# ENDOMETRIÓZA

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***Souhrn***

*Endometrióza (E) je definována jako přítomnost endometriálních buněk mimo dutinu děložní. Základním symptomem je bolest, velmi často je E asociována s primární či sekundární sterilitou, významně se podílí na vzniku a rozvoji ženské dyspareunie a algopareunie v sexuologii.*

***Summary***

*The factors of angiogenesis are involved in many physiological and pathological conditions. It is more and more discussing also in gynecology because we are looking for the new diagnostic and therapeutic procedures. Antibody against vascular endothelial growth factor (VEGF) is the first drug, which implies the prolongation of survival*

Jde o estrogen-dependentní onemocnění a postihuje především ženy v reprodukčním věku.(1) Výjimečně se vyskytuje i postmenopauzálně.

Spolehlivé údaje o incidenci nejsou k dispozici, lze se opřít o data DGGG (Deutsche Gesellschaft für Gynäkologie und Geburtshilfe, Německá společnost pro gynekologii a porodnictví), která socio-demograficky mohou odpovídat našim poměrům. Například jen v sousedním Německu se odhaduje výskyt 40 000 nových případů ročně.(1) Průměrná doba od prvních symptomů do stanovení korektní diagnózy je alarmujících deset let.

Incidence strmě roste, zásluhou laparoskopie jako zásadního diagnostického nástroje tak E diagnostikujeme častěji. Vidíme ale nárůst těžkých, infiltrujících forem v mladém věku a pandemii adenomyózy, i když na základě nepřímých důkazů. O důvodech můžeme spekulovat.

Plauzibilní je blokace peristaltiky dělohy hormonální antikoncepcí, iatrogenní navození dysperistaltiky mezi archimetrou a neometrou (Leyendeckerova teorie)(2), dále iatrogenní narušení kontinuity těchto vrstev diagnostickými a terapeutickými operacemi, explozí počtu císařských řezů, stálým posouváním gravidity do vyššího věku a v neposlední řadě změnou sociálního zadání ženy v západní společnosti (opouštění ženského archetypu), charakterizovaného cyklickou hormonální sekrecí ve prospěch výkonné, maskulinní, tonické. V tomto duchu by se pak jednalo o civilizační onemocnění, které destruuje prokreační schopnost člověka a tím ohrožuje jeho existenci.

Epidemiologie onemocnění, zejména rychlost šíření, pak není vysvětlitelná standardním lineárním uvažováním ve smyslu příčina –následek a musíme připustit i jiné teorie, například morfické rezonance.(3)

Jedná se o benigní onemocnění, které může mít biologický charakter malignity (metastazuje, infiltruje), je také prekancerózou karcinomu ovaria a endometria.

Etiologie a patogeneze není doposud známá, proto chybí kauzální terapie.

**Rozdělení do jednotlivých stadií má svá úskalí.**
Endometrióza je systémové onemocnění, proto je dělení na povrchovou a hlubokou E anachronismem, který má pouze deskriptivní smysl.

Cílem je sjednotit skórovací systémy v jeden univerzální. Nejdále je v tomto směru DGGG s doporučeným jednotným skórovacím systémem hluboké E s názvem ENZIAN.

Ten v analogii ke klasifikaci TNM zatím nejlépe postihuje stupně hluboké infiltrující endometriózy (DIE). Pro povrchovou E a ovariální formu E je vhodný r-AFS (American Fertile Society score).Kombinací obou dosáhneme akceptovatelného kompromisu v popisu anatomické situace.
Incidence postižení dělohy a vejcovodů není přesně známa. Stejně tak extragenitální forma E je relativně vzácná, ale vždy musíme myslet na možnost postižení bránice, slepého střeva, jizev po operacích, epiziotomii apod.

Etiologie a patogeneze jsou chronicky traktovány v odborné literatuře. Teorií je mnoho, žádná z nich ale nepostihuje komplexní stav onemocnění (teorie implantační, coelomové metaplazie, Leyendeckerova apod.). Teorie epigenetická je spíše módním slovem a východiskem z průkazní nouze. Téměř s jistotou můžeme postulovat šíření E lymfogenní cestou, postižení lokoregionálních lymfatických uzlin. Neznáme však význam, plauzibilní analogie s maligním šířením se nepotvrdila. Poslední snahou, výzkumným cílem, je odvodit od lymfatické infiltrace míru agresivity onemocnění, časnost recidiv.

Malignity asociované s endometriózou se mohou vyskytnout, riziko maligního zvratu E je kolem 1 %.(4) Kauzální souvislost však nebyla prokázána. V 80 % se jedná o ovariální karcinomy, ve 20 % o extragonadální tumory.

V případě karcinomů ovaria se jedná histologicky o endometrioidní, světlobuněčné nádory.

Pozitivní korelace se zvýšenou incidencí tohoto druhu ovariálního karcinomu zůstává i při anamnestickém údaji o ovariální formě E před mnoha lety. Nezávislými rizikovými faktory jsou velikost ovariálního endometriomu větší než 9 cm, postmenopauza a hyperestrinní stav.

Diagnostika E není obtížná, využívá základního armamentaria.

V anamnéze se koncentrujeme na „3× DYS“ (dysmenorea, dyspareunie, dyschezie), přítomnost čerstvé krve v moči a stolici, cyklicitu potíží korelující s menses, bolesti v jizvách. Mladé pacientky přicházejí zejména s problémem dyspareunie provázené anorgasmií. Stav má sociální přesah, mnohé partnerské vztahy se rozpadají, míra utrpení je taková, že zejména anorgasmie není tabuizované anamnestické téma.

Základním kamenem, který je bohužel stále více upozaďován, jsou vaginální a rektální vyšetření.

Ze zobrazovacích metod je suverénní metodou vaginální a rektální ultrazvuk, jeho výpovědní hodnota je vyšší než CT nebo MR. Nezapomínáme sonograficky vyšetřit ledviny a vyloučit hydronefrózu.

Není žádný specifický laboratorní marker, který by diagnostikoval E.

U pacientek s podezřením na infiltrující ovariální E je dobré doplnit vyšetření o AMH (antimüllerický hormon), určující reziduální ovariální kapacitu, i když výsledky nejsou tak povzbudivé, jak se očekávalo.

Nástrojem diagnózy a chirurgické léčby je laparoskopie. Máme postupovat tak, abychom měli operační strategický plán ante a nezvyšovali morbiditu dvěma výkony, diagnostickým a sanačním.

Patologická morfologie E je různorodá. Barvy peritoneální formy E nejsou relevantní.

Je třeba znovu zdůraznit, že rozdělení na povrchové a hluboké formy má pouze velmi omezený smysl, E je vždy systémové onemocnění. Věnujeme tedy vždy pozornost kupolím bráničním, zejména vpravo, ileocoeku, kompartmentům malé pánve. Endometrióza se ve svém výrazu pohybuje od diskrétních peritoneálních forem po těžkou deterioraci orgánů, k tvorbě destruujících pseudotumorů – endometriomů, které predilekčně infiltrují řídké perineurální pojivo zadního kompartmentu (bolest), infiltrují a penetrují pochvu, rektum, sigma, ojediněle ureter, nervové struktury (truncus lumbosacralis) a svalstvo.

Neznáme hranici mírného poškození, které je snad reverzibilní.

V terapii máme dva cíle, jež se prolínají – zachování či umožnění fertility a tlumení bolesti.

**Konzervativní léčba**

Obecně platí, že lékař obvykle doporučuje konzervativní léčebný přístup jako první. Pokud zjistíme, že léky proti bolesti (např. nesteroidní protizánětlivé preparáty) nejsou účinné, nastupuje některá z hormonálních terapií.

1. Ektopické endometrium zvyšuje produkci prostaglandinů, které je třeba potlačit. Nesteroidní antirevmatika (inhibitory COX-2, koxiby) produkci snižují a potlačují tak bolest při E, proto jsou často prvotním, obvykle ale dočasným lékem při řešení potíží při E.
2. Hormonální antikoncepce může snížit nebo eliminovat bolest především při menstruaci (dysmenorea) – jde nejlépe o kontinuální léčbu klasickými kontraceptivy, případně náplastmi nebo vaginálním kroužkem NuvaRing, některé preparáty ale vždy plně nevyhovují kritériím pro léčbu E.
3. GnRH (hormon uvolňující gonadotropin) antagonista – potlačení subjektivních potíží, zmenšení ložisek E

(klimakterické potíže, akné, zvýšení hmotnosti, nepravidelné krvácení aj.) – např. ganirelix acetát.

4. Agonista gonadoliberinu – potlačení subjektivních potíží, zmenšení ložisek E (vedlejší účinky – deprese, migrény, klimakterické potíže, úbytek kostní hmoty) – Zoladex (goserelin acetát).
5. Gestagenová terapie se opírá o jednosložkovou hormonální léčbu. Lékem první volby je obvykle Visanne (2 mg dienogestum), s léčbou delší než 15 měsíců nejsou ale zkušenosti. Dalšími běžně užívanými přípravky jsou například nitroděložní tělísko Mirena (levonogestrelum) nebo Depo-Provera (medroxyprogesteroni acetas). Případné zastavení menstruačního cyklu je součástí terapie, hlavním efektem léčby je eliminace bolesti při menstruaci.
6. Syntetické androgeny – původně léky první volby v 70. letech i přes řadu nepříjemných vedlejších účinků, použití se výrazně omezilo v 80. a 90. letech, kdy se rozšířilo použití GnRH.[5]
7. Selektivní modulátory estrogenových receptorů (SERM), tzv. syntetické nesteroidní antiestrogeny – např. Nolvadex (tamoxifen citrát).
8. Inhibitory aromatázy – pilotní projekt (2004) se opíral o perorální využití letrozolu (2,5 mg/den po dobu 6 měsíců), došlo k signifikantní redukci bolestivých symptomů a regresi ložisek při second-look laparoskopii. Nežádoucími účinky léku jsou mírná bolest hlavy, nevolnost a průjem.[6]
9. Selektivní modulátory progesteronových receptorů (SPRM) včetně antagonistů – syntetický steroid mifepriston (známý spíše jako abortivum pro tzv. chemickou interrupci) je antagonistou progesteronu, který obsazuje progesteronové receptory.
10. Ve stadiu experimentální léčby je použití angiostatinů, které mají ovlivnit cévní zásobení v endometriu, s jejich využitím se primárně počítá při onkologické léčbě.[7]
11. Obdobně jsou zatím experimentálně používány inhibitory matrixových metaloproteináz. Jde o skupinu enzymů schopných štěpit většinu komponent mezibuněčné hmoty. Jsou regulovány na úrovni transkripce, translace nebo přítomnosti přirozených inhibitorů.[8]

**Chirurgická léčba**

Chirurgická léčba je resekčního typu tak, abychom dosáhli kompromisu v míře resekce a zachování orgánů, fertility. Operační postupy jsou definovány a cílem je jistá unifikace postupů, opět analogická s onkologickou chirurgií.

U peritoneálních forem nevystačíme s destrukcí ložisek koagulací, správným postupem je deperitonealizace s free margin. Ovariální hluboká E se ošetřuje pouze od určité velikosti, která byla taxativně stanovena na 5 cm. Tato hranice je volná, jedná se o pseudocysty, invaginace, k tomu volíme adekvátní techniku „studené“ resekce, enukleace s minimálním použitím koagulačních nástrojů, zejména se vyhýbáme monopolární koagulaci. S každým zákrokem na ovariu klesá jeho folikulární kapacita.
Endometriomy resekujeme s ohledem na jejich anatomickou lokalizaci. Jedná se o velmi náročné chirurgické výkony, kde vždy máme na mysli maximální šetrnost k nervovým strukturám (hypogastrickému plexu), ureteru, rektu. Resekce rektosigmatu je až nejzazší variantou jen v případě obturující penetrující E. To se týká i zadní stěny poševní, močového měchýře.

Pokud však máme jasné důkazy penetrujícího, destruujícího onemocnění, pak s resekcí neváháme, neboť je to jediná cesta, jak zbavit pacientku obtíží. Průkaz penetrujícího onemocnění rektosigmatu není mnohdy snadný, rektoskopie není vhodným nástrojem, kolonoskopie může být falešně negativní nebo pro adheze neproveditelná.

Není třeba zdůrazňovat, že se jedná o multioborové operační výkony, kdy spolupráce gynekologa, chirurga a urologa je cestou k úspěchu. Je dobré odesílat pacientky tam, kde mají s takovou operativou zkušenost, nemůže být větší frustrace pro pacientku než sdělení, že operace E rektovaginálního septa je nebezpečná, a proto nebyla provedena. Každý operační výkon je zatížen akutní a chronickou postoperační morbiditou. Velmi nepříjemné jsou parciální denervace močového měchýře či rekta, pokud je nutný resekční výkon nerespektující orgánovou hranici, pak se snažíme omezit pouze na jednu stranu, pokud to anatomicko-patologická situace dovolí.

Míra recidiv se udává kolem 20 %, jako relevantní je udáván faktor věku a jistě i biologická povaha DIE, kterou zatím nedovedeme posoudit.

Velmi specifická je problematika adenomyózy. Postižení nemusí být homogenní, proto punch biopsie uteru nemá smysl. Jediná chirurgická metoda je Osadova redukce archimetry a rekonstrukce dělohy.(3)

V centrech zabývajících se chirurgickou léčbou E by měly histologické výsledky v 80 % korelovat s klinickým nálezem.

Hysterektomie je ultima ratio metoda, když byly předtím vyčerpány jiné eventuality. Vždy musí být provedena v rámci komplexní sanace E, nikoliv jako samostatný výkon v terénu aktivní E.

K problému konkomitantní sterility, ať již primární, či sekundární, je doloženo, že samostatná konzervativní terapie nezlepšuje fertilitu, pouze kombinace chirurgického výkonu a následné terapie v IVF centru.

Každé pacientce by měl být předložen individuální plán terapie podle toho, jaké cíle sleduje.

Operace by měly být prováděny v centrech, která se těmito složitými výkony zabývají, kde je zajištěna spolupráce uvedených odborností a návaznost IVF centra.
V neposlední řadě je potřeba psychologická podpora a konzultace sexuologa.

Endometrióza je onemocnění, které pacientky neohrožuje přímo na životě, ale narušuje fyzické a také sociální zdraví společnosti. Kauzální terapii neznáme, ale dovedeme čím dál lépe mírnit bolest, snižovat počet recidiv a zlepšovat fertilitu postižených žen.

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# ŽENSKÉ SEXUÁLNÍ DYSFUNKCE A ENDOMETRIÓZA II.

FEMALE SEXUAL DYSFUNCTIONS AND ENDOMETRIOSIS

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**Souhrn**

Ženské sexuální dysfunkce zahrnují skupinu různých sexuálních obtíží, které postihují ženy všech věkových kategorií, představují trvalou nebo opakující se poruchu sexuálního zájmu, nedostatečné subjektivní či genitální vzrušení, potíže s dosahováním orgasmu, bolesti nebo jiné obtíže při pohlavním styku.

Základním symptomem endometriózy je bolest, která se významně podílí na vzniku a rozvoji ženské dyspareunie.

**Summary**

Female sexual dysfunctions include a group of various sexual problems that affect women of all ages, represent a persistent or reccurent disorder of sexual interest, insufficiently subjective or genital excitement, problems with orgasm, pain or other problems in sexual activities and life.

A basic symptom of endometriosis is a pain, it significantly contributes to occurrence and development of female dyspareunia.

## ÚVOD

Ženské sexuální dysfunkce (FSD, female sexual disorders) zahrnují skupinu různých sexuálních obtíží, které postihují ženy všech věkových kategorií, představují trvalou nebo opakující se poruchu sexuálního zájmu/touhy, nedostatečné subjektivní či genitální vzrušení, potíže s dosahováním orgasmu, bolesti nebo jiné obtíže při pohlavním styku.[1] Přinášejí problémy reprodukční, vztahové i interpersonální. Jejich přesná etiopatogeneze není obvykle zcela zřejmá.

Dyspareunie je definována jako přetrvávající nebo opakující se bolest, která se vyskytuje při pokusech o vaginální penetraci penisem či při jejím dokončení. Bolestivý pohlavní styk ovlivňuje sexuální intimitu partnerského vztahu a zasahuje do emocionálního života partnerů. Ve většině případů má svůj biologický základ a může se následně stát nemocí samou o sobě. Bolest je vnímána jako komplexně prožívaná zkušenost, která v sobě zahrnuje psychologickou, ale i vztahovou složku. Chronická bolest to pak ještě více zintenzivní.

Na sexuální bolest je třeba pohlížet jako na poruchu:
- multifaktoriální;
- multisystematickou;
- komplexní.[2]

V květnu 2013 bylo prezentováno 5. vydání Diagnostického a statistického manuálu mentálních poruch (DSM-5), které výrazným způsobem změnilo původní definici ženských sexuálních poruch a odklonilo se též od starších diagnostických kritérií.

Jen pro rekapitulaci, DSM je americká národní klasifikace mentálních poruch používaná Americkou psychiatrickou společností (APA), která je na rozdíl od MKN (Mezinárodní klasifikace nemocí) podrobnější a konkrétnější. Původně vznikla pro potřeby americké armády při porovnávání psychiatrických diagnóz a pro potřeby statistiky.

V prvních dvou DSM (1952 a 1968) byly uvedeny pouze dvě sexuální dysfunkce – ženská frigidita a mužská impotence. Ve třetí verzi (1980) se poprvé objevily poruchy psychosexuální, které zahrnovaly poruchy sexuální touhy a psychofyziologické změny.

Při další revizi (1987) byla porucha sexuální touhy rozdělena do dvou kategorií – snížená sexuální touha a sexuální averze.

Světová zdravotnická organizace (WHO) v roce 1992 ve své desáté revizi Mezinárodní klasifikace nemocí (MKN-10) definovala sexuální poruchy jako řadu různých problémů, při kterých jednotlivci nejsou schopni sexuálního aktu tak, jak by si přáli.

Kategorie zahrnovaly nedostatek a ztrátu touhy, sexuální averzi, nedostatečný sexuální požitek, selhání genitální odpovědi, dysfunkce orgasmu, neorganický vaginismus, neorganickou dyspareunii a nadměrný sexuální apetit.

Čtvrtá verze DSM (1994) na MKN-10 navázala. Byla ale stále založena na lineárním modelu sexuální reaktivity, i když navíc vytvořila podtypy závislé na délce trvání, kontextu a etiologických faktorech.

V roce 1998 se skupina odborníků různých medicínských oborů shodla na úpravách a předchozí klasifikace byla rozšířena o psychogenní a organickou etiologii poruch. Byly také provedeny změny v definicích a kritériích jednotlivých diagnóz. Důraz byl kladen na osobní charakter potíží. Přidána byla též kategorie nekoitální sexuální bolesti.

Tento trend, který znamenal odklon od lineárního k cirkulárnímu modelu, se objevil ve verzi DSM-5 (2013). Poruchy sexuální touhy a vzrušení byly zahrnuty do jedné kategorie: ženské poruchy sexuálního zájmu/vzrušení. Sexuální averze byla vyňata vzhledem k raritnímu užívání a nedostatečné podpoře v rámci výzkumu. Vaginismus a dyspareunie byly sloučeny do kategorie bolesti/obtíže v genito-pelvické oblasti s penetrací.

Všechny kategorie nyní vyžadují trvání poruchy minimálně 6 měsíců a stanovují přísnější kritéria pro rozlišení přechodných a trvajících obtíží.[3]

Stále však platí, že ženským sexuálním dysfunkcím je nutno věnovat velkou pozornost. Kromě pečlivé anamnézy spolu se strukturovaným pohovorem, který je zaměřen na detaily gynekologického a sexuálního života, by mělo být součástí diagnostiky kompletní somatické vyšetření včetně gynekologického vyšetření malé pánve. Laboratorní vyšetření včetně hormonálního profilu jsou samozřejmě stále standardem, ukazuje se ale, že korelace mezi sexuální dysfunkcí a hormonálními hladinami není příliš spolehlivá. Některá pracoviště doplňují vyšetření vaginálním pletysmografem pro zjištění krevního průtoku, jiná zase neurologická vyšetření bulbokavernózního reflexu, popř. evokovaného potenciálu u nervus pudendus za pomoci EMG.

Nezbytnou součástí vyšetření však musejí být kvalifikované a mezinárodně uznávané dotazníky. Jedním z nejznámějších a velmi často používaných dotazníků je FSFI (Female Sexual Function Index), tedy Dotazník pro hodnocení ženské sexuální funkce (Rosen et al., 2000), který obsahuje 19 otázek, dalším je Dotazník ASFQ, tzv. zkrácená verze Dotazníku sexuálních funkcí (Quirk et al., 2002) obsahující 15 otázek. K doplnění informací bývají využívány i Dotazníky zakreslení bolesti s obrázkem ženského těla, kde žena vyznačí místo s výskytem bolesti. Používají se nejen v sexuologii, ale také např. při fyzioterapeutické léčbě dyspareunie.

K dispozici je mnoho dalších dotazníků, používaných při nejrůznějších studiích, jako např. The Brief Sexual Symptom Checklist for Women, The Brief Index of Sexual Functioning for Women, Decreased Sexual Desire Screener, nebo v souvislosti s vyhodnocením farmakologické léčby známý dotazník The Changes in Sexual Functioning Questionnaire (CSFQ), který sestavila Anita Claytonová.[4]

Jak bylo na začátku uvedeno, přesná etiopatogeneze ženských sexuálních dysfunkcí je obvykle ne zcela zřejmá. Endometrióza je prokazatelně jednou z příčin významně se podílejících na vzniku a rozvoji dyspareunie. Jde o estrogen-dependentní onemocnění a postihuje především ženy v reprodukčním věku. Výjimečně se vyskytuje i postmenopauzálně.[5] Kromě nadprodukce estrogenů má žena s endometriózou více receptorů pro estrogen.[6]

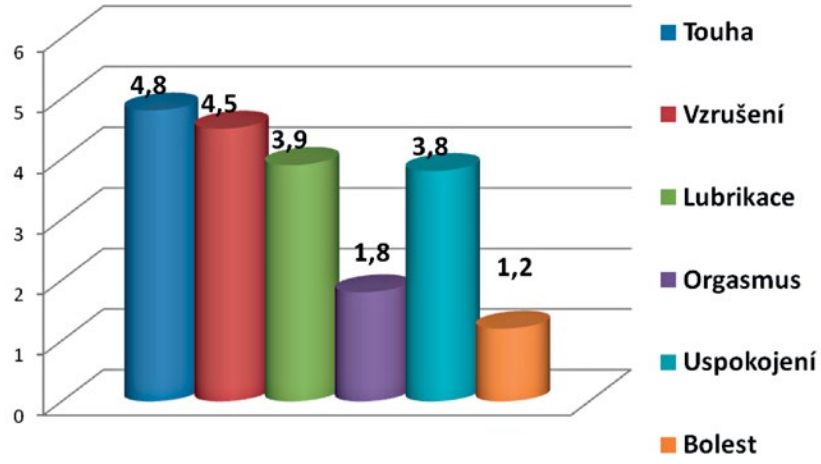
Naše studie obsahuje 100 žen s endometriózou, které byly gynekologicky, ale také sexuologicky vyšetřeny před zahájením konzervativní léčby. Konzervativní terapie se opírá o využití jednosložkového gestagenového preparátu Visanne (2 mg dienogestum), který bývá nejčastějším lékem první volby při tomto onemocnění.[7] Délka léčby se pohybuje obvykle kolem 6 měsíců, méně často pak mezi

**Tab. 1 Kategorie FSFI dotazníku pro hodnocení ženské sexuální funkce dle Rosena**

| Oblast | Otázky | Skóre (průměr) | Faktor | Skóre (minimum) | Skóre (maximum) | Skóre |
|---|---|---|---|---|---|---|
| **Desire (Touha)** | 1, 2 | 1–5 | 0,6 | 1,2 | 6,0 | |
| **Arousal (Vzrušení)** | 3, 4, 5, 6 | 0–5 | 0,3 | 0 | 6,0 | |
| **Lubrication (Lubrikace)** | 7, 8, 9, 10 | 0–5 | 0,3 | 0 | 6,0 | |
| **Orgasm (Orgasmus)** | 11, 12, 13 | 0–5 | 0,4 | 0 | 6,0 | |
| **Satisfaction (Uspokojení)** | 14, 15, 16 | 0 (nebo 1) až 5 | 0,4 | 0,8 | 6,0 | |
| **Pain (Bolest)** | 17, 18, 19 | 0–5 | 0,4 | 0 | 6,0 | |

6 až 12 měsíci. V našem případě ale kontinuálně posuzujeme pacientky i po době delší než 12 měsíců. Důvodem je také to, že s delším užíváním preparátu nejsou prakticky žádné zkušenosti a naše studie by ráda vyhodnotila pacientky nejen po 6 a 12 měsících, ale také po 15 měsících, popř. déle.

Jako součást sexuální anamnézy a zjištění možných projevů dyspareunie byl kromě Anglosaského dotazníku pro endometriózu – který obsahuje všeobecné otázky na pacientku, otázky na bolest a její jednotlivé typy a také otázky na symptomy, úzce související s projevy endometriózy, včetně tzv. Dotazníku zakreslení bolesti – použit právě FSFI dotazník pro hodnocení ženské sexuální funkce dle Rosena, a to před zahájením terapie a následně pak po 6 měsících léčby.




**Obr. 1 Soubor 100 pacientek před zahájením léčby při potvrzení diagnózy endometrióza, po gynekologickém a sexuologickém vyšetření s vyhodnocením Rosenova dotazníku FSFI (FSFI domain scores, maximum score 6,0)**

Otázky Rosenova dotazníku jsou zaměřeny na uvedené kategorie a každé je přiřazeno skóre s odpovídajícím faktorem a minimální a maximální skóre, jak ukazuje tabulka (Tab. 1).[8]

## ZÁVĚR 1

Sledovaná data před zahájením léčby endometriózy jednoznačně potvrzují dyspareunii s výraznými poruchami orgasmu a bolesti u tohoto onemocnění (Obr. 1).

## ZÁVĚR 2

Data získaná po šestiměsíční léčbě endometriózy preparátem Visanne:

- elevace v kategorii vnímání touhy;
- nepatrná elevace v kategorii vzrušení;
- kategorie lubrikace beze změn;
- výrazná elevace v kategorii orgasmus;
- mírná elevace v kategorii uspokojení;
- výrazná elevace v kategorii bolest.

Sledovaná data potvrzují terapeutický efekt při konzervativní léčbě dyspareunie preparátem Visanne v pěti kategoriích ze šesti, a to nejvýrazněji v kategoriích orgasmus a bolest (Obr. 2).

Hodnocení po 15měsíční léčbě bude předmětem dalšího výzkumu.

## KAZUISTIKA

Svobodná žena ve věku 33 let. Sledována v několika gynekologických ordinacích pro nepravidelnou a bolestivou menstruaci.

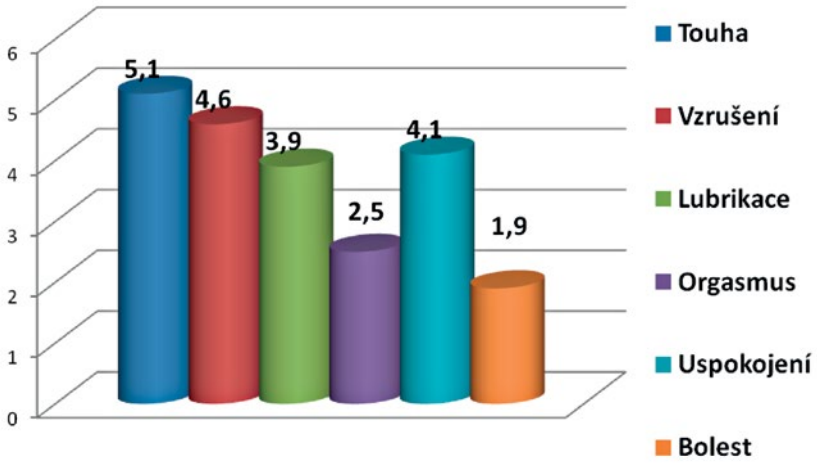
Nevýznamná rodinná, osobní a gynekologická anamnéza.

První menses ve 13 letech, nulligravida, o graviditu se dříve nepokoušela, primární pro ni bylo zbavit se potíží, které měla především při styku, ale i během menstruace.

Nejprve léčena analgetiky a antiflogistiky, antikoncepci odmítala.

Ve 21 letech vysloveno podezření na endometriózu (E), indikována dvousložková antikoncepce Jeanine na 3 měsíce před plánovaným operačním zákrokem.

Laparoskopie (LPSK) potvrdila drobná ložiska endometriózy v oblasti levého ovaria a rektovaginálního septa, která se podařilo bez problémů odstranit (potvrzeno také histologicky).




**Obr. 2 Soubor 100 pacientek po šestiměsíční léčbě endometriózy preparátem Visanne s vyhodnocením Rosenova dotazníku FSFI (FSFI domain scores, maximum score 6,0)**

Potíže se opět dostavily asi po třech měsících, byly obdobné jako před chirurgickou léčbou. Sonografie potvrzuje recidivu v oblasti levého ovaria.

Pacientka opět užívá analgetika a antiflogistika, antikoncepce nepředepsána, protože uvažuje o graviditě, ta se však nedaří.

Další chirurgický zákrok ve 31 letech, s obdobným nálezem a obdobným řešením, resekce levého ovaria – odstraněna drobná ložiska endometriózy a srůsty, opět jedno drobné ložisko v oblasti septa, v jiném místě než v předchozím případě. Potíže se dostavily tentokrát do jednoho měsíce po výkonu.

Doporučena další laparoskopie – pacientka ji odmítá.

Pacientka přichází do Sexuologického ústavu pro řešení problémů s dyspareunií a snahou o koncepci, včetně vyšetření partnera. Komplexní sexuologické vyšetření, odběry a hormonální profil v normě, krev v moči i ve stolici negativní, vyšetření per rectum negativní. Vyloučena trombogenní mutace.

Zahájena terapie preparátem Visanne.

Po 3 měsících léčby pacientka popisuje výrazný ústup potíží jak během menstruace, tak i při styku, který je ještě výrazněji akcentován po 6 měsících.

V současné době pacientka pokračuje v terapii, která je plánována zatím na 12 měsíců, protože předběžně zohledňujeme její požadavek na graviditu.

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# ŽENSKÉ SEXUÁLNÍ DYSFUNKCE A ENDOMETRIÓZA III

FEMALE SEXUAL DYSFUNCTION AND ENDOMETRIOSIS III

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**Souhrn**

Dyspareunie je definována jako chronická nebo opakovaná bolest během vaginální penetrace nebo pokusů o ni. Bolestivá soulož narušuje sexuální stránku vztahu a negativně ovlivňuje emocionální stav páru. Ve většině případů existuje biologická příčina a tento stav může být nemocí sám o sobě. Bolest je vnímána jako komplexní pocit, s psychologickými a vztahovými elementy. Chronická bolest způsobuje, že se tyto prožitky stávají ještě intenzivnějšími.

Bolest během souložе musí být řešena jako komplexní, multisytémová a multifaktoriální choroba.

**Summary**

Dyspareunia is defined as chronic or recurrent pain occurring during vaginal penetration or attempted vaginal penetration. Painful intercourse affects the sexual intimacy of a relationship and influences the couple's emotional life. In most cases it has a biological cause and it can be an illness in and of itself. The pain is perceived as a complex experience, which contains psychological and relational elements. Chronic pain makes this even more intense.

Pain during sex needs to be considered as a disorder which is multifactorial, multisystemic and complex.

V naší studii zabývající se dyspareunií se věnujeme 100 pacientkám s prokázanou endometriózou, z nichž část (85 žen) byla léčena konzervativně (Visanne)[(1)] po dobu šesti a 12 měsíců; část souboru zahrnuje také pacientky, které byly léčeny chirurgicky pomocí laparoskopie (15 žen), v některých případech šlo o opakovanou chirurgickou intervenci.

Soubor dat obsahuje základní informace:
**1. anamnéza – dotazník**
**2. základní biochemické vyšetření**
**3. hormonální profil**
**4. gynekologický nález**
**5. laparoskopický nález**

## ANAMNESTICKÝ DOTAZNÍK

V něm se soustředíme na základní údaje, které bývají s výskytem endometriózy často spojovány, jako jsou menstruace před 11. rokem věku, poruchy cyklu, především ale výskyt dysmenorey nebo požívání alkoholu. Součástí je také vyhodnocení základních biochemických hodnot, především hormonálního profilu včetně hodnot estradiolu, prolaktinu nebo TSH (Obr. 1).
**1. věk**
**2. váha**
**3. první menstruace**
**4. první sexuální aktivita**
**5. poruchy cyklu**
**6. dysmenorea**
**7. kouření**
**8. alkohol**

## DOTAZNÍKY 1. SKUPINA

Základem první části psychologického výzkumu je soubor dat, který přináší jednotlivé dotazníky:
1. nákresový dotazník bolesti podle Klikové (Obr. 2, 3)
2. Rosenův dotazník pro hodnocení ženské sexuální funkce

**Rosenův dotazník**
Otázky jsou zaměřeny na jednotlivé kategorie, a to

**Tab. 1 Škála vyhodnocení – FSFI Domain Scores**

| Kategorie | Otázky | Průměrné skóre | 1. faktor | Skóre minimum | Skóre maximum | Skóre |
|---|---|---|---|---|---|---|
| Touha | 1, 2 | 1–5 | 0,6 | 1,2 | 6,0 | |
| Vzrušení | 3, 4, 5, 6 | 0–5 | 0,3 | 0 | 6,0 | |
| Lubrikace | 7, 8, 9, 10 | 0–5 | 0,3 | 0 | 6,0 | |
| Orgasmus | 11, 12, 13 | 0–5 | 0,4 | 0 | 6,0 | |
| Spokojenost | 14, 15, 16 | 0 (or 1)–5 | 0,4 | 0,8 | 6,0 | |
| Bolest | 17, 18, 19 | 0–5 | 0,4 | 0 | 6,0 | |

Podle [2]

před zahájením léčby, dále pak po šestiměsíční a dvanáctiměsíční léčbě (Tab. 1).

**1. touha**
**2. vzrušení**
**3. lubrikace**
**4. orgasmus**
**5. uspokojení**
**6. bolest**

V Obr. 4 srovnáváme procentuální výskyt jednotlivých kategorií v jednotlivých etapách sledování – tedy před léčbou, po šesti měsících a po dvanácti měsících[3] a v Obr. 5 v jednotlivých etapách sledování – tedy před léčbou, po šesti měsících a po dvanácti měsících – skóre jednotlivých kategorií.

## DRUHÁ ČÁST STUDIE

Část pacientek je sledována a vyšetřována také po jednorázových, případně opakovaných operačních zákrocích. Ukazuje se, že i v těch případech, kdy byla ložiska prokazatelně odstraněna, u žen přetrvává nebo se následně vrací sexuální dysfunkce. To nás upozornilo na fakt, o kterém se v zahraničí stále více hovoří.

Jde o tzv. operační placebo efekt, popisovaný u 25–30 % pacientek, který přetrvává pouze dva až tři měsíce, a to i tehdy, pokud byla zcela odstraněna ložiska ETRS. A také v těchto případech si ženy stěžují na návrat dyspareunie.[4]

Existují také studie, které srovnávají efekt konzervativní a chirurgické léčby endometriózy. Zaměřeny byly ale primárně na posouzení vlivu léčby na obecnou pánevní bolest (pelvic pain) a na případné pozitivní ovlivnění bolesti při menses - dysmenorey.[5]

Žádná studie se ale nevěnovala porovnání mezi těmito dvěma léčebnými metodami ve vztahu k samotné dyspareunii.[6]

Obr. 6 ukazuje průběh výskytu dyspareunie u 15 sledovaných pacientek.

Obr. 7 se věnuje průběhu výskytu dyspareunie po konzervativní léčbě preparátem Visanne.

Podle klinického hodnocení, které proběhlo na gynekologicko-porodnické klinice University of British Columbia (UBC), je možné pacientky s endometriózou a hlubokou dyspareunií rozdělit na čtyři základní typy:

- **Typ 1 Hluboká dyspareunie je způsobena endometriózou.**
- **Typ 2 Hluboká dyspareunie je komorbiditou.**
- **Typ 3 Hluboká dyspareunie je penetrační poruchou při genito-pelvické bolesti.**
- **Typ 4 Hluboká dyspareunie má více příčin.**[4]

Toto je důvodem, proč se začínáme více věnovat faktoru psychogennímu, a kvůli tomu si klademe následující otázky:

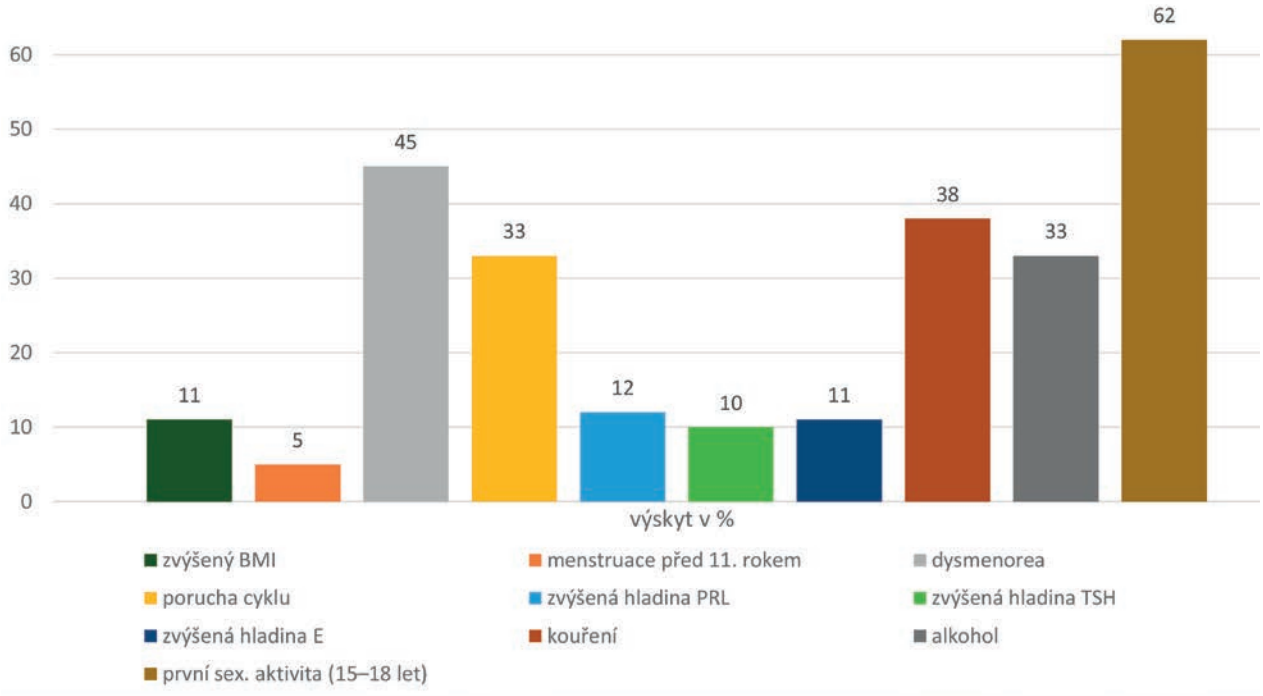
O jaký typ onemocnění u některých případů dyspareunie a endometriózy tedy může jít? Jde o onemocnění psychosomatické, či somatopsychické, nebo v některých případech může jít o koincidenci obou onemocnění?

**1. psychosomatické onemocnění**
**2. somatopsychické onemocnění**
**3. koincidence obou onemocnění – endometrióza a sexuální dysfunkce/dyspareunie?**

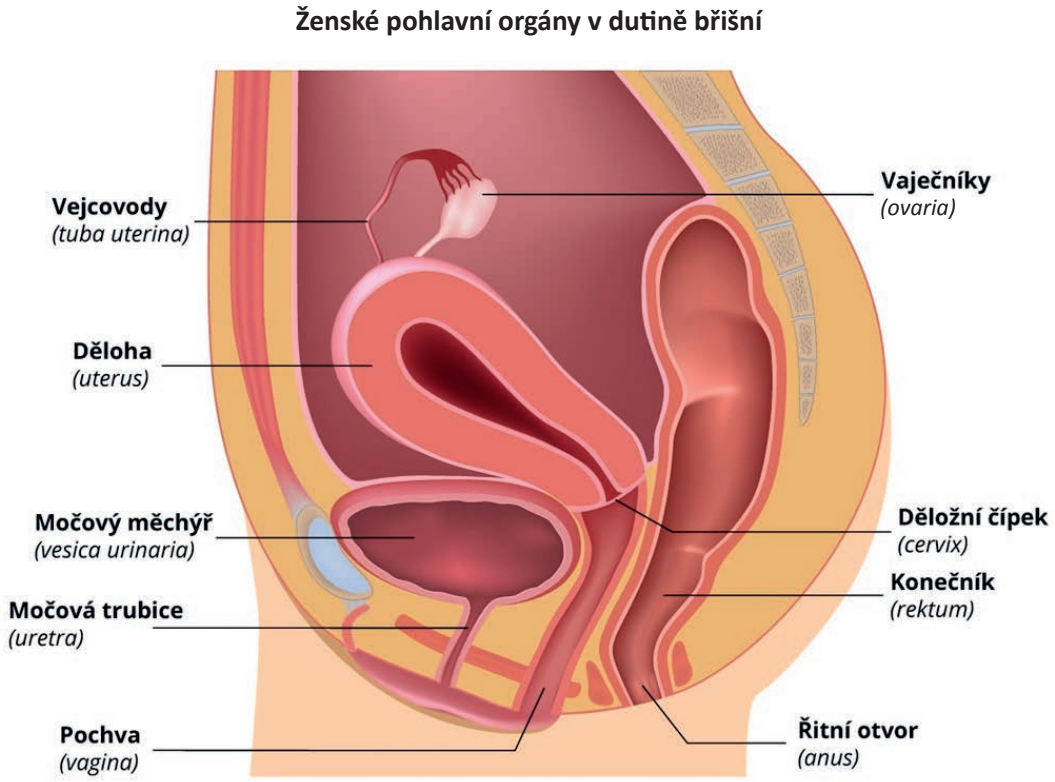
V diagnostice nám budou nápomocny další speciální dotazníky, které budeme postupně vyhodnocovat a statisticky zpracovávat.

## DOTAZNÍKY 2. SKUPINA

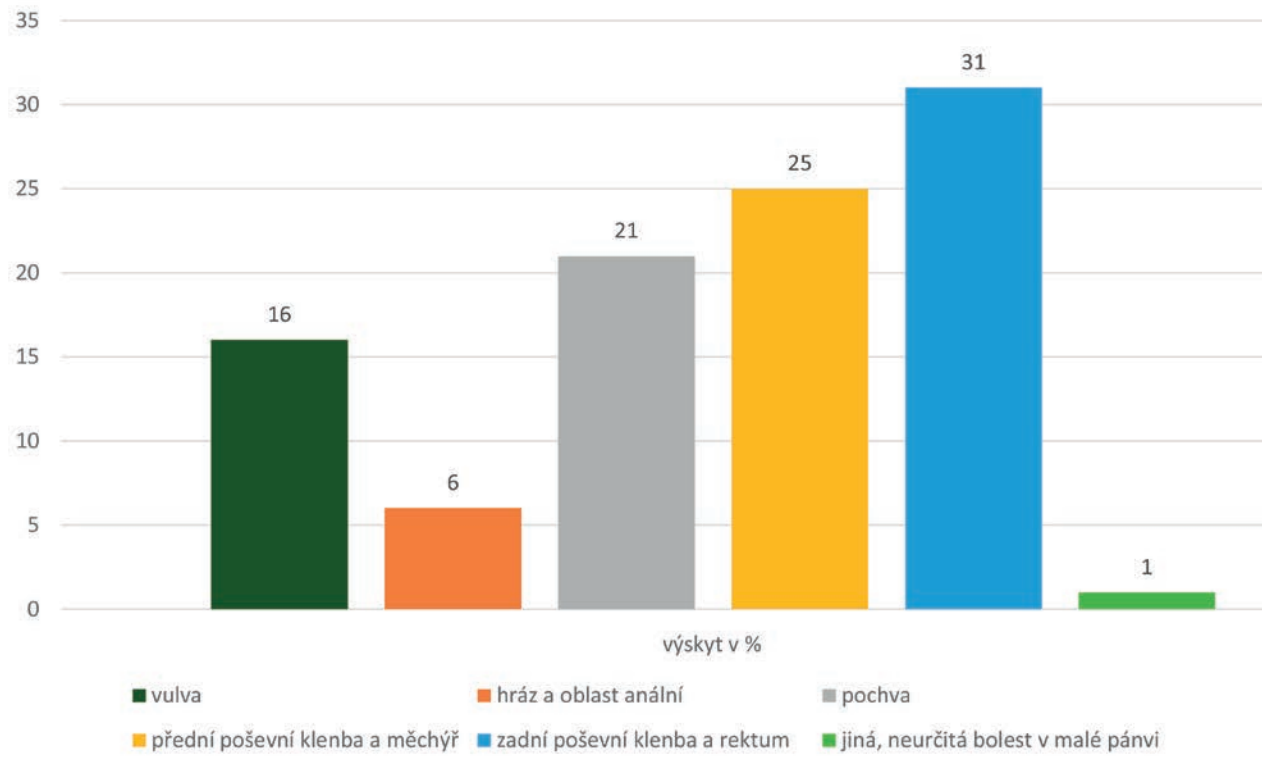
**1. DSS**
**2. TSC-40**



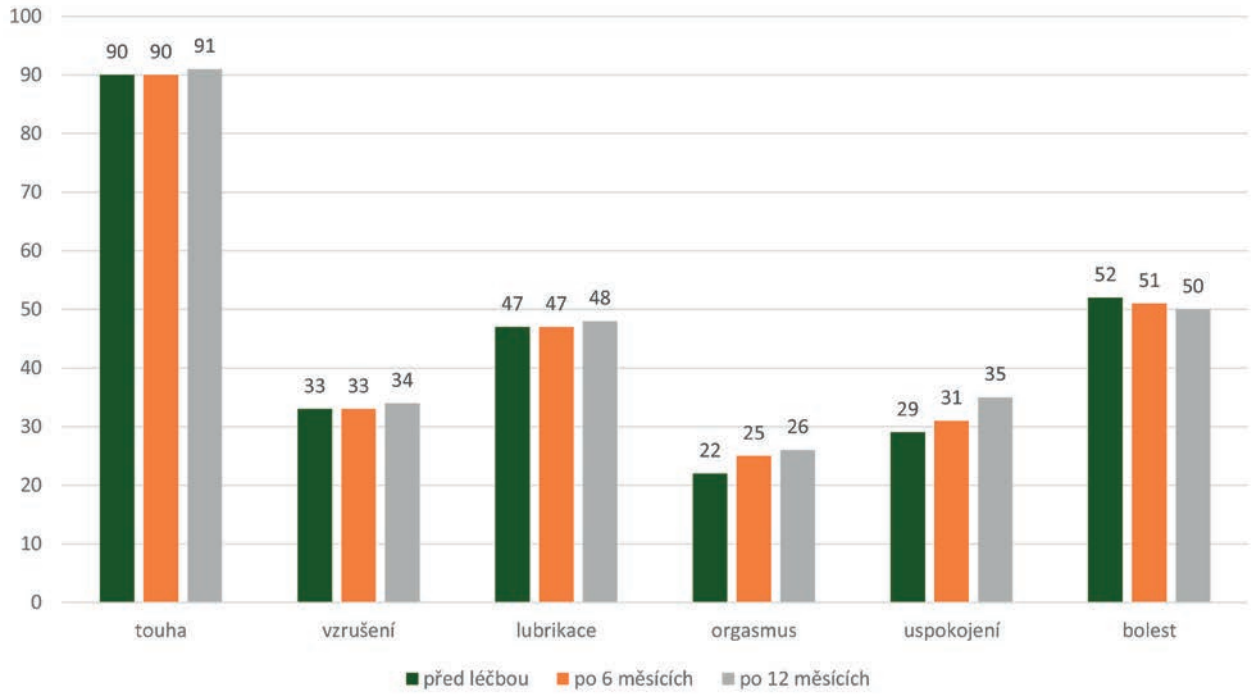

**Obr. 1** **Anamnestické údaje**



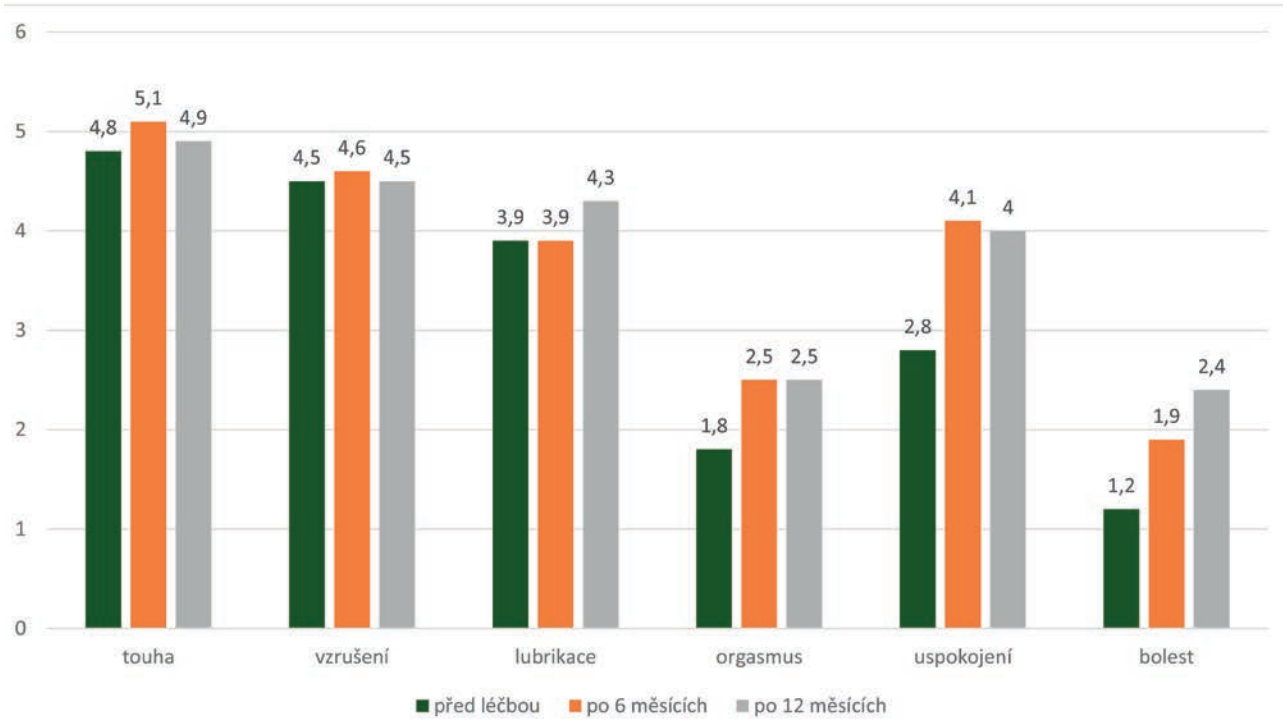

**Obr. 2** **Nákresový dotazník bolesti podle Klikové**



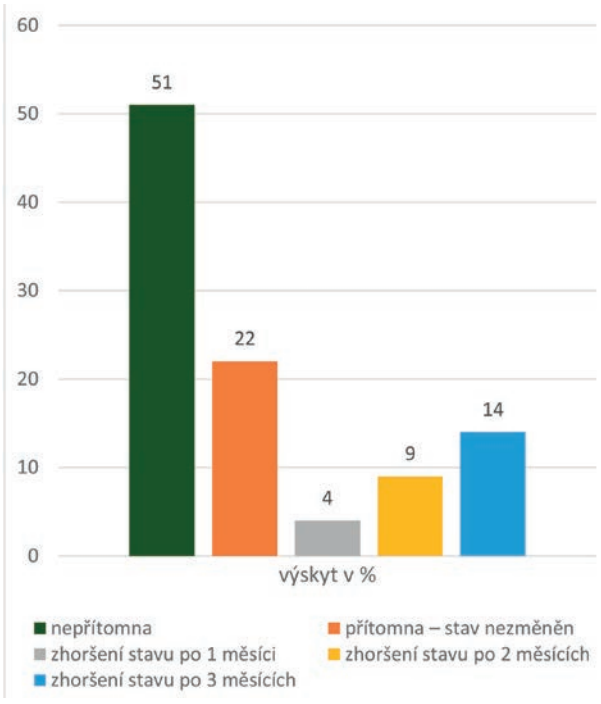

**Obr. 3 Lokalizace bolesti podle Klikové**



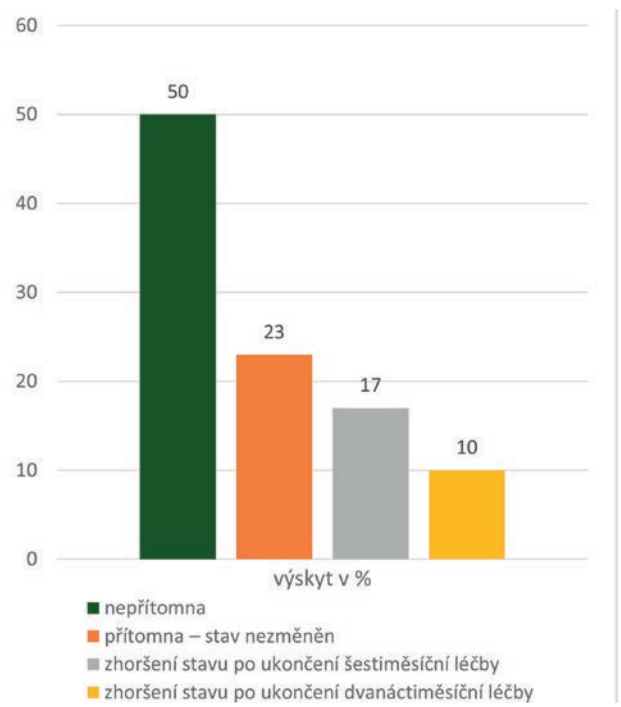

**Obr. 4 Srovnání procent výskytu jednotlivých kategorií**




**Obr. 5 Srovnání FSI skóre**




**Obr. 6 Výskyt dyspareunie po LSKPP řešení**




**Obr. 7 Výskyt dyspareunie po konzervativní léčbě**

**3. SDQ-20**
**4. CAT – barevně škálový dotazník**
**5. Posuzovací škála LSCL-33 McLeanovy nemocnice**
**6. Asociační dotazník**

## ZÁVĚR

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# Altered Immunity in Endometriosis: What Came First?

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**ABSTRACT**

**Background**: This study was conducted to summarize current knowledge of the changes within the immune system, from action of macrophages, lymphocytes and NK cells to biological effects of their products. Endometriosis is a complex gynecological disorder defined as a presence of endometrial tissue outside the uterus affecting over 5 million reproductive-aged women in the U.S. alone.

**Result:** In recent years, the potential role of the immune system in the development of endometriosis has increasingly gained attention. Data summarized in our study showed that the most relevant immunocytes are macrophages residing inside the peritoneal cavity and the ratios of Th1 to Th2 cells. Another crucial immunological parameter is the balance in production of cytokines and chemoatractants.

**Conclusions:** This review confirms that despite decades of intensive research, the involvement of the immune system remains elusive, as we can recognize the changes, but still do not understand if these changes represent the results of endometriosis or if they are contributing factors. Based on these findings, we also discuss new treatment possibilities.

**KEYWORDS**
Cytokines; endometriosis; immunity; lymphocytes; macrophages

## Introduction

Endometriosis was first described almost 160 years ago (Von Rokytansky, 1860) and has been intensively studied ever since. However, despite being the most studied gynecological disorder, the causes of endometriosis, which is most commonly defined as a presence of endometrial tissue outside the uterus, remain unsolved. Numerous hypotheses exist: embryonic stem cell origin, retrograde menstruation, implantation, genetic influences (Song and Lee, 2014), or coelomic metaplasia. None of these hypotheses have been fully confirmed (Kralickova et al., 2014), presenting the likelihood that endometriosis might be a result of some or even all of these possibilities. Endometriosis is the leading cause of morbidity among premenopausal women (Baldi et al., 2008). This disease negatively affects 10–15% of women in their reproductive age. Despite several available treatment options, no real cure exists.

One of the possible causes of endometriosis development is changes in immune reactions (Herington et al., 2011). In theory, endometrial cells seeding in the peritoneal cavity should be destroyed by the immune reactions and cells, but in endometriosis, they

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are allowed to penetrate and proliferate. In the peritoneal cavity, the immune cells are either overwhelmed (by the amount of displaced endometrial tissue) or dysfunctional, causing tissue to proliferate and form lesions.

Alterations in both cell-mediated and humoral immunity contribute to the pathogenesis of endometriosis; for review see Ulukus et al. (2006). Basic immunological functions, particularly nonspecific immunity, usually do not change in patients with endometriosis. On the other hand, other parts of immune reactions are known to be altered (Steele et al., 1984). In addition, direct damage of the immune system by irradiation resulted in increased prevalence of endometriosis and increased severity of the disease (Wood et al., 1983). This suggests that the normal immune system plays a significant role in blocking the development of endometriosis. Cells in the peritoneal cavity can initiate inflammatory response, helping vasodilation and increased permeability of blood vessels. The persistent nature of inflammation may contribute to initial endometrial growth, but also to other medical problems that patients with endometriosis commonly suffer. This includes endocrine and autoimmune problems, allergies, and irritable bowel syndrome (Sinaii et al., 2002). The goal of this report is to review the most relevant literature about the possible role of immune system components' endometriosis development.

## Macrophages

Macrophages represent the primary defense cells in our body. As they reside in the peritoneal cavity, their defensive role is manifested mainly via phagocytosis and support of cytokine secretion. Phagocytosis evolved from feeding to eliminating pathogen invasion and cellular debris. Phagocytosis is, among other factors, regulated through activation of matrix metalloproteinases and expression of CD36 receptors. Expression of these components is reduced in endometriosis (De Villiers et al., 1994; Wu et al., 2005), most likely by changes in prostaglandin E2 levels (Wu et al., 2005). Macrophage recruitment might be an underlying mechanism of pathogenesis of endometriosis; for review see Wu et al. (2017a). As both CD36 and metalloproteinases are heavily involved in clearance of cellular debris, this downregulation might significantly affect their role in endometriosis development.

Macrophages are primary immunocytes inside the peritoneal cavity, so it is not surprising that patients with endometriosis had elevated numbers and products. This increase is plausible due to larger influx, as their activity is suppressed and not stimulated (Dmowski et al., 1981). On the other hand, some studies found activation state of monocytes and macrophages (Christodoulakos et al., 2007). At the onset of acute inflammation initiated by resident macrophages, inflammatory mediators are secreted and are responsible for changes in blood flow and for transfer of cells from blood vessels into the tissue.

An interesting study found that Tie-2-expressing macrophages infiltrated areas surrounding newly formed endometriotic blood vessels (Capobianco et al., 2011). As these macrophages are involved in promoting angiogenesis and tumor growth, it might be probable that when these cells are depleted, endothelial cells do not organize effectively and develop glandular and stromal architecture. This possibility makes this subset of macrophages a solid target for potential treatment of endometriosis.

## Lymphocytes

Lymphocytes localized inside the ectopic tissue significantly contribute to lesion growth, mostly by low ratios of Th1to Th2 cells (Takamura et al., 2015) and by absence of natural killer (NK) cells (Jones et al., 1998). The Th1-Th2 ratio depends on stage. Once the endometriotic foci are established, the strict interaction between endometriotic and immune cells addresses toward a prevalence of Th1 cytokines in the peritoneal fluid at minimal and mild stages, whereas Th2 cytokines prevailed in severe stages (Andreoli et al., 2011) (Kralickova and Vetvicka, 2015). Determination of various T and B lymphocyte subpopulations in blood and peritoneal fluid found no differences between control group and patients (Hassa et al., 2009).

In the case of lymphocytes, one hypothesis is based on the possibility of Th1/Th2 imbalance. A study testing the predominant pattern of Th1 over Th2 in pelvic endometriosis found a potentiation of Th1 response (Podgaec et al., 2010).

Recently, more attention has been focused on the role of anti-inflammatory T cells called "Tregs." In the progression of endometriosis, a key role could be played by impaired ratio of Th17 (Hirata et al., 2008), (Hirata et al., 2010) and Tregs populations (Basta et al., 2010), (Berbic and Fraser, 2011). In particular, the high level of estradiol, typical of endometriosis, can also play an important role in the expansion and activation of Tregs and cause a local decrease of immune surveillance (Polanczyk et al., 2005), (Polanczyk et al., 2007). A review of our knowledge of Treg revealed higher concentration of Treg cells in the peritoneal fluid and endometrial lesions. However, the reviewed studies did not allow us to reach a conclusion about Treg involvement (De Barros et al., 2017). An abundance of Tregs might reflect reduced progesterone responsive endometrial phenotypes connected with endometriosis. Some authors suggested the role of Th2/Treg-dominant immune reactions in the development of endometriosis (Budiu et al., 2009). Again, with the lack of direct proof, it remains only a hypothesis. A later study found possible involvement of the estrogen-IDO1-MRC2 axis in differentiation and function of Tregs (Wei et al., 2016). One promising study showed that positive effects of experimentally induced increase of Th2 cell response inhibited development of endometriosis (Szymanowski et al., 2013). An additional study evaluating the subpopulation of blood lymphocytes found that the fluctuation of regulatory T lymphocytes in endometriosis is caused by altered immune response (Slabe et al., 2013).

A fascinating observation focused on mechanisms potentially allowing endometrial fragments to evade immunosurveillance. It showed the possible involvement of LFA-1-ICAM-1 pathway. In healthy women, LFA-1-positive lymphocytes adhere to ICAM-$1^{+}$ endometrial cells and offer them to NK cells as a target. In endometrial women, soluble ICAM-1 secreted from endometrial lesions compete with the LFA-1 and subsequently block the NK cell-mediated killing.

Another potentially important subset are Th17 cells, which were recently found to be involved in endometriosis. An interesting study showed the presence of Th2 cells and Th17 cells in endometriotic tissues and revealed multiple effects of IL-4 and IL-17A, cytokines secreted from respective Th cells. IL-17A also increases secretion of CCL20, a chemokine for Th17 cells, from endometrial cells. This seems to induce migration of Th17 cells to the endometriotic tissues and further enhance the effects of IL-17A. TNF-α in combination with IL-17A synergistically enhances secretion of IL-8 and CCL-20. This suggests cooperation of inflammation and Th17 immune response (Yutaka et al., 2016).

The importance of Th17 cells was further showed by findings that increased percentages of these cells in peritoneal fluid are well associated with severity of endometriosis (Gogacz et al., 2016). This makes targeting these cells a potential new way to affect proliferation of ectopic tissue and/or clinical manifestation of endometriosis. Furthermore, Th17 cells produce IL-10-limiting inflammatory response, (particularly important in endometriosis) as these IL-10-producing cells are elevated, together with elevated levels of IL-27, IL-6, and TGF-β. It is probable that IL-10 production by Th17 cells is influenced by IL-27 produced by macrophages and endometrial stromal cells (Chang et al., 2017). If confirmed, IL-27 might provide an interesting therapeutic target.

In addition to the role of NK cells (mentioned in details below), cytotoxic $CD8^+$ T lymphocytes are also involved. A clinical study found increased levels of these cells in endometriosis, particularly in the luteal phase (Slabe et al., 2013). The authors believe that these changes are secondary and caused by altered immune response. Deeper investigations suggested that higher levels of cytotoxic T cells in endometrium are probably more associated with development of endometrial carcinomas (Pascual-Garcia et al., 2016). An interesting observation was the loss of CD8 antigen on these lymphocytes, most likely mediated by soluble GDF 15 present in plasma. The downregulation of CD8 marker is known to occur in heavy infections including HIV. This might result in lower recognition of cancer cells during conversion of endometrial tissue into cancerous tissue.

With respect to B lymphocytes, almost nothing is known about their possible role in endometriosis. Besides production of autoantibodies, even systematic review of available literature offered no significant information (Riccio et al., 2017). From the limited number of studies, most of them found increased number and/or activation of B lymphocytes. However, significant part of manuscript found either no changes or even a decrease of B cell numbers; for review see Riccio et al. (2017). There are several possible reasons for this discrepancy, from the different methods used in these reports to different types of tissues used for the experiments. Another possibility might be that the B cell status in endometriosis is secondary to action of other cells, particularly macrophages and T lymphocytes.

## Cytokines and other bioactive molecules

Cytokines represent the key mediators of intracellular communication in both healthy and unhealthy individuals. Cytokines are important for cooperation between immune and endocrine systems. Peritoneal cytokines, which are produced by mesothelial cells, leukocytes, and ectopic endometrial cells, interwork locally and systemically in women with endometriosis (Wu and Ho, 2003). Increased levels of several cytokines which are secreted by immune or endometrial cells and growth factors seem to promote implantation and growth of ectopic endometrium via induction of proliferation and angiogenesis. It is known that COX-2 and IL-1β can regulate the invasion of ectopic EN-MSCs. In the future, these effects might be utilized in developing a new therapeutic strategy for endometriosis. Better characterization of EN-MSCs will need an ex vivo invasion model (Kao et al., 2011).

Immunological balance disturbance can be observed also in the case of cytokines. Inflammatory cytokines such as IL-8, IL-1β, IL-6, and TNF-α are often considered to be involved in the pathophysiology of endometriosis. This hypothesis is confirmed by finding increased levels of these cytokines in peritoneal cavity of women with endometriosis

(Pizzo et al., 2002). A slightly different situation was found in serum—elevated levels of IFN-γ, MCP-1, and IL-8, but decreased levels of IP-10 and eotaxin (Malutan et al., 2017). This suggests highly unbalanced immune responses. Elevated IL-4 expression was found in lymphocytes isolated from endometriotic tissue (Antsiferova et al., 2005). IFN-γ shows opposite inclination (Gmyrek et al., 2008).

Most studies measuring cytokine levels suggest changes in the Th1/Th2 balance toward the Th2 subset. Subsequent experiments showed that IL-4 increased proliferation of cultured endometriotic stromal cells and production of eotaxin, which is a strong chemoattractant for Th2 lymphocytes. Based on these data, a positive feedback loop of eotaxin-IL-4 cooperation in enhancing Th2 response has been proposed (Osuga et al., 2011). However, not all studies found differences in cytokine levels. A study of patients with early- and late-staged endometriosis found no differences in the levels of IL-2, IL-4, IL-10, and IFN-γ in blood and peritoneal fluid (Hassa et al., 2009).

Expression of IL-22 and its receptors was found higher in eutopic endometrium and ectopic lesions than in control women. In addition, IL-22 stimulated proliferation of endometrial stromal cells, which can be reversed by inhibitors of STAT5, ERK1/2, and AKT signal pathways. IL-22 also upregulated expression of IL-8 receptors (Guo et al., 2013). The authors speculate that this increase is caused by local inflammation and in an autocrine action, it further stimulates endometrial tissue inflammation.

IL-2 was suggested to promote angiogenesis by inducing angiogenic factors such as IL-6 and vascular endothelial growth factor (VEGF) (Lebovic et al., 2000). Another effect of IL-1 might be the promotion of sICMA-1 shedding from endometrial cells, helping them to escape immunosurveillance (Vigano et al., 1998). However, the studies evaluating the levels of IL-1 gave only conflicting results; for review see Herington et al. (2011).

Endometrial chemokine expression in human endometrium is high particularly in the mid-secretory phase, with the highest levels of CCL8, CXCL1, and CCL14 (Jones et al., 2004). Their role might be recruitment of macrophages and NK cells and possibly even the guidance of blastocyst to the implantation side.

A new approach tested the expression of Th1 and Th2 cytokine-associated transcription factors, T-bet and GATA-3. The results suggested that these factors might act as cytokine regulatory genes and subsequently influence endometriosis development (Chen et al., 2012).

In a mouse model, five daily injections of IL-12 reduced the weight and area of inoculated endometrium by 77% (Vignali et al., 2002). In a human model, laparoscopic administration of IFN-α2b significantly reduced all symptoms and signs (Ali et al., 2000). Similarly effective was treatment with TNF-α (D'Antonio et al., 2000). It is important to note, however, that the use of cytokines and/or their inhibitors in treatment of endometriosis is still not in sight. Therefore, despite extensive research, no consensus exists on the use of cytokines in diagnosis; for review see Fassbender et al. (2015).

A proteomic analysis of the effects of IL-1β and lipoxin $A_4$ in stromal cells found that lipoxin $A_4$ inhibits progression of endometriosis by changing the effects of IL-1β . These effects are not direct, but are mediated by inflammation-related protein such as vinculin and by IL-4 (Wu et al., 2017b).

RANTES is a strong chemoattractant for various cell types including monocytes, macrophages, and lymphocytes. Endometriosis-derived stromal cells produce high

amounts of RANTES. Similarly, the expression of CD191 (receptor for RANTES) is also elevated in patients with endometriosis (Wieser et al., 2005).

An engaging role seems to belong to IL-15. This cytokine is produced and released by human endometrial stromal cells. It was shown that IL-15 directly stimulated growth and invasion of stromal cells. At the same time, IL-15 also helped stromal cells to escape immune defenses by suppressing activity of NK cells (Yu et al., 2016). In addition, higher levels of IL-17A were found in seminal plasma of women with endometriosis (Sabbaghi et al., 2014). Therefore, the role of IL-15 in endometriosis is still unclear.

Another important factor is VEGF-A, known to be a potent angiogenic factor. VEGF-A is increased in patients with endometriosis and its levels correlate well with the disease stage (Shifren et al., 1996). Originally thought to be under hormonal influence, VEGF-A expression is regulated by TGF-β1 via an ID1 pathway. Levels of mesothelium-localized VEGF-A and TGF-β1 are well correlated.

Transforming growth factor-beta 1 (TGF-β1), an essential growth factor, is responsible for regulating cell proliferation, differentiation, angiogenesis, and immune responses. TGF-β is abundantly and differentially expressed in the endometrium, most likely under hormonal control. The increasing evidences indicate that TGF-β1 expression is high in endometriotic lesions. Many mechanisms must contribute to the development of endometriosis and TGF-β1 was hypothesized to play a key role in endometriotic lesion formation (Omwandho et al., 2010) (Hull et al., 2012). Levels of all three TGF-βs are increased around menstruation, with particular high levels of TGF-β3 in postmenstrual period; it is hypothesized that they might participate in postmenstrual regeneration of endometrium (Omwandho et al., 2010). In addition, TGF-β1 increased the concentration of ID1 mRNA and the VEGF-A-ID1 axis was confirmed by the use of siRNA (Young et al., 2015). The study suggested that ID inhibitors might be beneficial in endometriosis treatment (Fong et al., 2004).

Hypoxia, one of the most important local factors, is related to angiogenesis and is also a basic requirement for lesion formation. The hypothesis that TGF-β1 is involved in the pathogenesis of endometriosis through regulating VEGF expression was supported by experiments showing that endometrial cells exposed to hypoxia expressed more VEGF mRNA, which was even more pronounced in response to TGF-β1 (Yu et al., 2017). The authors conclude that altered expression of VEGF (observed in endometrial primary culture cells through regulating TGF-β1 and HIF-1α expression) supports the idea that both TGF-β1 and hypoxia affect ectopic endometrial cells by inducing angiogenesis. The results suggest hypoxia and TGF-β1 could promote endometriosis formation through synergistic action by regulating VEGF at the transcriptional level (Yu et al., 2017).

Almost every cytokine and other biologically active molecule levels have been found to be either elevated or depressed in patients suffering from endometriosis; for review see Herington et al. (2011). However, despite our vast knowledge of the cytokine network, our understanding of which change comes first and which is just a result of the primary changes is far from complete. Unfortunately making measurements of cytokine levels in endometriosis is nothing more than an interesting exercise.

## NK cells

NK cells are large granular lymphocytes representing approximately 10% of peripheral blood lymphocytes and represent an important component of innate immunity. As endometrial cells mimic cancer cells in their ability to adhere, infiltrate, and proliferate at ectopic locations, NK cells are often suggested to be involved. Increased $KIR^+$ NK cells in peripheral blood may represent a risk factor for endometriosis (Maeda et al., 2002). An increased number and activation of peritoneal macrophages, and decreased T cell and NK cell cytotoxic effects observed in endometriosis (Herington et al., 2011) represent significant changes in cellular immunity. This might result in inadequate removal of ectopic endometrial cells from the peritoneal cavity. Some studies even suggest that NK cells are key players in endometriosis; for review see Thiruchelvam et al. (2015). Activated NK cells are able to migrate and infiltrate endometriotic lesions, suggesting the potential use in treatment of this disease (Montenegro et al., 2015).

Changes in NK cell activity still remain an enigma. A hypothesis about the role of HLA-G antigens which are normally involved in maternal tolerance of the semi allogeneic fetus in suppressed NK cell response was not confirmed by experimental data (Hornung et al., 2001). Another explanation might be findings of highly elevated levels of killer cell inhibitory receptors on NK cells of patients with advanced-stage endometriosis (Wu et al., 2000). NK cells in the peritoneum have reduced levels of killing activity, probably due to changes in cytokines and inhibitory factors; for review see Jeung et al. (2016).

## Inflammation

Following the florid inflammation associated with menstruation, endometrium shows strong regenerative capacity. For details on inflammatory processes possibly influencing development of endometriosis, see Maybin et al. (2011). Endometriosis is usually characterized by a chronic inflammatory state, which leads to the release of several cytokines.

Initial inflammatory response occurs via increased influx of cells. The subsequent acute inflammation involves local vasculature, somatic cells, and immunocytes. Numerous studies document an increased level of inflammatory cytokines in peritoneum. Like with many changes of immune parameters in endometriosis, even now we are not sure whether these inflammatory conditions represent cause or consequence. Mouse studies reveal that induction of endometriosis in an already inflamed peritoneum decreased endometriosis, suggesting that the second option is more probable (Nowak et al., 2008). Anti-inflammatory drugs helped ameliorate numerous symptoms (Vignali et al., 2002) connected with endometriosis probably via growth inhibition of endometriotic implants. This suggests the involvement of inflammatory activity. However, no mechanisms or direct proof was described (Olovsson, 2011).

A novel approach is the study of possible involvement of inflammasomes. A detailed study of pathogenic mechanisms involving the inflammasome in endometriosis offered some clues (Bullon and Navarro, 2017). So far, this information consists more of evaluation of cytokine levels and comparison with the role of inflammasomes in other diseases than of direct proof.

The relation between immunological changes and inflammation in endometriosis was further investigated by measuring the immune-inflammation gene signatures. Studies

showed that almost 70% of screened genes were significantly different in ectopic tissues compared with control tissues. In addition, eutopic endometrium isolated from patients showed unique molecular profile, particularly of genes involved in decidualization and apoptosis regulation (Ahn et al., 2016). It is important to note that although this study offered an important explanation why endometrial fragments are able to implant and elicit inflammatory response, it still not fully explains the pathophysiology of the disease.

In chronically inflamed peritoneum, an extracellular matrix is constantly degraded and resynthesized, resulting in changes in its architecture. The expression and functions of extracellular matrix-modifying enzymes and inflammatory cells affect the dissemination of ectopic cells and their attachment to the serosa. So far, we have only limited information about factors involved in efficient adhesion of cells to the peritoneum. This information is usually extrapolation from cancer studies. Animal studies suggested involvement of mesothelial cells (Fassbender et al., 2011) followed by angiogenesis (Vetvicka et al., 2016). The role of macrophages is important, as they provide signals attracting vessels enabling the survival of ectopic endometrial cells. The subpopulation of macrophages responsible for these effects is the tier-2 expressing macrophages (TEMs) macrophages, found to support angiogenesis in numerous cancer models (De Palma and Naldini, 2011). In hormonal levels, VEGF family and associated receptors are involved.

## Autoimmunity

Some studies showed increased levels of autoantibodies in endometriosis (Taylor et al., 1991), (Eisenberg et al., 2012). Some of these antibodies are organ-specific, probably a result of an excess of endometrial antigens triggering immunological tolerance. Most of these autoantibodies were directed against endometrial antigens, so they might be the result and not the cause of the disease. A detailed study showed that most of these autoantibodies are directed against carbohydrate epitopes, which led to several hypotheses about the involvement of autoantibodies in endometriosis (Osuga et al., 2011), mostly by aberrant matrix metalloproteinase function or genetic defects in glycosylation (Dmowski et al., 1981).

Based on these results, a link between endometriosis and autoimmunity has been suggested. One of the first observations was the similarity in symptoms between patients with systemic lupus erythematosus and endometriosis (Pasoto et al., 2005). A subsequent study followed over 37,000 women with endometriosis found an increased risk for lupus, scleroderma, and multiple sclerosis (Nielsen et al., 2011). In theory, endometriosis fulfills most of the criteria commonly used for definition of autoimmune diseases: immunologically abnormal functions of T and B lymphocytes, polyclonal activation of B lymphocytes, elevated apoptosis, and multiorgan involvement. Numerous studies trying to find an association with HLA antigen described interesting results without reaching any definitive conclusions (Eisenberg et al., 2012). Several methods used for the treatment of autoimmune diseases were also suggested for the treatment of endometriosis; so far, the results are disappointing. In addition, some later findings did not confirm this option (Matorras et al., 2007). It is possible that the presence of autoantibodies, particularly against endometrial membrane proteins, might be useful for diagnosis of early endometriosis (Bohler et al., 2007). Although, the direct

link between endometriosis and autoimmunity is still elusive; for review see Olovsson (2011).

## Other parts of the immune system

Relatively less studied parts of the defense reactions potentially taking a part in endometriosis is the lymphatic system. Lymphangiogenic growth factor and receptor expression together with vessel density is altered in endometriosis (Takehara et al., 2004), promoting the entry of endometrial tissue. The presence of endometriotic lesions in some pelvic lymph nodes suggested inadequate clearance of endometrial cells. Readers seeking a review on the role of the lymphatic system in endometrium should see an excellent article written by Jerman and Hey-Cunningham (Jerman and Hey-Cunningham, 2015). Specific inhibition of lymphangiogenesis in endometriotic lesions might provide a novel approach to treatment.

A compelling approach studied immune gene expression in patients with benign endometriosis, atypical endometriosis, and endometriosis-associated ovarian cancer. The first group showed mixed profile, but the second group showed over 85% of patients having a cancer-like immune environment. Surprisingly, the most changed expression was of complement (Edwards et al., 2015). This study suggested that the link between endometriosis and ovarian cancer might be stronger than originally expected.

Some experiments suggested potential involvement of mast cells. Mast cells are an important, albeit rather overlooked part of defense reactions. Mast cell progenitors are recruited upon start of inflammation and after differentiation, thus further initiating and shaping inflammation via their response to the different stimuli by the IgG-dependent pathway. These events result in secretion of Th2 cytokines such as IL-4, IL-5, and IL-13, some of which were found to be elevated in patients with endometriosis. Individual mast cells, however, are rather scarce in the endometrium. Animal models showed infiltration of peritoneal stromal tissue by mast cells (Uchiide et al., 2002). In a rat model, activation of mast cells by estrogen promoted growth of endometriotic lesions (Lin et al., 2015). The possibility of mast cell involvement was further strengthened by findings in the human models. Endometriotic lesions contained more mast cells than normal tissue, probably due to the higher levels of stem cell factors, which is a known chemoattractant factor for mast cells (Osuga et al., 2000). Several agents targeting mast cell degranulation were tried as possible treatments of endometriosis. The results were mostly nonsignificant; for review see Binda et al. (2017).

Significant attention has been recently focused on a possible role of apoptosis in the development of endometriosis; for review see Vetvicka et al. (2016). Several intracellular factors such as the CD40 ligand, viral genes, and antiapoptotic members of the Bcl-2 family play a detrimental role suppressing apoptosis. It may be triggered through the extrinsic pathway when the interaction of Fas ligand (FasL/CD95L) (Sturlese et al., 2011), TNF-α (Salmeri et al., 2015), TGF-β, and cytokines shifts the balance toward proapoptotic signaling.

Escaping the immune surveillance might be the results of reduction of apoptotic-mediated pathways. Under normal conditions, endometriotic cells refluxed into the cavity are recognized and removed by NK cells and macrophages. With activities of these

immunocytes diminished (see above), the peritoneal homeostasis is broken and endometriotic cells are allowed to survive; for review see Vetvicka et al. (2016).

## Conclusions

Endometriosis is a serious disease with unclear causes. Lately, numerous studies suggest the significant role of both endocrine and immune dysregulations, which further underlines the complexity of this gynecologic disorder. Despite intensive research and interesting advances, it is still unclear if the changes in various immune parameters found in women suffering from endometriosis are the cause of the disease or body's reaction to the disease. Data presented in our review showed changes in leukocyte numbers and activities within the endometrium and peritoneal cavity without allowing us to reach a clear conclusion. As endometriosis is an estrogen-dependent inflammatory disease, immune-endocrine interactions might be involved; for review see Cakmak et al. (2009). Estrogens are known to influence numerous signaling pathways (including MAPK and NF-B) which are involved in endometrial cell properties and behavior. Clearly, further research into a possible role of the endocrine-immunologic axis is necessary.

Our understanding of the interaction between ectopic cells and immune cells in the peritoneal environment is critical for the development of potential drugs. The identification of new cellular and/or molecular target is necessary, but still a distant goal. Future studies need to clarify the complex interactions between genetic influences, estrogen influences, cytokine balance, and entire immunological microenvironment in the development of endometriosis. Despite numerous studies, we still do not know if dysregulation of the immune system in endometriosis is the cause or subsequence of this disease.

## Conflict of interest

Authors declare no conflict of interest.

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# Oncological markers CA-125, CA 19-9 and endometriosis

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**Abstract**

The endometrium tissue is functionally androgen related which plays an important role in women's fertility regulation. In addition recent findings show that endometrium related pathology is closely linked to disrupted androgen biosynthesis and associated regulatory functions. These findings also suggest that androgens might play an important role in endometrium related cancer pathology with significant implications for treatment.

Based on these findings, we have assessed 50 female outpatients with endometriosis and the clinical investigations were focused on biochemical serum analysis of DHEAS, oncological markers CA-125 and CA 19-9, estradiol, thyreothropic hormone, and prolactin.

The results show significant Spearman correlations of CA-125 and CA 19-9 with dehydroepiandrosterone- DHEA-S (R=0.52 resp. R=0.49).

This result represents 1st reported finding documenting androgen related increase of CA-125 and CA 19-9 levels as significant markers of endometrium pathology and it is possible to assume that these potential biomarkers could have clinical importance with respect to timely diagnosis.

**Abbreviations:** BMI = body mass index, DHEA-S = dehydroepiandrosterone sulfate.

**Keywords:** CA 19-9, CA-125, dehydroepiandrosterone sulfate, endometriosis



## 1. Introduction

The endometrium is the inner epithelial tissue which is functionally androgen related and plays an important role in regulation of women's fertility and menstrual cycle.[1,2] The endometrial tissue creates the uterine lining and its pathology may lead to endometriosis when the tissue is present in other parts of the body mainly within the peritoneal cavity at lower abdomen or pelvis.[1,2] Recent findings suggest that androgens might play an important role in endometrium related pathology which is closely linked to disrupted androgen biosynthesis and associated regulatory functions.[2] These findings also indicate that androgens may play a role in hormone-dependent cancer pathology and these studies suggest a link between risk of endometrial cancer and androgen functions.[3,4,5,2] There are some controversial findings suggesting that dehydroepiandrosterone sulfate (DHEA-S) is associated[6] or not associated[7] with increased risk of the endometrial cancer. Recent data indicate that CA-125 and CA 19-9 molecules represent important markers of endometrial and cancer pathology.[8,9] Nevertheless according to the recent literature there is no evidence about relationships of DHEA-S with CA-125 and CA 19-9 as indicators of endometrial and cancer pathology. With respect to these findings we have tested this hypothesis and assessed 50 female outpatients with endometriosis and the clinical investigations were focused on biochemical serum analysis of DHEA-S, oncological markers CA-125 and CA 19-9, estradiol, thyreothropic hormone, and prolactin.

## 2. Methods

To test the above hypothesis, we have assessed 50 female outpatients mean age (32.78±4.36), age range (26–44) with endometriosis who were treated at the Institute of Sexology of the Charles University Hospital in Prague. The diagnosis was confirmed by laparoscopic and histological investigations. All women included in this study had dyspareunia, pelvic pain, orgasm disorders, lubrication disorders, and irregular and painful bleeding. Most women had pains during the menstrual and non-menstrual stages; other reported symptoms were fatigue, sleep disturbances, painful sex, and partner relationship disturbances. In this study, 11% of patients had heightened Body Mass Index (BMI > 26), 5% had 1st menstruation at age 10 to 11, 33% had menstrual disorders including heavy menstrual and intermenstrual bleeding, 45% had menstrual painful symptoms. Of these 9% of patients manifested positive ultrasound changes.

Exclusion criteria were gravidity, oncological diseases, urological disorders, intestinal diseases metabolic disorders drug, and alcohol abuse including smoking. All the outpatients provided written informed consent and the study was approved

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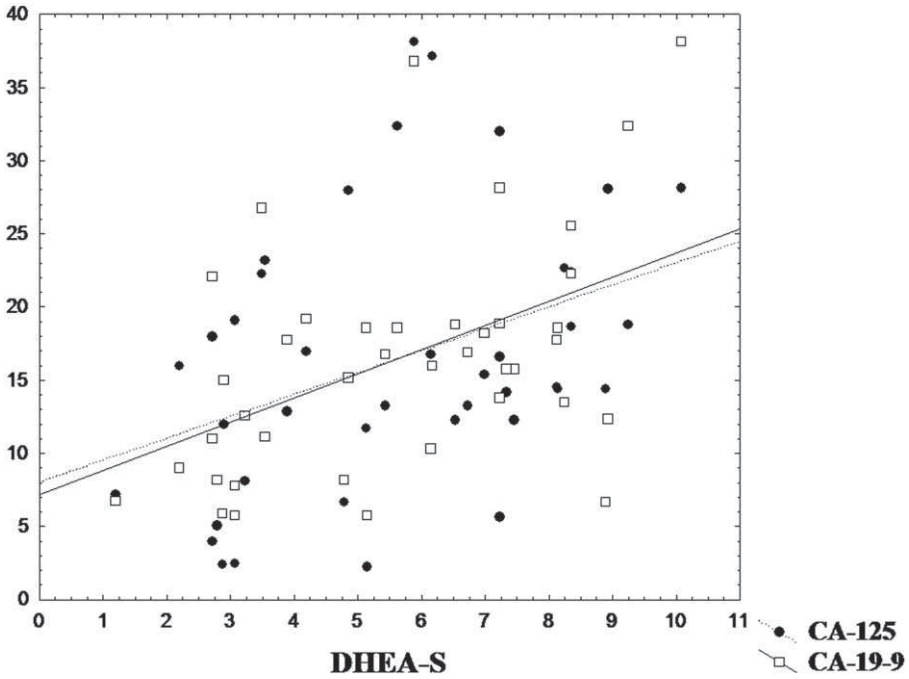


**Figure 1.** Dependence of DHEA-S with CA-125 and CA-19-9. DHEA-S = dehydroepiandrosterone sulfate.

by Charles University Hospital Ethical Committee and all methods were performed in accordance with the relevant guidelines and regulations.

The clinical investigations were focused on biochemical serum analysis of dehydroepiandrosterone sulfate (DHEA-S), oncological markers CA-125 and CA 19-9, estradiol, thyreothropic hormone, and prolactin. The DHEA-S is an androgen, a male sex hormone which is present in both men and women. It plays a role in the development of secondary male sexual signs in puberty and can be metabolized in the body to more potent androgens such as testosterone and androstendione or can be converted to female hormone estrogen. The DHEA-S is produced by the outer layer of adrenal cortex. To a lesser extent, it is also produced by female ovaries and male testicles. Values of hormone are high after birth and they are rapidly declining during childhood until the age of 30. The CA-125 is a glycoprotein with a high carbohydrate component and its molecular weight is at about 200 kDa. The CA-125 is produced in the fetal period by epithelial tissues and in adulthood it may occur in the normal epithelium of the fallopian tubes, cervix or bronchus. The CA-125 is particularly important as a marker of serosa membrane carcinomas and undifferentiated ovarian carcinomas and its serum concentrations may reflect tumor size.[9] The CA 19-9 is a pentasacharide with carbohydrate component containing fructose components and it belongs to a group of oncofetal antigens. In the fetal period, it is synthesized in the epithelial structures of the stomach and in adulthood its production is significantly decreased. In addition recent findings show that CA 19-9 may be produced in glandular structures of the gall bladder, pancreas, bronchus, and some gynecological tumors.[11] Some studies show that CA-19-9 may be demonstrably elevated in endometriosis and exhibit the same or decreased sensitivity as CA-125.[11]

In addition DHEA-S as an androgen hormone plays a very important role in the development of male gender but it is present in both men and women. The DHEA-S can be metabolized in the body to other androgens such as testosterone and androstendione or it can be transformed to female hormones estrogen. The DHEA-S is mainly produced by the zona reticularis of the adrenal cortex, partially produced male testicles and in pathophysiological conditions by female ovaries.[12]

## 3. Results

The results show significant Spearman correlations of CA-125 and CA-19-9 with DHEA-S ($R = 0.52$ resp. $R = 0.49$, Fig. 1). This result represents 1st reported finding documenting increased androgen levels as significant markers of endometrium pathology. Results of the Mann–Whitney test for the subgroups lower or higher than median DHEA-S are in agreement with these correlations ($Z = -2.259$, $P = .024$ for CA-125 and $Z = -2.529$, $P = .011$ for CA-19-9). In addition we have analyzed comparison of women who manifested ultrasound changes with other participants in the sample using Mann–Whitney test and this comparison do not show any significant differences in other assessed variables ($P > .09$, $Z < 1.68$).

## 4. Discussion

The results of this study are in agreement with the tested hypothesis focused on the relationship of DHEA-S with oncological markers CA-125 and CA 19-9. These results are in accordance with recent findings indicating that CA-125 and CA 19-9 molecules represent important markers of endometrial and cancer pathology.[8,9] According to current literature, there is no evidence of DHEA-S relationship with CA-125 and CA 19-9 as indicators of endometrial pathology and it is possible to assume that these potential biomarkers could have clinical importance with respect to timely diagnosis. The search for new biomarkers and validation of predicted biomarkers continues to be a priority of endometriosis research to shorten the time

between diagnosis and treatment initiation. Mainly because diagnosis of endometriosis is generally delayed by 8 to 10 years due to misinterpretation of symptoms in juveniles and young women.[10] This research needs to be replicated in a larger group of patients which might represent a limitation of this study and interpretation of the results. Nevertheless the current results have only statistical limitations and further research including higher number of participants is warranted.

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**Traumatic stress, oncoproteins CA-125, CA 19-9 and endometriosis**

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Abstract

Objective: The endometrium tissue plays an important role in women's fertility regulation and there is evidence that endometrium related pathology is closely related to endocrine dysregulation. These hormonal changes also may be significantly influenced by psychosocial stress. In addition these endocrine dysregulations may play an important role in endometrium related cancer pathology. With respect to these findings we have tested a relationship between neuroendocrine changes in endometriosis and indicators of stress related experiences. We have assessed some specific hormonal indicators of endometriosis and their relationship to cancer pathology, and psychological indicators related to traumatic stress and sexual dysfunctions.

Methods: In this study we have included 55 female outpatients with endometriosis. The clinical investigations were focused on biochemical serum analysis of estradiol, prolactin, cortisol and oncological markers CA-125 and CA 19-9, and psychometric assessment of traumatic stress, somatoform dissociation and sexual dysfunctions.

Results: The results show significant Spearman correlations of TSC-40 with CA-125 and CA-19-9 (R=0.52 resp. R=0.30) and SDQ-20 with CA-125 and CA-19-9 (R=0.53 resp. R=0.31)

Conclusion: This finding represents first reported evidence documenting psychosocial stress related increase of CA-125 and CA 19-9 levels as significant markers of endometrium pathology.

Key words: Endometriosis; Stress; Somatoform dissociation; CA-125; CA 19-9

## 1. Introduction

Recently there is no direct evidence about a role of stress and disturbed partnerships in the endometrium pathophysiology although various neuroendocrine and immune changes are

significantly stress related and may play a role in endometrial diseases (Kralickova and Vetvicka, 2015; Cloke and Christian, 2011; Simitsidellis et al., 2017). In addition there is evidence that neuroendocrine disturbances might play an important role in endometrium related pathology and some findings indicate that they may play a role in hormone-dependent endometrial cancer (Gibson et al., 2018; Barry et al., 2014; Ito et al., 2016; Simitsidellis et al., 2017). For example, recent data indicate that CA-125 and CA 19-9 molecules represent important markers of endometrial and cancer pathology (Socolov et al., 2017, Hirsch et al., 2017).

Nevertheless according to the recent literature there is no evidence about relationships of stress and dissociative symptoms with CA-125 and CA 19-9 as indicators of endometrial and cancer pathology. With respect to these findings we have tested this hypothesis and assessed 55 female outpatients with endometriosis and the clinical investigations were focused on biochemical serum analyses of oncological markers CA-125 and CA 19-9, estradiol, prolactin and cortisol.

## 2. Participants and method

To test the above hypothesis we have assessed 55 female outpatients mean age (32.78±4.36), age range (26-44) with endometriosis who were treated at the Institute of Sexology of the Charles University Hospital in Prague. All women included in this study had dyspareunia, pelvic pain, orgasm disorders, lubrication disorders and irregular and painful bleeding. Most women had pains during the menstrual and non-menstrual stages, other reported symptoms were fatigue, sleep disturbances, painful sex, and partner relationship disturbances. All participants provided written informed consent and the study was approved by University Hospital ethical committee. Exclusion criteria were gravidity, oncological diseases, urological disorders, intestinal diseases and metabolic disorders.

The clinical investigations were focused on biochemical serum analyses on biochemical serum analyses of oncological markers CA-125 and CA 19-9, estradiol, prolactin and cortisol. CA 125 is a glycoprotein with a high carbohydrate component and its molecular weight is at about 200 kDa. CA 125 is produced in the fetal period by epithelial tissues and in adulthood it may occur in the normal epithelium of the fallopian tubes, cervix or bronchus. CA 125 is particularly important as a marker of serosa membrane carcinomas and undifferentiated ovarian carcinomas and its serum concentrations may reflect tumor size (Hirsch et al., 2017).

CA 19-9 is a pentasacharide with carbohydrate component containing fructose components and it belongs to a group of oncofetal antigens. In the fetal period, it is synthesized in the epithelial structures of the stomach and in adulthood its production is significantly decreased. In addition recent findings show that CA 19-9 may be produced in glandular structures of the gall bladder, pancreas, bronchus and some gynecological tumors (Fassbender, et al.,2015). Some studies show that CA-19-9 may be demonstrably elevated in endometriosis and exhibit the same or decreased sensitivity as CA – 125 (Fassbender, et al., 2015).

## 3. Results

The results show significant Spearman correlations of TSC-40 with CA-125 and CA-19-9 (R=0.52 resp. R=0.30, Figure 1) and SDQ-20 with CA-125 and CA-19-9 (R=0.53 resp. R=0.31, Figure 2). Other correlations with exception of correlation between CA-125 and CA-19-9 (R=0.60) were not statistically significant. These results represent findings documenting relationship of CA-125 and CA-19-9 with stress related psychopatological symptoms suggesting influence of stress on endometrium pathology. In addition we have analyzed comparison of women who manifested higher levels of stress symptoms (TSC-40) than median with other

participants in the sample using Mann-Whitney test and this comparison confirms significant differences in other assessed variables as indicated by Spearman correlations ($p<0.001$, $Z\geq3.76$; and for CA-19-9 $p=0.041$, $Z=2.05$).

Insert Figure 1 and 2 about here

## 4. Discussion

The results of this study are in agreement with the tested hypothesis focused on the relationship of stress and dissociative symptoms with CA-125 and CA 19-9 as indicators of endometrial and cancer pathology. These results are in accordance with recent findings indicating that CA-125 and CA 19-9 molecules represent important markers of endometrial and cancer pathology (Socolov et al., 2017, Hirsch et al., 2017). In addition the results indicate relationships of stress and somatoform symptoms with CA-125 and CA 19-9 which suggests that chronic stress symptoms likely influence endometrial pathology. According to current literature, there is no evidence of stress and somatoform dissociative symptom in their relationship with CA-125 and CA 19-9 as indicators of endometrial pathology. It is possible to assume that C-125 and CA 19-9 as well as chronic stress assessment within this psychosomatic approach could have clinical importance with respect to prevention and timely diagnosis, mainly because diagnosis of endometriosis is generally delayed by 8-10 years due to misinterpretation of symptoms in juveniles and young women (Ahn et al., 2017).

## Acknowledgement

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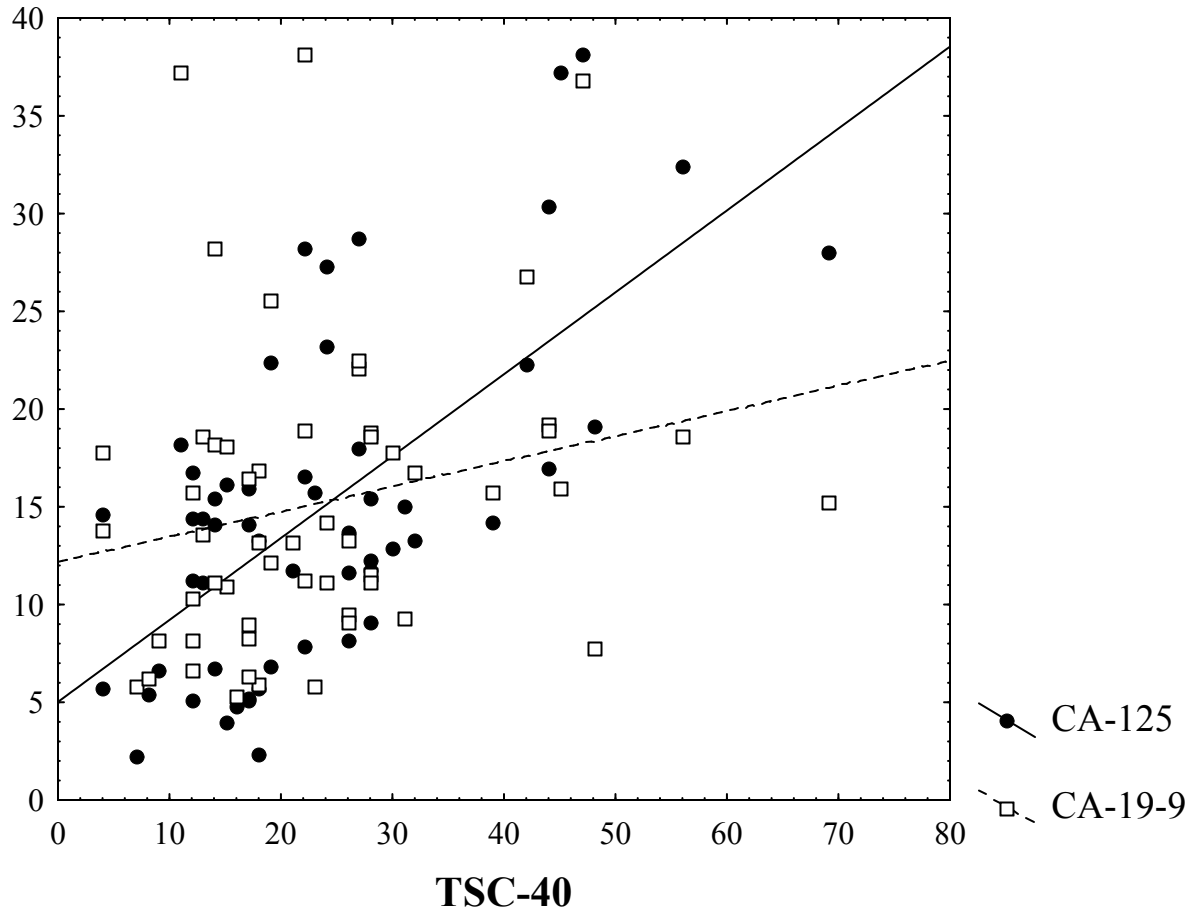


Figure 1. Relationship of TSC-40 with CA- 125 and CA-19-9.

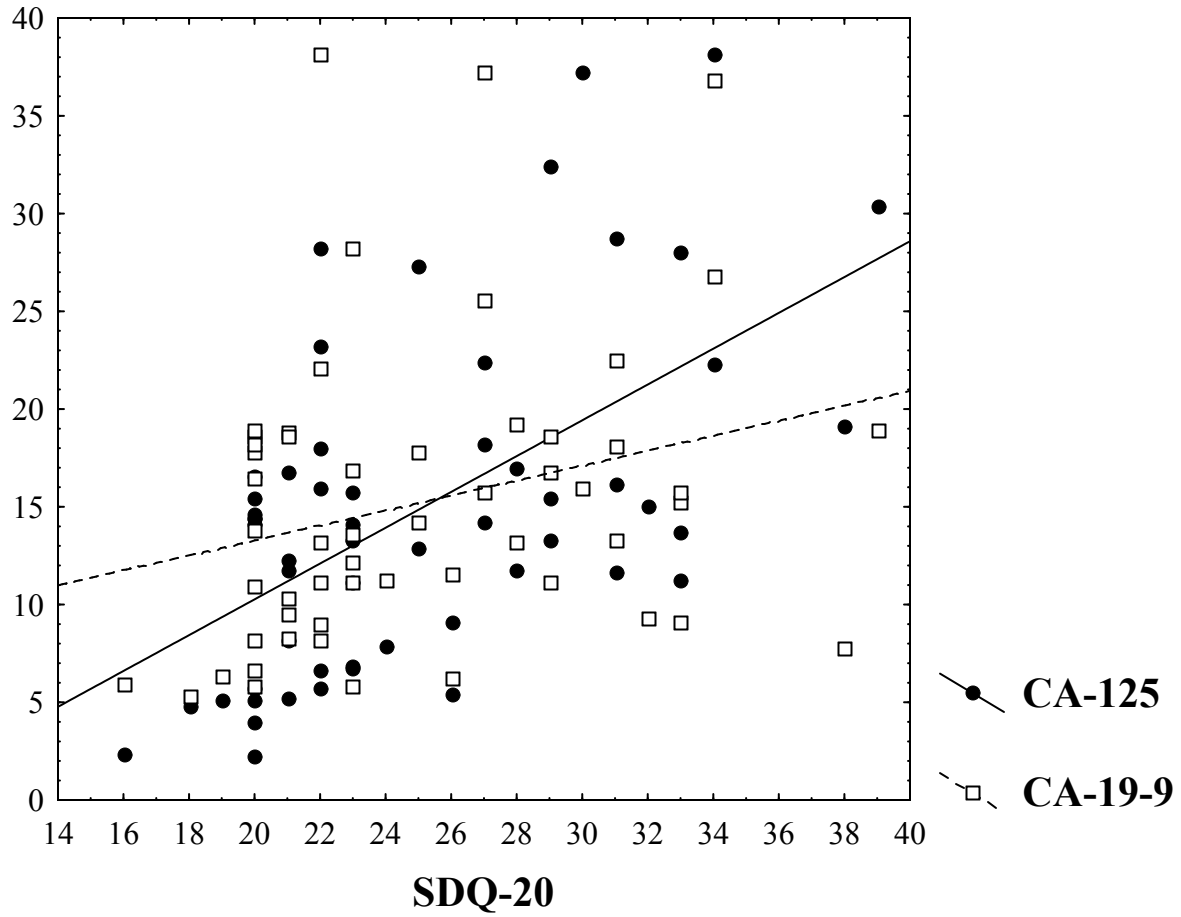


Figure 2. Relationship of SDQ-20 with CA- 125 and CA-19-9.

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# Rectal perforation caused by deep infiltrating endometriosis in non-pregnant woman:
## Case report and short review of the literature

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**Rectal perforation caused by deep infiltrating endometriosis in non-pregnant woman: Case report and short review of the literature**.

AIM: *The aim of this paper is to describe an unique case of deep infiltrating endometriosis of the rectum in non-pregnant woman with unusual clinical and pathological presentation resulting in spontaneous perforation.*
MATERIALS AND METHODS: *A female (20 years of age) with a two year history of chronic recurrent abdominal pain of unknown etiology treated by a psychiatrist underwent diagnostic laparoscopy which revealed many peritoneal implants of endometriosis involving the right ovarian fossa, the vesico-uterine pouch and sacrouterine ligament; the bowel wall showed no structural abnormalities. Peritonectomy of the broad and uterosacral ligaments was used and eight days after the operation, the patient developed crampy abdominal pain and enterorrhagia necessitating laparoscopic revision; pelvic haematoma and rectosigmoiditis were found. Over the next three days, perforation of the rectum resulted in the presence of fecal material in the surgical drain.*
RESULTS: *Lower rectal resection with ileostomy was performed. Microscopic examination revealed discrete small endometriotic lesions in submucosa, muscular layer and serosa of the rectum associated with perforation.*
DISCUSSION: *Laparoscopy and laparotomy may be insufficient in the case of an inactive endometriosis. Definitive diagnosis is thus reached only by the histological examination. The pathophysiology of the bowel perforation secondary to endometriosis is not entirely clear.*
CONCLUSION: *The presented case confirms the importance of interdisciplinary cooperation between surgeons, gynaecologists, and pathologists. We also want to emphasize the need for extensive pathological examination of the resected specimens which is essential for a proper diagnosis.*

KEY WORDS: Endometriosis, Rectum, Spontaneous perforation

## Introduction

Endometriosis is defined as the presence of endometrium outside the uterine corpus [1,2]. It usually affects many organs as the ovaries (endometriomas), fallopian tubes, uterus, urinary bladder, rectosigmoideum, uterosacral ligaments, the pouch of Douglas, and peritoneum [3,4]. It is a common, chronic, oestrogen-dependent disease affecting between 5% and 20% of women of reproductive age [5]. The intestinal involvement by endometriosis occurs in 3% to 37% of patients. Up to 73% of cases affect the lower rectosigmoid colon followed by the rectovaginal septum, terminal ileum, caecum, and the

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appendix [6]. Superficial intestinal diseases in the form of serosal implants usual do not cause any symptoms, but bulky, deeply invasive diseases can cause real problems. Spontaneous perforation of intestinal endometriosis is a very rare complication but occurs most frequently during pregnancy [7,8].

## Case Report

### Case Presentation

A female, 20 years of age, gravida 0, para 0, was admitted to a surgical unit. She was suffering from acute and worsening anorexia, vomiting and abdominal pain. She had been experiencing the symptoms for about three months. The abdominal pain was mainly in the right lower quadrant and epigastrium. The patient also complained of dysmenorrhea. A complete gynaecological ultrasound examination was inconclusive.
Esophagogastroduodenoscopy (EGD), c-reactive protein (CRP) and white blood cells (WBC) were within normal ranges. As there was no obvious etiology of her symptoms, the patient was referred for psychiatric evaluation. Her symptoms persisted and she later underwent a diagnostic laparoscopy. Endometriosis of the vesico-uterine pouch, right ovarian fossa, right sacrouterine ligament and Allen-Masters syndrome were identified (Fig. 1 a,b). There were no signs of inflammation, infection nor other structural abnormalities on the appendix, sigmoid colon or rectum. The revised American Society for Reproductive Medicine (rASRM) score (stage IV) was used to classify endometriosis. Two months later the patient underwent deperitonealization of the posterior compartment, bilateral ureterolysis and revision of the sacrouterine ligaments. Four days after the operation, the patient was discharged in a stable condition without complaints of hematochezia. Eight days after the operation, the patient was returned to hospital with cramping abdominal pain, rectal and vaginal bleeding. Ultrasound showed pelvic haematoma consistent with postoperative changes. CRP was 130 mg/l, WBC 16,500 and procalcitonin was negative. A computer tomography (CT) scan of the abdomen and pelvis confirmed haematoma in the pelvic cavity and the patient was found to have a distended sigma. Flexible sigmoidoscopy revealed nothing due to poor bowel preparation. Later, the patient deteriorated clinically with worsening leukocytosis, fevers and increasing abdominal pain suggesting acute abdomen. A repeat laparoscopic evaluation was undertaken. The findings included a pelvic abscess and secondary inflammation of the rectosigmoideum (Fig. 1 c,d). No evidence of bowel perforation was found. The patient's clinical status deteriorated further and the devel-

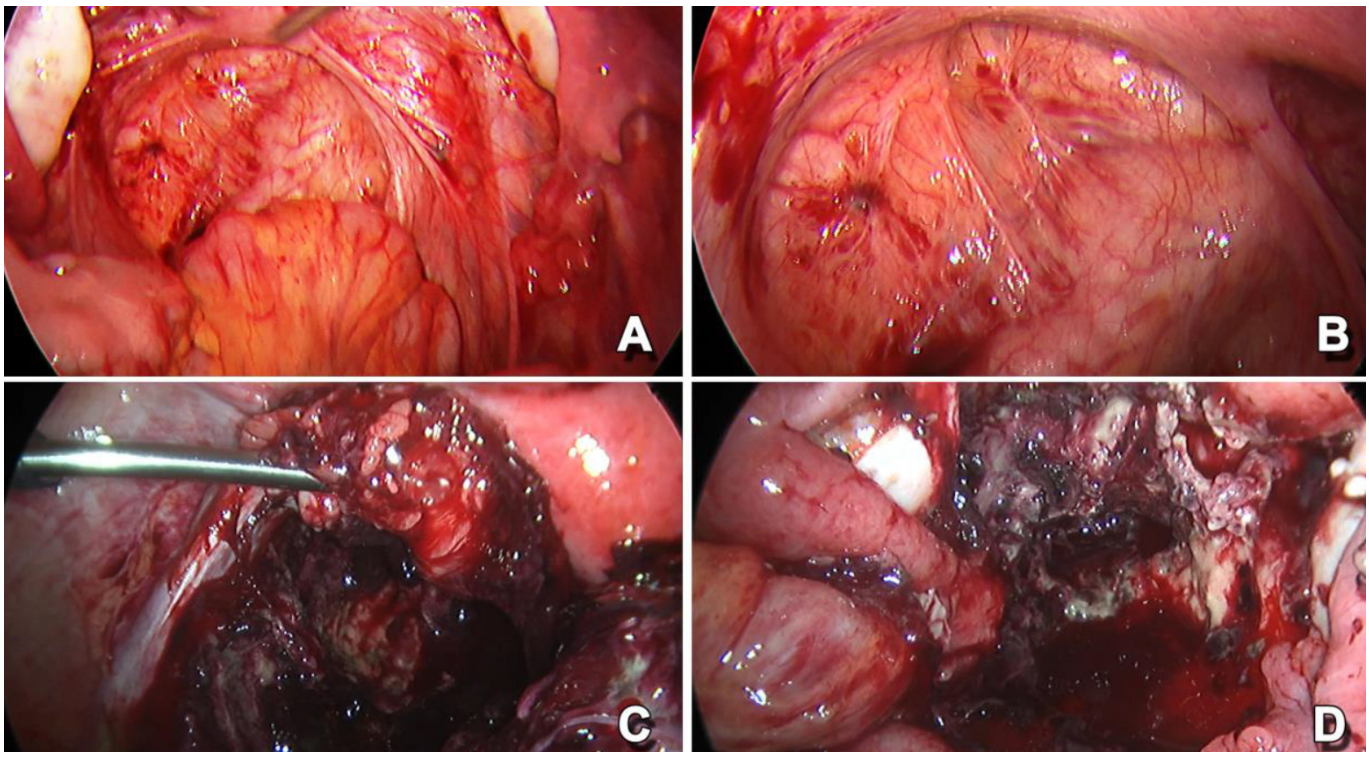


Fig. 1: Intraoperative laparoscopic images.
A,B: Initial diagnostic laparoscopy showing endometriosis of the lesser pelvis – vesico-uterine pouch, right ovarian fossa, right sacrouterine ligament, Allen Masters syndrome.
C,D: Laparoscopic revision of the abdominal cavity on the 8th postoperative day – pelvic haematoma and rectosigmoiditis.

opment of sepsis and stercoral peritonitis required emergent exploratory laparotomy. Acute pelviperitonitis along with a small perforation of the anterior rectal wall was identified. Low anterior resection of the rectosigmoid colon with protective ileostomy was indicated. After three months the patient underwent revision and reconstruction of the rectosigmoideum and is currently without symptoms.

### Pathology

Three separate specimens were evaluated at the department of pathology: rectosigmoid colon resection specimen, 18 cm in the length (1), colon resection rings (2) and appendix (3). Macroscopic investigation of the colon revealed regressive and inflammatory changes including one 8 mm perforation. Thirty one tissue sections in total were stained with hematoxylin-eosin and extensively investigated. Cardinal histologic finding represented discrete endometriotic lesions in the submucosa, muscular layer and serosa of the rectum associated with full thickness bowel wall necrosis and acute inflammation (Fig. 2 a,b). These findings were confirmed by using immunohistochemistry - both stromal and glandular immunopositivity for oestrogen and progesterone receptors (ER, PR) (Fig. 2c), only stromal immunopositivity for CD10 (Fig. 2d), only glandular immunopositivity for cytokeratin 7 (CK7) and stromal and glandular immunonegativity for cytokeratin 20 (CK20).

The final diagnosis was of deep infiltrating endometriosis (DIE) of the rectum causing perforation and fibrinous-purulent peritonitis.

## Discussion

Intestinal endometriosis typically involves areas where the peritoneum is irregularly folded, such as the rectovaginal septum, rectum, and sigmoid colon [1,6]. Most cases occur during surgical intervention or are revealed incidentally by pathological examination of tissues removed for different surgical indications [9].

The symptoms of gastrointestinal tract involvement by endometriosis are nonspecific and depend on a) the severity and b) the location of the disease. Superficial intestinal endometriosis may be asymptomatic or cause cyclical spastic pain [10]. When endometriosis deeply invades the bowel wall, it causes a scarring and retraction and can form a mass lesion which partially obstructs the bowel wall [11]. In such cases symptoms may include constipation, diarrhoea, melena, rectal bleeding, meteorism and tenesmus. It is very rare that the colon is perforated by endometriosis. When searching the literature, 12 cases of perforation of the small bowel, 16 cases of perforation of the large bowel and 3 cases of perforation of the appendix, due to intestinal endometriosis were found (a total of 31 cases). The first case report was published in 1931 by Haufler. A 30-year old women was reported with jejunal perforation due to rupture of

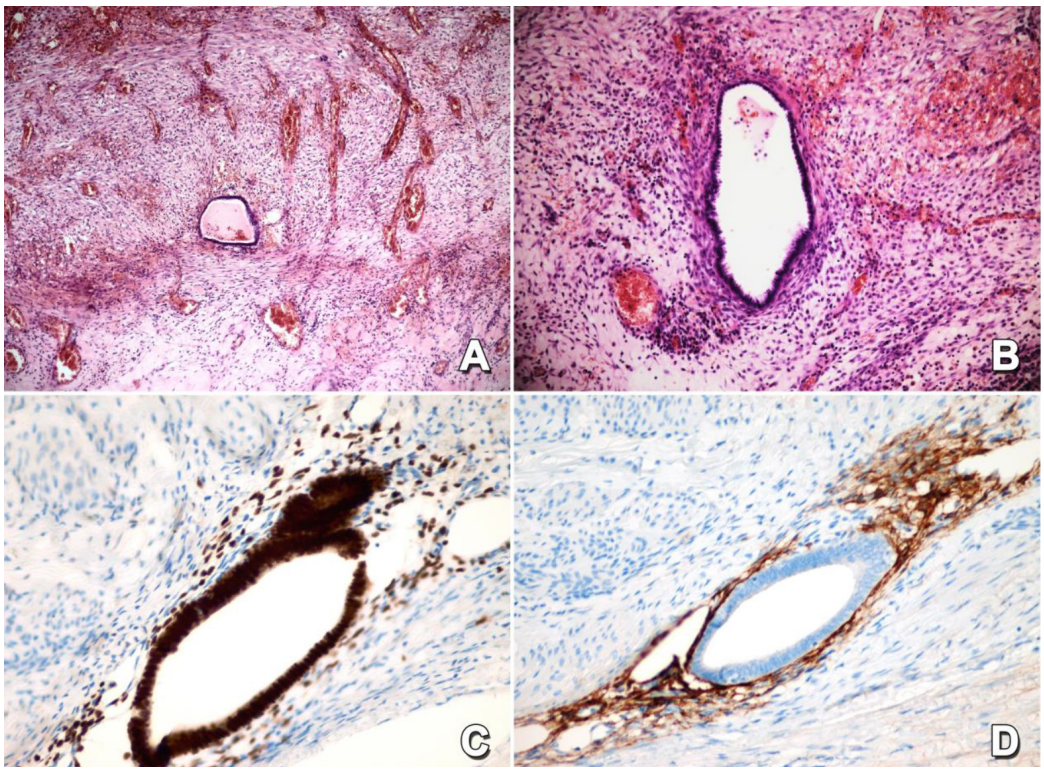


Fig. 2: Intestinal endometriosis, immunohistochemical expression of oestrogen receptors and CD10 in intestinal endometriosis.
A,B: Discrete endometriotic lesion and florid regressive and inflammatory changes in the subserosa of the bowel wall (hematoxylin-eosin staining, original magnification x100, x200).
C: Oestrogen receptors stain both endometrial gland and endometrial stromal cells (immunohistochemistry, original magnification x200).
D: CD10 stains a few endometrial stromal cells adjacent to the gland in the muscular layer of the bowel wall, confirming the diagnosis of intestinal endometriosis (immunohistochemistry, original magnification x200).

an endometriotic cyst during the sixth month of pregnancy [12]. Most recently, in 2017, Marujo et al. described a case of transmural perforation of the rectum wall by the left fallopian tube in a patient with DIE. A 38-year-old women, nulliparous, with a history of primary infertility, complained of chronic pelvic pain, dysmenorrhea, dyschezia, dyspareunia and the occasional rectal bleeding. On gynaecological examination, a painful retrocervical nodule and elastic mass on the left adnexal area was discovered. Given the clinical probability of DIE, the patient was initially treated with hormonal contraceptives. Using magnetic resonance imaging (MRI), rectal endoluminal formation was described; a biopsy taken during colonoscopy revealed an inflammatory polyp of the colon. Consequently, because of the symptoms and the presence of lesions compatible with DIE of the rectovaginal septum, with probable intestinal infiltration, the patient was recommended for surgery. During adhesiolysis it was found that the rectum had been pierced by the tube. Histological examination showed tubal endometriosis; involvement of the excised rectal segment by endometriosis was not diagnosed [13].

We have a few comments on this case. It is felt that a conservative approach should not be the first-choice of treatment (in this clinical context). Currently, many papers approve of the strategy of completely removing the bulky deeply invasive disease by laparoscopy in trained centers, followed by in vitro fertilization (IVF) in the case of sterility or hormonal treatment [14-18]. It is widely accepted that, because endometriosis is a systemic disease, the division between deep and superficial endometriosis is an anachronism. Endometriosis, in the form of DIE, does not show any respect for organ borders. The disease merges all concerned tissue into one bulky mass consisting of an active part of endometriosis, inflammatory tissue and hyalinisation. Pathological findings of the resected specimens are regionally heterogeneous and a large number of sections are required to determine the correct diagnosis. We would recommend a second-look histopathological examination of the resected rectal specimen focusing on the area of the perforation. Piercing is a very dubious mechanism of rectal penetration and we lack a competent commentary from the pathologist on this subject.

The current paper is interesting from two points of view: clinical and pathological. Misinterpretation of abdominal symptoms, initially treated by a psychiatrist and not surgically. Macroscopically, endometriosis involved the lesser pelvis, not the bowel, caused by inapparent lesions of inactive endometriosis and absence of fibrous adhesions within the lesser pelvis. Microscopically, discrete small lesions of endometriosis, in contrast to the cases of extensive transmural involvement that have so far been published, and absence of decidualized stromal cells. Spontaneous perforation of the rectum occurred after a simple surgical procedure – peritonectomy, without any manipulation with the bowel (e.g. rectal shaving) and with no use of coagulation devices, i.e. monopolar or bipolar.

The pathophysiology of the bowel perforation, being secondary to endometriosis, is not clear. Generally, two mechanisms should be considered. Firstly, endometriosis involving the intestinal tract may weaken the bowel wall while, on the one hand, the elasticity of the endometriotic tissue is impaired and causes a loss of elasticity and on the other hand, in the case of pregnancy, the whole endometriotic tissue is decidualised so that the elasticity of the tissue vanishes completely. Secondly, the intestine becomes a part of a convolute consisting of the uterus, adnexa and fibrous tissue (frozen pelvis) and is under tension of adhesions secondary to peristalsis. Both of these phenomenona together may compromise the intestinal wall integrity and result in perforation, especially during pregnancy [11].

There are few if any characteristic symptoms for intestinal endometriosis making it difficult to diagnose. FU et al. published a paper in 2007 recommending that intestinal endometriosis should be considered when a reproductive woman who has had a history of pelvic endometriosis developes a cyclical bowel discomfort [10]. In the case of chronic nonspecific abdominal pain, diagnostic laparoscopy is suggested. In accordance with some other papers, we recommend, in the case of asymptomatic superficial intestinal endometriosis, follow-up without any treatment. Resection of the involved bowel segment remains the treatment of choice for patients with intestinal endometriosis since the effect of gonadotropin-releasing hormone (GnRH) analogs and progestin is limited; also for patients with symptoms of obstruction or bleeding, and if malignancy cannot be excluded [7,18-20].

The most accepted etiological theories concerning endometriosis are still the peritoneal implantation of endometrium by retrograde menstruation, vascular dissemination or the possible metaplasia of peritoneal cells. Intestinal endometriosis predominantly involves the extra mucosal layers but may be found in all the layers of the bowel wall. Most endometriomas are ill-defined serosal and subserosal nodules that are rarely larger than 5 cm. On the cut surface, the spectrum of colors is quite broad, ranging from black through brown to red and white [21].

When examined microscopically, they consist of endometrioid glands and stroma that are often accompanied by fibrosis in the adjacent bowel wall.

Occasionally only endometrioid-type stroma, including a variety of changes such as decidua, smooth-muscle metaplasia, pseudodecidua, fibroblastic metaplasia and sarcoma, are present. Such lesions are referred to as stromal endometriosis and are considered to be most likely due to limited sampling [22]. In such cases a broad differential diagnosis should be considered including

gastrointestinal stromal tumor or benign nerve sheath tumor [23].

From a histopathological point of view, it is necessary to differentiate between colorectal adenocarcinoma and endometriosis. Chen et al. in 2015 described a case report of a 39-year-old women with rectal mucosal endometriosis primarily misinterpreted as adenocarcinoma. Initial colonoscopy showed a rectal mass with ulceration and circum wall involvement. A combination of all the histological features, i.e. irregular glands with mucin depletion, nuclear stratification, subtile subnuclear vacuoles and spindle cells with abundant pink cytoplasm and an unclear boundary in the stroma, was subjectively interpreted as dysplastic glands in a desmoplastic setting with an initial suspicion of primary rectal adenocarcinoma. Subsequently, immunohistochemical examination with positivity for CK7, ER and CD10 identified the essence of ectopic endometrium [24]. As was shown in this case, the distinction between adenocarcinoma and endometriosis can be particularly challenging in mucosal biopsy specimens, mostly due to the limited amount of tissue present, misinterpreting of the reactice glandular changes and, because the endometrial tubules tend to be separated from their stroma, secondary to trauma from the biopsy procedure [23,25]. Routine light microscopy is usually sufficient to make the correct diagnosis. Malignancy is excluded by lack of significant cellular atypia, low mitotic activity and an absence of a desmoplastic stromal reaction. By the use of immunohistochemistry a diagnosis of colonic endometriosis can be confirmed. The first known case of pelvic lymph node endometriosis with aberrant immunophenotype with a complete loss of oestrogen and progesterone receptor expression of the endometrioid glands, mimicking metastasis of adenocarcinoma has been described by the authors [26]. Thus, it is important to keep in mind that the final interpretation must always be determined within the context of the morphological findings.

Laparoscopy and laparotomy, often considered as the gold standards for diagnosing pelvic endometriosis, may be insufficient in the case of an inactive endometriosis. As in the paper published in 2014 by Galazis et al, no active endometriosis of the bowel wall was seen during laparoscopy and laparotomy [27]. It is the histological examination that provides the definitive diagnosis. In our case, we initially found only regressive and inflammatory changes, including one perforation of the bowell wall. Due to unclear pathogenesis of these changes, another 15 sections of the resected colon were submitted. Evidence of endometriotic lesions in the submucosa, muscular layer and subserosa of the bowel wall were found in 3 hematoxylin and eosin stained slides. As a rule, in a non-neoplastic bowel resection specimen, it is necessary to submit representative sections of the proximal and distal margins and any focal lesions. It is also recommend that all areas of the bowel are sampled by submitting sections at regular 5-cm intervals. That way an extensive examination of the resection specimen is achieved leading to a proper diagnosis.

## Conclusion

Intestinal endometriosis should be considered in the differential diagnosis of any gastrointestinal or abdominal symptoms of every women. It is difficult to diagnose and may even mimic other diseases, including neoplasm. The risk of intestinal involvement by endometriosis is increased by simultaneous gynaecological symptons and diagnostic laparoscopy should be considered. Patients should be closely followed up after the operation.

We also want to emphasize the need for extensive pathological examination of the resected specimens which is essential for a proper diagnosis.

This report is believed to be a unique case of spontaneous rectal perforation secondary to endometriosis in non-pregnant women.


## Riassunto

Viene descritto il caso di una perforazione spontanea del retto da infiltrazione endometriosica profonda, in una donna non gravida, e la sua insolita presentazione clinica e patologica,

Donna di 20 anni, con storia di dolore addominale cronico recidivante da due anni di etiologia ignora, trattata da uno psichiatra. A seguito di una laparoscopia diagnostica sono stati rilevati molti impianti peritoneali di endometriosi interessanti la fossa ovarica destra, la tasca vescico-uterina ed il legamento utero-sacrale, mentre la parete dell'intestino non mostrava anomalie strutturali.

Sottoposta quindi a peritonectomia dei legamenti larghi ed uterosacrali, dopo otto giorni dall'intervento sono insorti dolori addominali, crampi ed enterorragia che richiese una revisione laparoscopica che dimostrò un ematoma pelvico ed una rettosigmoidite, e tre giorni dopo una perforazione del retto con comparsa di materiale fecale nel drenaggio chirurgico. La paziente venne pertanto sottoposta a resezione del retto inferiore con ileostomia.

L'esame istologico ha dimostrato piccole e discrete lesioni endometriosiche nella sottomucosa, nello strato muscolare e nella sierosa del retto in associazione con la perforazione.

Laparoscopia e laparotomia possono essere insufficienti a riconoscere una endometriosi in fase di quiescenza, e la diagnosi definitiva è raggiungibile solo con l'esame istologico. La fisiopatologia della perforazione intestinale secondaria all'endometriosi non è del tutto chiara.

il caso presentato conferma l'importanza della cooperazione interdisciplinare tra chirurghi, ginecologi e anato-

mo-patologi, ed a questo proposito si sottolinea la necessità di un ampio esame patologico dei tessuti resecati, essenziale per una corretta diagnosi.

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