovary, except for occasional cases arising in extraovarian endometriosis, the same is not true for HGSCs.

Histological tumour type

Mixed ovarian carcinomas are now considered to be uncommon. It is recommended that all distinct morphological types in an ovarian carcinoma are documented, even if they comprise less than 10% of the neoplasm. The most prevalent combination being clear cell and endometrioid (both of these tumour types often arise in endometriosis). Most neoplasms which were previously classified as mixed serous and endometrioid, and mixed serous and clear cell, represent HGSCs with pseudoendometrioid areas and areas of cytoplasmic clearing respectively. In such cases, immunohistochemical markers, especially WT1, may be useful

Coexistent pathology/Precursor lesions

Borderline and malignant endometrioid, clear cell and seromucinous ovarian tumours may arise from endometriosis. The presence of endometriosis, particularly if contiguous with the tumour, may assist in determining the histotype in cases.

Carcinoma of the Bladder / Urinary Tract Carcinoma Histological tumour type

These are rare tumours and most often when clear cell adenocarcinoma presents as a primary bladder tumour it represents secondary involvement most often originating in a urethral diverticulum. Diagnosis therefore requires clinical correlation to support diagnosis as a primary bladder tumour. Clear cell adenocarcinoma and endometrioid carcinoma may arise from endometriosis or rarely Müllerianosis.

Carcinoma of the Vagina Clinical information

A history of vaginal adenosis is important since some primary vaginal adenocarcinomas of clear cell, gastric or human papillomavirus (HPV)-associated types arise in adenosis, which may be sporadic or secondary to in utero exposure to diethylstilbestrol. Some primary vaginal endometrioid adenocarcinomas arise in endometriosis and this may be stimulated by hormones, including unopposed estrogens.

Coexistent pathology/precursor lesions

There are also recognised precursor lesions of some primary vaginal adenocarcinomas and these should be recorded on the pathology report; the presence of these lesions may be useful in helping to confirm a vaginal primary and in excluding a metastasis from elsewhere. Some of these adenocarcinomas, for example those of gastric, HPV-associated and clear cell type may be associated with and arise from vaginal adenosis via 'atypical adenosis' which is usually sporadic but which may be secondary to in utero exposure to diethylstilbestrol. Primary vaginal endometrioid adenocarcinomas may arise in endometriosis, and intestinal-type adenocarcinomas may arise in tubular and tubulovillous adenomas. Mesonephric adenocarcinomas may arise from benign mesonephric remnants.

Carcinoma of the Cervix Histological tumour type

Most true endometrioid neoplasms involving the cervix are likely due to direct extension from an endometrioid carcinoma in the corpus or, rarely, arises from cervical endometriosis.

Endometrial Cancer Adnexa

Clinicopathologic criteria can help to distinguish patients with good prognosis (such as those with two independent primary tumours/'low-risk') and patients with bad prognosis (such as those with an endometrial carcinoma with ovarian metastasis/'high-risk'). Distinction between these two prognostic types is based on several criteria including: 1) size of the tumour 2) histologic type and grade 3) extent/depth of myometrial invasion 4) presence of LVI 5) tubal invasion, 6) presence of endometrial hyperplasia, 7) presence of ovarian endometriosis, 8) pattern of ovarian invasion, including bilaterality, and 9) presence of additional metastases. Endometrial carcinomas metastatic to the fallopian tube wall or its serosa should be interpreted as metastatic unless there is evidence of an origin in endometriosis.

Mesothelioma in the Pleura and Peritoneum Coexistent pathology

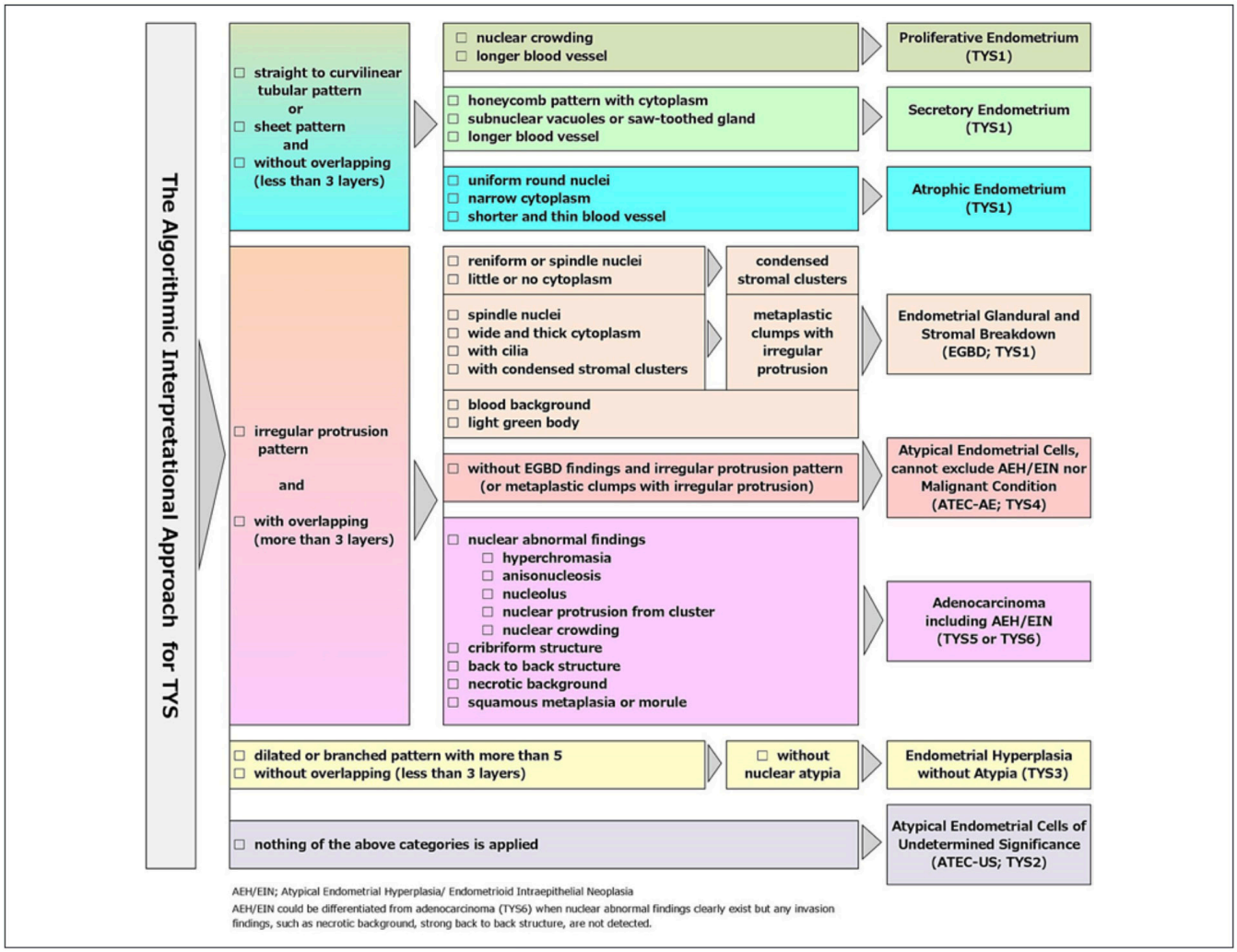
For peritoneal resection specimens, additional findings such as endometriosis, endosalpingiosis and mesothelial inclusion cysts should be noted.

Endometriosis-Related Pleural Effusion: a PRISMA-Compliant System

High clinical awareness of pleural endometriosis is essential in all female with hemorrhagic PE, especially in young females who have infertility and/or pelvic endometriosis. Plerual fluid cytology might be a simple minimally invasive and cost-effective modality in the diagnosis of endometriosis-related PE. Treatment is challenging due to high recurrence and the optimal management of endometriosis-related PE needs further evaluation. Thoracic endometriosis syndrome (TES) is a rare disorder characterized by the presence of functioning endometrial tissue in pleural, lung parenchyma, and airway. A majority of patients with TES present catamenial pneumothorax (73%), while ~14% of the cases show hemothorax. Diagnosis of endometriosis-related PE is challenging and depends on cytological and/or histopathological examinations demonstrating endometrial cells in pleural fluids (PF) or tissue. PF cytology might be a simple, minimally invasive, and cost-effective modality in the diagnosis of endometriosis-related PE by experienced cytopathologists if it is performed in appropriate time.

Wang P, Meng Z, Li Y, Xu Z. Endometriosis-Related Pleural Effusion: A Case Report and a PRISMA-Compliant Systematic Review. Front Med (Lausanne). 2021 Mar 30;8:631048. doi: 10.3389/fmed.2021.631048. PMID: 33859990; PMCID: PMC8042286.

Algorithmic Interpretational and Diagnostic Approach to Endometrial Cytology



Norimatsu, Y., Kobayashi, T.K., Hirai, Y., Fulciniti, F. (2022). Algorithmic Interpretational and Diagnostic Approach to Endometrial Cytology for the Yokohama System. In: Hirai, Y., Fulciniti, F. (eds) The Yokohama System for Reporting Endometrial Cytology. Springer, Singapore. https://doi.org/10.1007/978-981-16-5011-6_5

Endometriosis

ICD-11

Harmful effects of drugs, medicaments or biological substances

EDCs hurt various aspects of women's health, particularly fertility, endometriosis, endometrial and breast cancer. A strong association between cases of ovarian germ cell tumours (OGCT) and endometriosis has been proven.

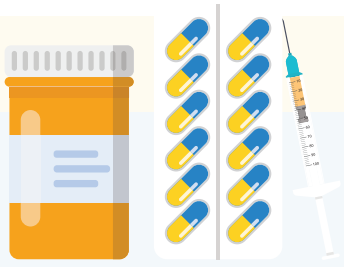
BPA: two phenols and a molecule of acetone
PAHs: Polycyclic aromatic hydrocarbons
HFRs: Halogenated flame retardants
PCB : Polychlorinated Biphenyls
Alkylphenol Ethoxylates
Mycotoxins: ZEN zearalenone
Cadmium: A carcinogenic heavy metal

Endocrine Disruptors and Endometrial Cancer: Molecular Mechanisms of Action and Clinical Implications. Int. J. Mol. Sci. 2022

Microbiota disrupting chemicals (MDCs)

The role played by human exposure to EDC in the development of diseases such as breast cancer, diabetes, obesity and some neurobehavioral disorders is widely known. The gastrointestinal tract is the main route of entry for EDC; however, their absorption through the intestinal wall is low and they are transported by the peristaltic movement to the distal small intestine and caecum where microbial flora is more abundant and they can be directly metabolized by the microbiota thereby increasing or decreasing their toxicity to the host. Endobolome refers to the group of gut microbiota genes and pathways involved not only in the synthesis of estrogens, but also in the metabolism of other steroid hormones and endocrine disruptor chemicals. The communication between gut microbiota and hormones guides to biological modifications through a diversity of tissues ranging from neuronal development to reproductive health. When dysibiosis occurs, these physiological responses are altered and contribute to development of disease.

Aguilera M, Gálvez-Ontiveros Y and Rivas A (2020) Endobolome, a New Concept for Determining the Influence of Microbiota Disrupting Chemicals (MDC) in Relation to Specific Endocrine Pathogenesis. Front. Microbiol. 11:578007. doi: 10.3389/fmicb.2020.578007



Unsafe medication practices and errors such as incorrect dosages or infusions, unclear instructions, use of abbreviations and inappropriate or illegible prescriptions are a leading cause of avoidable harm in health care worldwide. Unsafe and poor-quality care leads to $1.4 trillion to 1.6 trillion worth of lost productivity each year in low- and middle-income countries.

PL00 Drugs medicaments or biological substances associated with injury or harm in therapeutic use, hormones or their synthetic substitutes or antagonists.

NE60: Harmful effects of drugs, medicaments or biological substances: Oestrogen poisoning

Harmful effects of estrogens or progestogens
XM51S9 Diethylstilbestrol

Harmful effects of antigonadotrophins, antiestrogens, antiandrogens
XM2UX2 Tamoxifen

PH51 Exposure to or harmful effects of organic solvents
XM5B21 Phthalate
XM3MM6 Bisphenol A-glycidyl methacrylate (BPA)

PH53 Exposure to or harmful effects of pesticides
XM7D46 Pesticide
XM3K66 Insecticide
XM9EL1 DDT

NE61: Harmful effects of or exposure to noxious substances, chiefly nonmedicinal as to source
XM9Y80 Dioxin

Disorders of the adrenal glands or adrenal hormone system

5A71.1 46,XX disorders of sex development induced by androgens of maternal origin
This refers to 46,XX disorders of sex development induced by any natural or synthetic compound, usually a steroid hormone, that stimulates or controls the development and maintenance of male characteristics in vertebrates by binding to androgen receptors, of maternal origin.

LB44.6 Uterovaginal malformation due to diethylstilbestrol syndrome
Fetal diethylstilbestrol syndrome is characterised by a group of symptoms likely to occur in children and grandchildren of a woman who was treated while pregnant with diethylstilbestrol (DES). The drug is a synthetic nonsteroidal oestrogen, used in the US until 1971 and in Europe until 1978 to try and prevent miscarriage, premature delivery, and other pregnancy complications. It has been estimated that 25% of female fetuses exposed to DES in utero during the first trimester have subsequently developed genital tract anomalies including vaginal adenosis, cervical malformations, vaginal septae, uterine cavity anomalies, or fallopian tube anomalies causing subsequent fertility problems.

Drug reaction and poisoning affecting the fetus and newborn (KA00-KD5Z)

Hypersensitivity reaction to correctly administered drug (4A80-4A8Z)

PH40 Exposure to opioids
PH41 Exposure to sedative hypnotic drugs
PH42 Exposure to psychostimulants
PH43 Exposure to hallucinogens
PH45 Exposure to antidepressants
PH46 Exposure to antipsychotics

External Causes: Mechanism of injury
XE3SH Exposure to or harmful effects of substances
XE13E Poisoning or toxic effect of exposure to substance

Identification of risks from exposure to Endocrine-Disrupting Chemicals

Millions of women are affected by reproductive disorders: polycystic ovary syndrome (PCOS), uterine fibroids, and endometriosis. Genetic and environmental factors and access to good healthcare services play a role in a woman's overall reproductive health. Exposure to harmful substances affect the development of functional body systems and as a result, have a lifetime effect on an individual's health. Periods of increased vulnerability range from preconception to the final stages of adolescence. When chemicals with endocrine-disrupting activity are present during fetal development, they will affect the programming of cell and tissue development and, thus, their effects are expected to be permanent. When the same endocrine disruptor is present later – in childhood or adulthood – the effects will be different and could be transient. An example of the influence of environmental factors is changes in nutrition and general health are widely recognized as underlying reasons for the advancement of the menarche over the last 200 years from an average age of approximately 17 years to 13 years.

World Health Organization. Regional Office for Europe. (2014). Identification of risks from exposure to endocrine-disrupting chemicals at the country level. World Health Organization. Regional Office for Europe. https://apps.who.int/iris/handle/10665/344588

Associations between persistent organic pollutants and endometriosis: A multiblock approach integrating metabolic and cytokine profiling.

Humans are exposed daily to complex mixtures of chemical pollutants through their environment and diet, some of which have the potential to disrupt the bodies' natural endocrine functions and contribute to reproductive diseases like endometriosis. Epidemiological evidence supports the association between endometriosis and certain persistent organic pollutants like dioxins. Women have been shown to be especially vulnerable to the effects of EDCs which have been related to a handful of female reproductive systems including hormone-sensitive cancers, infertility, disruption of menstrual cycles and endometriosis. The profiling of POP biomarkers and endogenous biomarker profiling (metabolomics and cytokines) should be used to gain better insight. Metabolomic profiling has revealed an altered lipid profile associated to the development and progression of endometriosis.

Matta, K., Lefebvre, T., Vigneau, E., Cariou, V., Marchand, P., Guitton, Y., Royer, A. L., Ploteau, S., Le Bizec, B., Antignac, J. P., & Cano-Sancho, G. (2022). Associations between persistent organic pollutants and endometriosis: A multiblock approach integrating metabolic and cytokine profiling. Environment international, 158, 106926. https://doi.org/10.1016/j.envint.2021.106926

Exposure to phthalates and female reproductive health

An escalating amount of scientific evidence has suggested a worldwide trend of reduced human reproductive capacity. Infertility is a significant problem in society, being estimated that the condition affects over 15% of reproductive-aged couples. The increase of infertility rates in the past years is influenced by many factors, and environmental influences upon reproduction are under growing assessment.

Phthalates

Phthalates are synthetic chemicals manufactured after the esterification of the phthalic acid with different alcohols and with applications in a wide variety of consumer products. They are used primarily as plasticizers, mainly to soften and increase the flexibility of plastics, most commonly polyvinyl chloride (PVC) products, and as fragrance ingredients used as carriers to allow the scent to endure [28]. The presence of phthalates can be found in several everyday products as clothing and food.

OvarIAN effects

The ovary is a crucial component of the female endocrine system, being vital for reproductive health and processes, including folliculogenesis, steroidogenesis, and proper maturation of female gametes, but also having an important role on cardiovascular, mood, brain, and skeletal health. The ovarian development and its function are carefully regulated, and any defect or disturbance of these processes can lead to impaired reproductive function.

Uterine/ endometrial disorders

The uterus is a key organ in mammalian development, being an important component for reproduction and embryogenesis processes. Uterine cells respond to estrogen and progesterone, which regulate endometrial cell proliferation and differentiation. Estrogen promotes endometrial cell proliferation and growth and increases vascular permeability. Progesterone reduces estrogen levels and promotes cell differentiation and angiogenesis.

Pregnancy

Pregnancy is a vulnerable period for a woman and her offspring. Pregnancy complications occur in approximately 19% of pregnancies, including metabolic alterations, gestational hypertension, preeclampsia, eclampsia, preterm birth, and placenta disorders. During the gestational period, a change in reproductive hormone levels is required to maintain and develop a healthy pregnancy.

Basso, C. G., de Araújo-Ramos, A. T., & Martino-Andrade, A. J. (2022). Exposure to phthalates and female reproductive health: A literature review. Reproductive toxicology (Elmsford, N.Y.), 109, 61–79. https://doi.org/10.1016/j.reprotox.2022.02.006

Multigenerational Endometriosis : consequence of fetal exposure to diethylstilbestrol

Exposition to estrogen-like endocrine-disrupting chemicals (EDCs) has been reported to contribute to the fetal origin of endometriosis. The pathophysiology of endometriosis stems from a broad spectrum of genetic factors and environmental influences. Retrograde menstruation is influenced by a genetic predisposition and is involved in inflammation, angiogenesis and vascularization processes. Other factors such as oxidative stress, resistance to apoptosis and immunological dysregulation also contribute to this disease. Environmental factors also exert a considerable impact through epigenetic mechanisms. Increased estrogen activity during fetal life seems to be an important factor of endometriosis onset and progression, and epidemiological studies supports a higher rate of endometriosis among women exposed to diethylstilbestrol (DES) in utero. The link between endometriosis and fetal exposure to endocrine-disrupting chemicals (EDCs) with estrogen-like activity, such as dioxins, organochlorine pesticides, bisphenols and phthalates, has been established.

Gaspari, L., Soyer-Gobillard, MO., Paris, F. et al. Multigenerational endometriosis : consequence of fetal exposure to diethylstilbestrol ?. Environ Health 20, 96 (2021). https://doi.org/10.1186/s12940-021-00780-5

NE60 Harmful effects of drugs, medicaments or biological substances, not elsewhere classified
Harmful effects of heavy metal poisoning antidote
NE61 Cadmium poisoning
NE61 Mercurialism
MF9A Abnormal urine levels of substances chiefly nonmedicinal as to source
Abnormal urine level of heavy metals
MA13.0 Finding of abnormal level of heavy metals in blood
MA13.00 Abnormal level of lead in blood
MA18.1 Abnormal level of blood mineral
MA18.1 Abnormal blood level of cobalt

Metal
XM0V73 Cadmium
XM9YJ8 Chromium
XM1NV2 Cobalt
XM0ZH6 Lead
XM1FG4 Mercury
XM4E11 Nickel

Pollutants and Metaloestrogens

Many pollutants resemble these steroid hormones and affect these receptors as endocrine-disrupting chemicals (EDCs). As described in a recent review, these include phthalates, parabens, environmental phenols, alternate plasticizers, diethylstilbestrol, organophosphate esters, and tributyltin. The US National Institute of Environmental Health Sciences (NIEHS) defines EDCs as "chemicals that interfere with the body's endocrine system and produce adverse developmental, reproductive, neurological and immune effects." EDCs have been described to bind to nuclear receptors, such as estrogen receptors, and alter hormone functions by mimicking endogenous hormones and/or blocking them from interacting with their receptors.
EDCs may also induce genomic and nongenomic signaling. For example, bisphenol A and diethylstilbesterol have been shown to activate nongenomic signaling through estrogen receptors. The Endometriosis: Natural History, Diagnosis, and Outcomes (ENDO) study demonstrated a direct link between fibroids and increased serum levels of cadmium and lead and urinary cobalt levels. Heavy metals as metaloestrogens activate the estrogen receptor in the absence of estradiol and affect the hypothalamic–pituitary–ovarian axis as do endocrine-disrupting compounds

Heavy metals are highly present in the environment.
As components of various vitamins and enzymes, trace elements play a key role in many biochemical and physiological processes. Although small amounts of metal ions have protective properties against reactive oxygen species (ROS), their excess can induce cell damage, resulting in various diseases caused by stabilization of abnormal proteins, lipid peroxidation, and oxidation of ROS-scavenging enzymes.

Several trace elements, including iron, gold, selenium, nitrogen, were found to participate in angiogenesis (stabilizing and promoting the generation of new blood vessels). However, excess of selected trace elements such as free iron could result in uncontrolled vasculo and angiogenesis as well as the formation of abnormal vessels by increasing VEGF production. On the other hand, selenium was found to regulate apoptosis and the cell cycle and is used in cancer therapy. It reduces microvessel formation and angiogenesis by decreasing the VEGF levels of human umbilical vein and arterial cells.

Disrupted Iron homeostasis in the peritoneal cavity of women with endometriosis plays a role in the pathogenesis of this disease. The concentration of iron was higher in peritoneal fluid obtained from women with endometriosis as compared to the control group. It is suggested that copper (a redox-active metal) appears to be associated with the etiopathogenesis of oxidative stress in endometriosis.

The concentration of Copper was significantly higher in the patients with endometriosis. It is well known that some metalloestrogens such as cobalt, copper, nickel are essential minerals that are required in trace amounts for physiological human body function. When the amounts of these minerals exceed the amount essential for proper body function, they begin to interfere with the hormone receptors. Some metals, such as lead, mercury, cadmium, or vanadium, may bind to cellular estrogen receptors and then mimic the effects of physiological estrogens. They are related to the etiology of estrogen-dependent diseases, such as breast and endometrial cancer, as well as endometriosis. A connection is observed between the trace elements such as cadmium, chromium, copper, and endometriosis.

Cadmium compounds are present in stabilizers, fertilizers, production of batteries as well as plastic. The exposure may act through respiratory (smoking) as well as digestive system. Lead and cadmium were proven to induce the lipid per oxidation as well as the formation of ROS, which interferes with many antioxidant defense enzymes such as catalase, glutathione peroxidase, super-oxidase. This generates an imbalance between the production and removal of ROS in cells, causing damage to DNA as well as proteins; however, its role in endometriosis still remains unknown. Co-exposure to cadmium as well as lead was associated with a higher incidence of hospitalization in patients suffering from endometriosis.

Cobalt (II) and Chromium (III) show cytotoxic properties. These metals have a destructive effect on the cell membrane, lysosomes, and mitochondria, which leads to disorders of cell metabolism.

Mercury contamination occurred mostly through dental treatment, recycling of fluorescent lamps as well as gold mining.

Osuchowska-Grochowska, I.; Blicharska, E.; Gogacz, M.; Nogalska, A.; Winkler, I.; Szopa, A.; Ekiert, H.; Tymczyna-Borowicz, B.; Rahnama-Hezavah, M.; Grochowski, C. Brief Review of Endometriosis and the Role of Trace Elements. Int. J. Mol. Sci. 2021, 22, 11098. https://doi.org/10.3390/ijms222011098