MEDICAL MANAGEMENT OF ENDOMETRIOSIS- New Concepts

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MEDICAL MANAGEMENT OF ENDOMETRIOSIS (New Concepts)

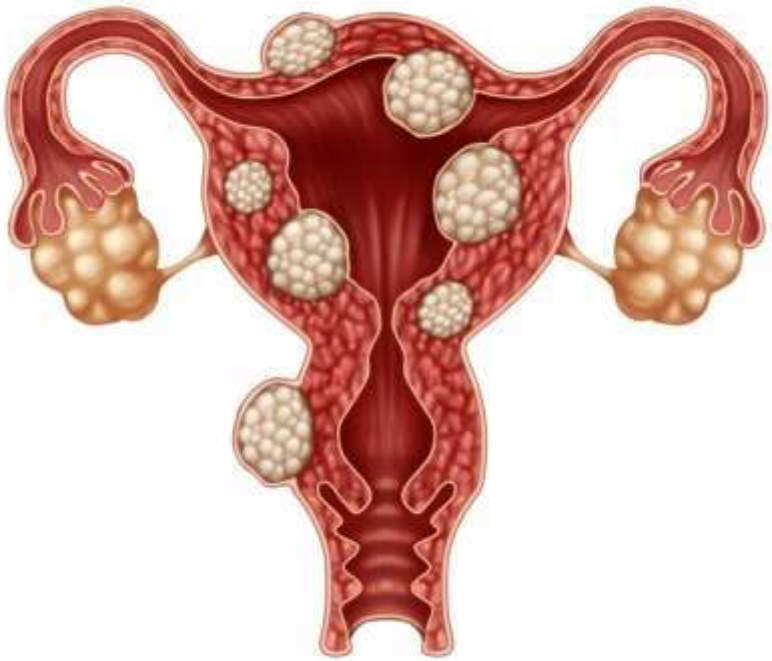
Presentation Overview

1. INTRODUCTION
2. PREVALENCE
3. TYPES, DIAGNOSIS & STAGING SYSTEM
4. MEDICAL TREATMENT
5. TREATMENT RELATED TO INFERTILITY
6. CONCLUSION

1 INTRODUCTION

INTRODUCTION

Endometriosis is a chronic and recurrent disease characterized by the presence and proliferation of functional endometrial glands and stroma outside the uterine cavity



ETIOLOGY

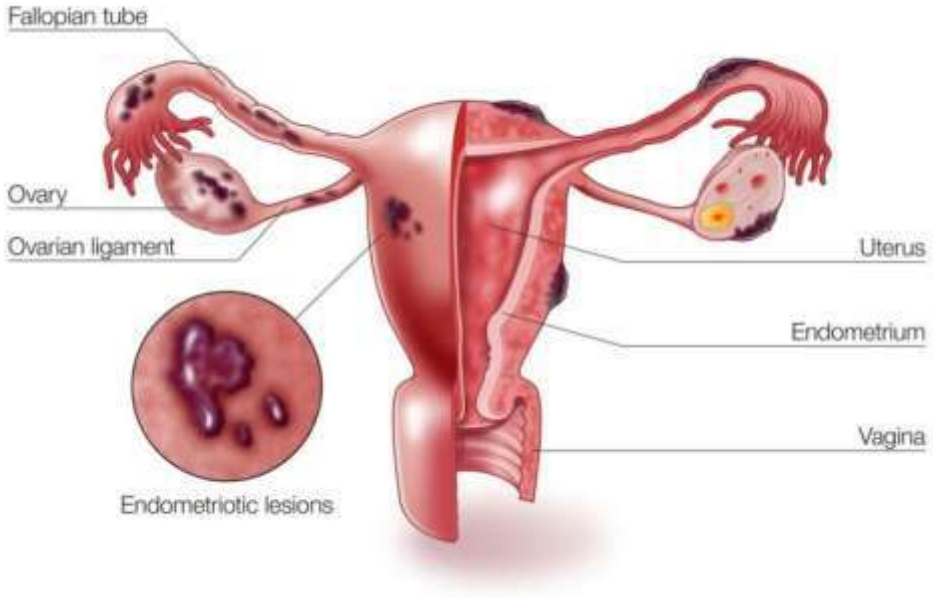
Cause of **Endometriosis** is unknown

Endometriosis leads to *displacement of tissue outside uterus* – results in lesions:

Ovaries

Fallopian tubes

Ligaments supporting uterus



ENDOMETRIOSIS INVOLVING **OVARIES**

When ovaries are involved, cysts are called

Endometriomas

Surrounding tissue can develop:

Irritation

Scar Tissue

Adhesions

Pain

Infertility

AFFECTS OF ENDOMETRIOSIS

Endometriosis affects every part of women's reproductive system including:

- Ovarian Function
- Oocyte Quality
- Embryo Development
- Implantation
- Uterine Function
- Endocrine function
- Infertility or Spontaneous Pregnancy Loss

AFFECTS OF ENDOMETRIOSIS

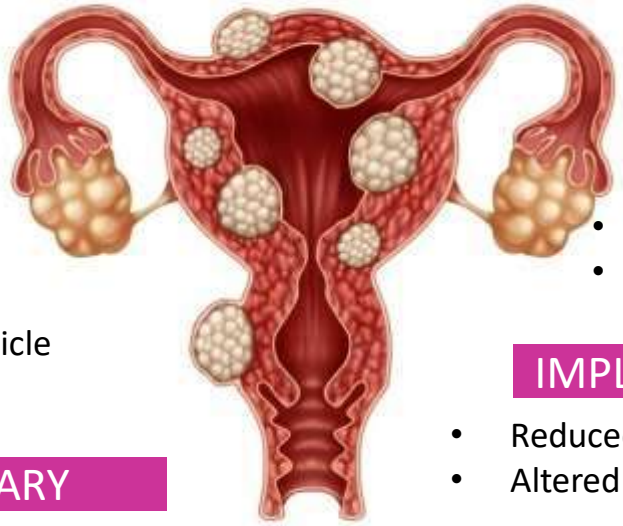
Summarizing the affects of Endometriosis:

PITUITARY

- Altered pituitary-ovarian axis
- Altered LH surge

FERTILIZATION

- Oocyte linked reduced fertilization rate
- Poor sperm binding
- Reduced sperm motility



OVULATION

- Fewer oocytes
- Altered oocyte quality
- Luteinized Unruptured Follicle Syndrome

PREIMPLANTATION EMBRYO

- Poor embryo quality
- Early embryo arrest

IMPLANTATION

- Reduced uterine receptivity
- Altered hormone regulation

OVARY

- Impaired folliculogenesis
- Fewer follicles
- Luteal defect
- Altered steroidogenesis

PREGNANCY

- Increased pre-term loss
- Recurrent miscarriages

2 PREVALENCE

PREVALENCE

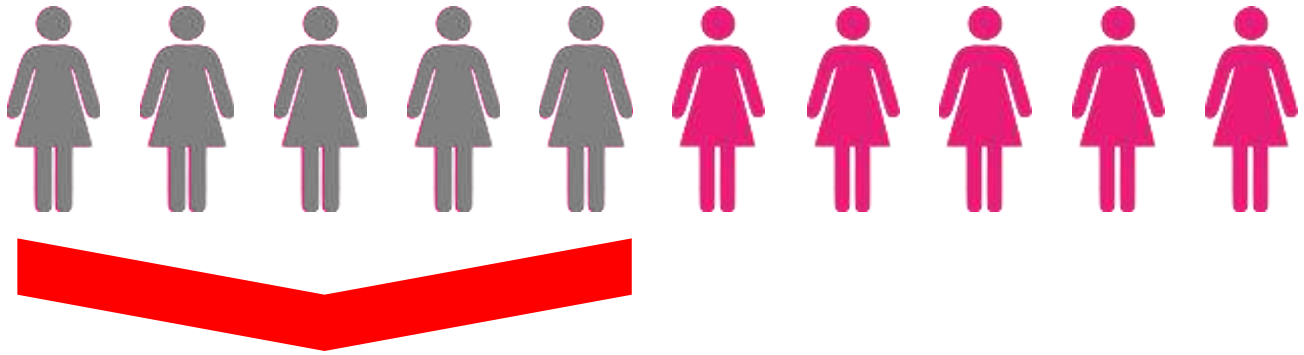
1 in 10 women of reproductive age* suffer from Endometriosis

*Reproductive age – 15-49 yrs.

176 million women in the world suffer from Endometriosis

PREVALENCE

It is suggested that **25-50%** of **infertile women** have endometriosis



30-50% of women with endometriosis are **infertile**

Prevalence of endometriosis is difficult to quantify as wide ranges have been reported in literatures.

-(Winkel CA 2003)

3

TYPES, DIAGNOSIS & STAGING SYSTEM OF EMDOMETRIOSIS

BASED ON LOCALIZATION & APPEARANCE

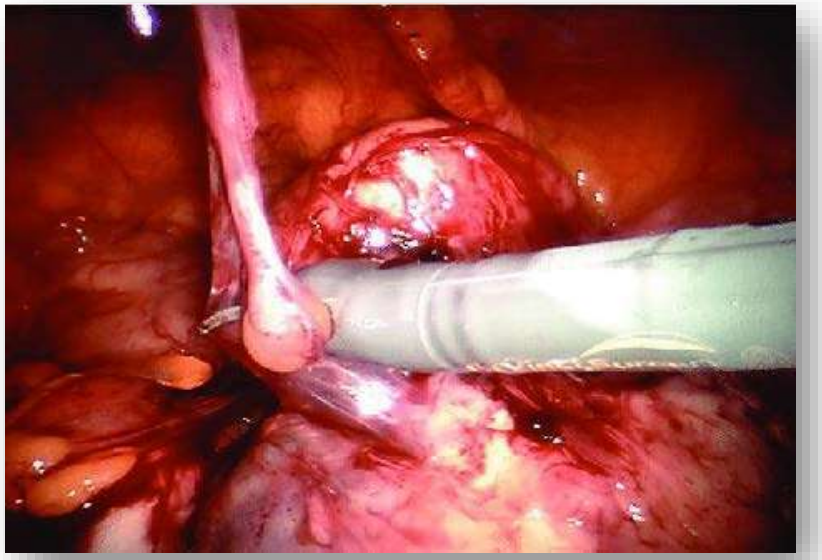
There are three types of endometriosis:

1. **Superficial** Endometriosis
2. **Ovarian** Endometrioma
3. **Deep Infiltration** Endometriosis **(DIE)**

1 - ENDOMETRIOTIC **LESIONS**

It may be **superficial** or may **deeply** invade the peritoneum or pelvic organs

It appears as superficial **“powder burn”** or **“gunshot”** Lesions on the ovaries, serosal surfaces and peritoneum, nodules or small cysts containing old hemorrhage surrounded by variable extent of fibrosis

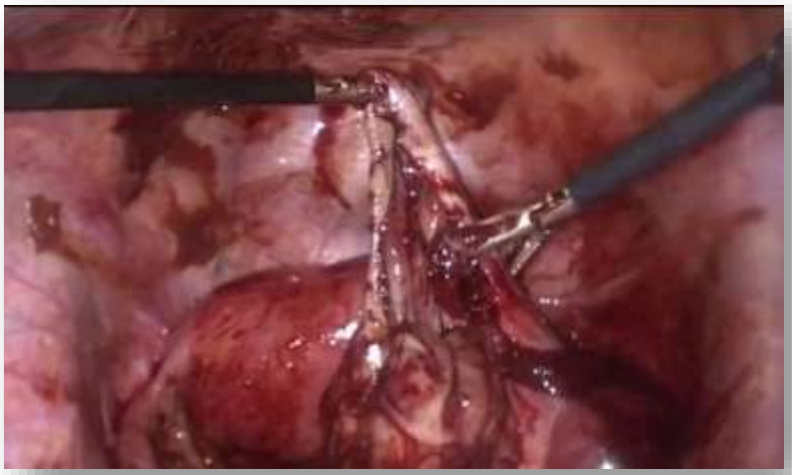


2 – OVARIAN ENDOMETRIOMAS

Endometriomas are **cystic endometrial lesions** contained within the ovary

Appearance – Smooth walled, brown cysts filled with thick, chocolate appearing liquid

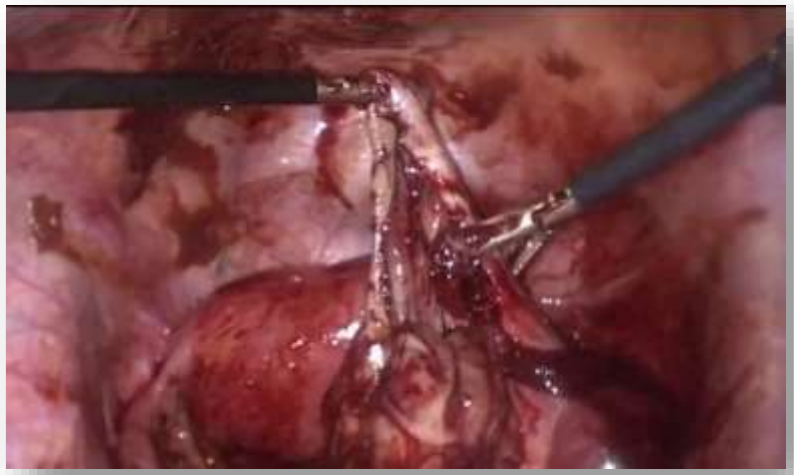
Ovarian masses may be unilocular but are often **multilocular** and **bilateral**



2 – OVARIAN ENDOMETRIOMAS

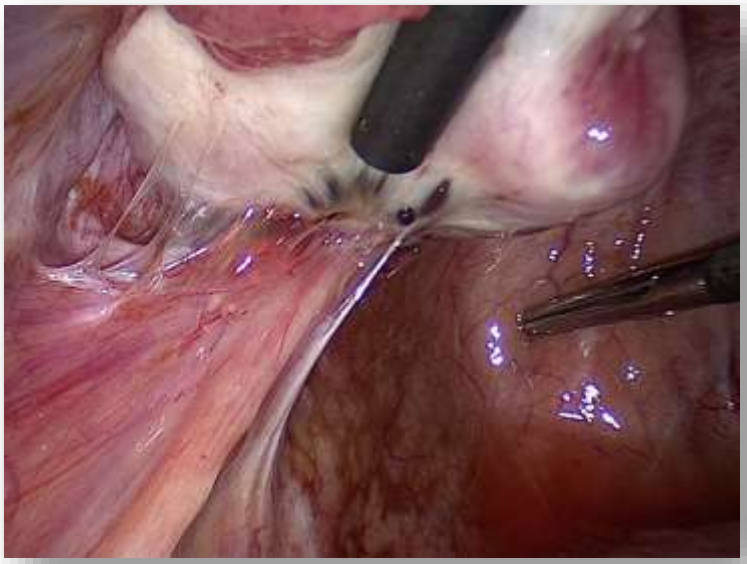
Laparoscopic visualization of ovarian endometriomas has a sensitivity of **97% *(unilocular)*** & **95% *(bilocular)***

Ovarian **Biopsy** is required rarely



3 – **PELVIC** ADHESIONS

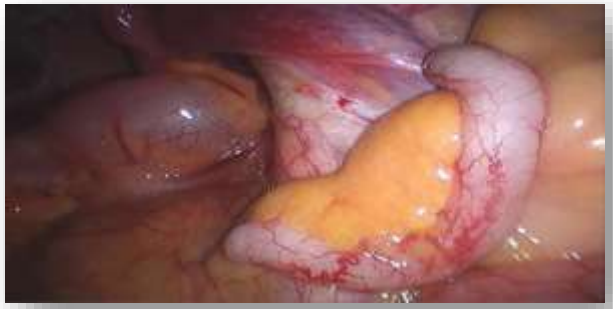
Extensive fibrosis in structures such as tubes, ovaries, uterosacral ligaments and rectum leading to **adhesion formation**, causing marked distortion of pelvic anatomy



3 – **PELVIC** ADHESIONS

Rectal Sigmoid Endometriosis (DIE)

Frozen Pelvic Endometriosis



DIAGNOSIS

Laparoscopy is required for definitive diagnosis of endometriosis

Disease severity is assessed by simply describing the findings at surgery or quantitatively using ASRM

STAGING SYSTEM

In the ASRM (1996) classified staging system based on **severity** of endometriosis by the **size, depth of implant** and **severity of adhesions** as

1. **Stage I - Minimal**
2. **Stage II - Mild**
3. **Stage III - Moderate**
4. **Stage IV - Severe**

INFERTILE WOMEN WITH **STAGE I/II** ENDOMETRIOSIS

'Evidence recommends that clinicians should perform **operative laparoscopy** ***(excision and adhesiolysis)*** rather than performing **diagnostic laparoscopy** only to increase pregnancy rates.'

- (Nowroozi, 1987, Jacobson 2010)

WOMEN WITH **STAGE III/IV** ENDOMETRIOSIS

Women with chocolate cyst larger than 3 cm, there is **NO evidence** that cystectomy prior to treatment with ART improves pregnancy rates **(A)**

Consider cystectomy prior to ART, ONLY to improve:

- **Endometriosis-associated pain**

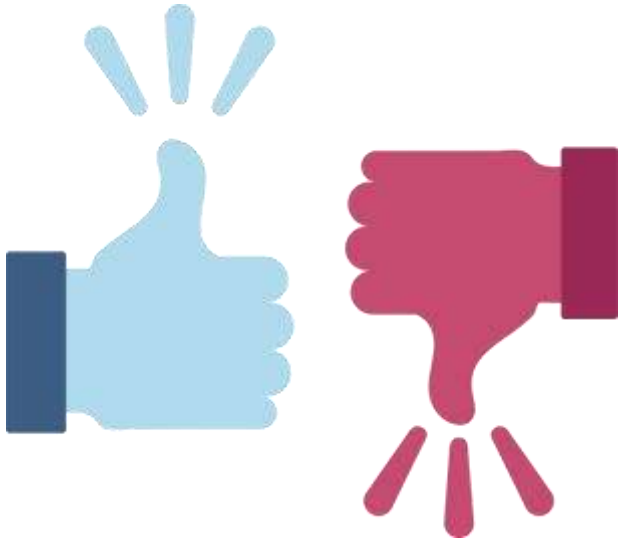
Or

- **Difficulty in oocyte retrieval (GPP)**

4 MEDICAL TREATMENT

ENDOMETRIOSIS TREATMENT – A **CONTROVERSY**

The efficacy of **medical** and **surgical** treatment of endometriosis associated infertility and pelvic pain is a source of ongoing controversy



It is possible that a **consensus will never be reached** on the optimal treatment of **minimal & mild** endometriosis

ENDOMETRIOSIS **TREATMENT** – *(infertility)*

In case of **moderate to severe** endometriosis-associated **infertility**, this combined approach should be considered as the **'First Line Therapy'**

Operative Laparoscopy + GnRH Agonist

THERAPY OBJECTIVES

Complete resolution of endometriosis is not yet possible and current therapy has **three** main objectives

To reduce pain

To increase the possibility of pregnancy

To delay recurrence for as long as possible

TREATMENT – PRIMARY AIM

Removal or reduction of ectopic endometrial implants

Restoration of normal anatomy

Reducing Disease Progression

Alleviation of Symptoms

Enhancing Fertility

MEDICAL TREATMENT – ENDOMETRIOSIS

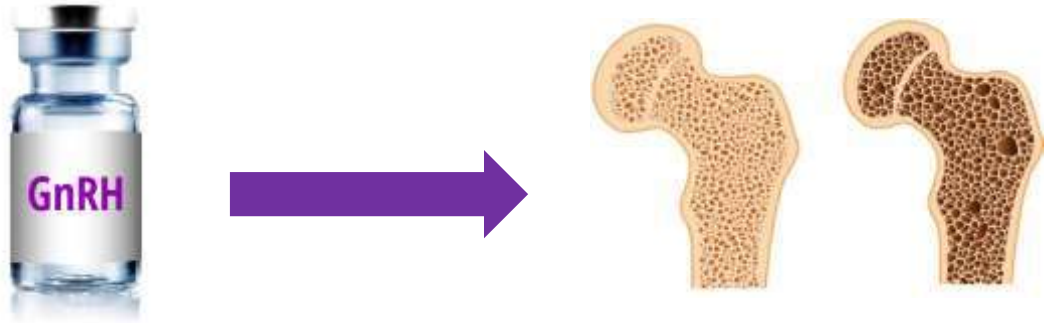
Suppression of ovarian function by using hormonal treatment for 6 months reduces endometriosis associated pain

Symptom recurrence is common following medical treatment of endometriosis

Recurrent symptoms require **long term** or **repeated** course of medication

MEDICAL TREATMENT – ENDOMETRIOSIS

Treatment with **GnRH analogs** such as Leuprolide is limited to **6 months only**, as it induces hypoestrogenic state that **decreases bone marrow density**



Add back therapy is an option, regimens are **complicated** and **costly**

Daily oral combined **oral contraceptives** can be used safely for **long term**

MEDICAL TREATMENT – SUMMARY

1. **Combined Oral Contraceptives**
2. **Oral Contraceptive Pills**
3. **NSAIDs**
4. **Progestins** – *Medroxyprogesterone, Norethindrone, Dienogest, Crypterone Acetate, Depot Medroxyprogesterone, Levonorgestrel containing IUS, Etonogestrel Implant.*
5. **Selective Progesterone Receptor Modulators (SPRMS)**
6. **Selective Estrogen Receptor Modulators (SERMS)**
7. **Androgens** – *Danazol, GnRH Agonists, GnRH Antagonists, Aromatase Inhibitors, Letrazole.*
8. **Newer Therapies** – *Anti-Angiogenesis Factors, Statins, TNF-α Blockers, PPAR-ϒ, Pentoxifylline, Elagolix.*

COMBINED ORAL CONTRACEPTIVES

Main stay for treatment of pain associated with endometriosis

Drugs which appear to act by **inhibiting gonadotropin release**, decreasing menstrual flow and decidualization of implants

Oral contraceptives **reduces menstrual flow** and retrograde menstruation and thereby reseeding of refluxed endometrial tissue

Inhibition of ovulation induced by oral contraceptive pill may **reduce the risk** of endometrioma development

ORAL **CONTRACEPTIVE** PILL

Induce **atrophy** of the endometriotic implant

Down regulate **cell proliferation**

Increase **apoptosis** in endometrial tissue

OCP therapy might prevent **implant growth** & reduce endometriosis-related **pain** as it is correlated to the **cyclic micro bleeding** within the endometriotic lesion

Long term administration of OCP is a **valuable adjuvant** postoperative measure in women undergoing conservative surgery for **symptomatic endometriosis**

NON-STEROIDAL ANTI-INFLAMMATORY DRUGS **(NSAIDs)**

Used as a **first line agents** in the management of endometriosis related **pain** and dysmenorrhoea

Pain in endometriosis is mostly secondary to **elevated levels** of PGs, interleukins and cytokines

Work by **blocking** the **enzyme COX** that is crucial for the production of inflammatory mediators

Selective and non-selective COX inhibitors are widely used for **symptomatic relief**

Selective COX-2 inhibitors like **Rofecoxib** can also **inhibit** the growth of **endometrial tissue**

PROGESTINS

Progestins are known to **antagonize estrogenic effects** on the endometrium causing initial decasualization and subsequent endometrial atrophy

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Progestins have multiple mechanisms of action that form the pathophysiologic basis of its use in endometriosis

1. **Inhibits** Estrogen
2. **Induces** Mitosis
3. **Alters** Estrogen Receptors
4. **Inhibits** Angiogenesis

Expression of matrix metalloproteinase needed for the growth of the endometriotic implants

MEDROXYPROGESTERONE

Medroxyprogesterone is available as **oral** and **injectable** preparation and can be administered **150 mg** intramuscularly **every three months**

Injectable progesterone offers the added advantage of **better compliance** by avoiding daily administration and erratic gastrointestinal absorption

Long term treatment of endometriosis by medroxyprogesterone is **breakthrough bleeding**

NORETHINDRONE ACETATE

2.5 mg per day for **12 months**

ADVANTAGE

Offers advantages for long term treatment of endometriosis that includes good

1. **Good control** of uterine bleeding *(compared to other medical treatments)*
2. **Positive effect** on calcium metabolism
3. **Lack of** negative effects on lipoprotein profiles

NORETHINDRONE ACETATE

Combination drugs like
AI(**Letrozole** and **Norethindrone** Acetate)
Is useful for treating
Painful symptoms due to rectovaginal endometriosis

Emerging data to support use of Norethindrone Acetate as an alternative to surgery for symptomatic rectovaginal endometriosis.

- (Vercellini P et al, 2009)

DIENOGEST

Anti-Inflammatory
Anti-Angiogenic
Anti-Proliferative

2 to 4 mg DAILY

Lowers incidence of **hot flushes** and minimal change in **bone mineral density** & **bone metabolism** in comparison to GnRH agonist

20 mg DAILY

High dose of Dienogest 20 mg daily has been effective in preventing progression of disease after surgical excision *(Schindler AE et al, 2006)*

CRYPTERONE ACETATE

Antiandrogen with weak **progestational activity**

10-12.5 mg DAILY

Daily dose of 10-12.5 mg is administered to treat endometriosis

Pain, sexual satisfaction and **quality of life** were improved substantially after **6 month of treatment**

Side Effects: Depression, marked decrease in libido, hot flushes and vaginal dryness

DEPOT MEDROXYPROGESTERONE

104 mg subcutaneously

1 2 3 4 5 6 7 8 9 10

Administered every 3 months

Patients with progestins experienced higher incidence of **bloating**, **spotting** but **benefitted** from a greater incidence of **amenorrhoea**

Helps in **reducing pain** and **improving** productivity and quality of life

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Disadvantages: Prolonged delay in the resumption of **ovulation** and bone **demineralization**

LEVONORGESTREL CONTAINING INTRA-UTERINE SYSTEMS (LNG-IUS)

LNG-IUS

Delivers progesterone locally

Used as a contraceptive

Treatment of menorrhagia

Avoids systemic side effects

Precise mechanism of action is **unclear**

0.2 mg DAILY

Have similar efficacy to a **depot GnRH agonist** in the control of endometriosis related pain over a period of **6 months**

LNG-IUS successfully controls endometriosis related pelvic pain, reduce the size of rectovaginal nodules and improves patient satisfaction. - *(Romer T et al, 2008, Vecellini P et al, 2005)*

Gestrinone

Progestational withdrawal effect at the endometrial cellular level and inhibition of ovarian steroidogenesis.

2.5-10 mg DAILY

Side effects relate to both androgenic and antiestrogenic effects.

Gestrinone was shown to be as effective as **danazol** and GnRH analogues

ETONOGESTREL IMPLANT (Subdermal)

Subdermal implant offers **contraceptive** benefit for 3 years

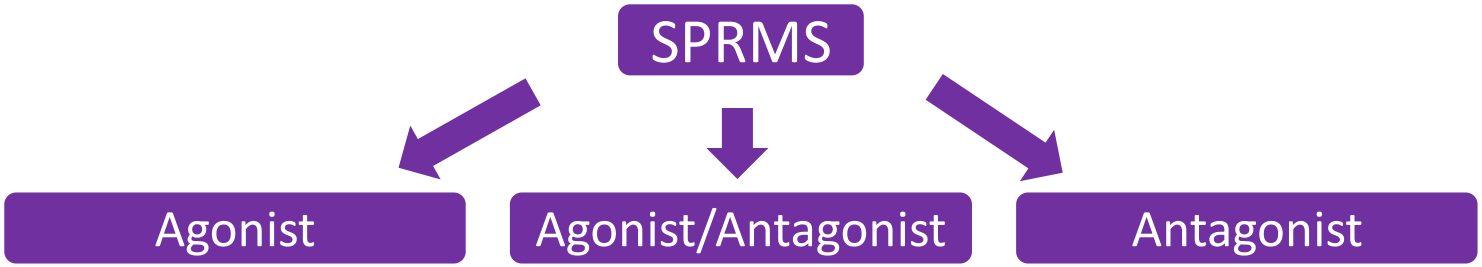
3 YEARS

Selected women who do not desire fertility, etonogestrel implant could be another option for treating **symptomatic endometriosis**

Side Effects: Irregular menstrual bleeding, weight gain, nausea, headache, breast tenderness and acne
(similar to depot medroxyprogesterone)

SELECTIVE PROGESTERONE RECEPTOR MODULATORS **(SPRMS)**

Progesterone receptor molecules that bind and activate progesterone receptor and have both progesterone **agonist** and **antagonist** activities



Have variable effect on progesterone receptors from different tissues ranging from being **pure agonists**, **mixed agonists/antagonists** to **pure antagonists**

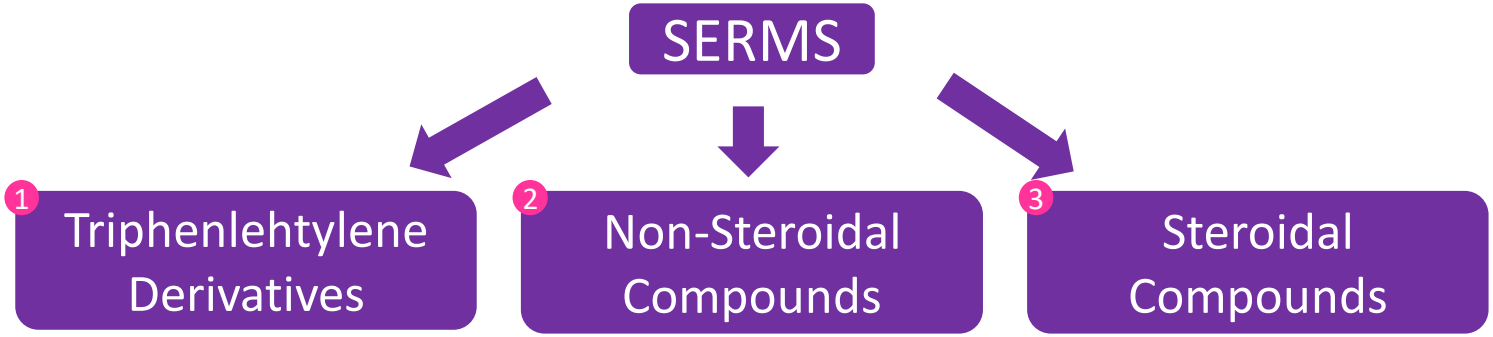
COMMONLY USED **SPRMS**

Predominant progesterone **antagonist** effect, has been used for **Medical Abortions**

Used for **Contraceptive Emergency**

SELECTIVE ESTROGEN RECEPTOR MODULATORS (SERMS)

Have the ability to **target endometriotic implants** more specifically rather than systematically reduce estrogen levels



Tamoxifen

Raloxifene

(A Benzothiophene Derivative)

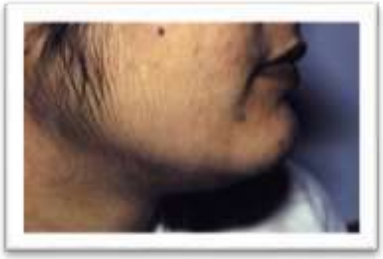
ANDROGENS – DANAZOL

An androgenic agent that **suppresses the midcycle LH surge** and decreases ovarian steroidogenesis by direct inhibition of ovarian enzymes

600-800 mg DAILY

Danazol creates a **hypoestrogenic-hypoandrogenic** state including endometrial atrophy in endometriotic implants

Androgenic Side Effects: Acne, Hirsutism, Deepening of Voice, Weight Gain, Muscle Cramps, Liver Dysfunction and Abnormal Lipid Profile



GONADOTROPIN RELEASING HORMONE AGONIST (GnRH Agonist)

GnRH results in **pituitary desensitization** and subsequent **loss** of ovarian steroidogenesis

Use of a GnRHa with **"add-back"** (estrogen and progesterone) therapy protects against bone mineral density loss during treatment and up to 6 months after treatment

Only up to **6 months**

Due to concerns od side effects secondary to hypoestrogenism like:
Bone loss, vaginal atrophy, hot flushes, abnormalities in lipid profile

GONADOTROPIN RELEASING HORMONE AGONIST (GnRH Agonist)

Available forms

Injectable

Nasal Spray

Offers high rates of **PAIN** relief and **LONGER** symptom free period for up to 12 months

Leuprolide Acetate

3.75 mg	**11.5 mg**
Monthly Injection	**Three** Monthly

Goserelin and **Nafarelin** are the most commonly used preparation

GnRH agonists cause **significant reduction** in pelvic pain in women with endometriosis

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Norethindrone Acetate, a progestin is the only FDA approved add-back therapy

Only up to
12 months

The combination of **GnRH agonists** and **Norethindrone Acetate** are only approved for use for duration of **12 months**

GONADOTROPIN RELEASING HORMONE ANTAGONIST (GnRH Antagonist)

Have lower degree of **Hypoestrogenism**

Administration of GnRH antagonist **Cetrorelix** provided **symptomatic relief** and **regression** of the endometriotic implants as visualized on laparoscopy

With a lower degree of **hypoestrogenemia** and better tolerance than the GnRH agonists they offer great potential in the treatment of endometriosis

AROMATASE INHIBITORS

Aromatase enzyme helps in the **conversion** of the steroid precursors into estrogen

Aromatase inhibitors act as a **sex steroid dependent** neoplasm's by suppressing in situ estrogen production

Aromatase inhibitors **block estrogen synthesis** both in the **periphery** and the **ovaries**

Helpful in postmenopausal women with endometriosis where peripheral fat is the predominant source of estrogen

AROMATASE INHIBITORS – 2nd & 3rd GENERATION

2nd Generation

Fadrozole and **Formestane,** which have *more specific effects on aromatase* and *less toxicity*

3rd Generation

Approved by FDA

Anastrazole(Arimidex)

Letrozole(Femara)

Exemestane(Aromacin)

AROMATASE INHIBITORS

Used in **combination** with combined oral contraceptives, GnRH agonists or progesterone

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Aromatase Inhibitors administered in **combination** with an **ovarian suppressant** comprise a **novel treatment** of premenopausal endometriosis

AROMATASE INHIBITORS

Letrozole

Acts as a progestin **add back**

75% reduction in endometrioma volume

Improve pain symptoms after 3 months

2.5 mg is administered daily

Anastrazole

Reduces VEGF and PGE in the peritoneal fluid

1 mg is administered daily

AROMATASE INHIBITORS – SIDE EFFECTS

Mild Headache
Nausea
Diarrhoea
Ovarian Follicular Cyst
Bone Loss (long term use)
Adverse effect on lipid profile
Cardiovascular Diseases

- (Jaani W et al, 2010, Nawathe A et al, 2008)

Combination with GnRH agonists and birth control pills can help prevent follicular development and add back oral contraceptives and progestins can decrease the bone loss

NEWER THERAPIES

Since Endometriosis is a chronic medical condition, it requires long duration of therapy

Newer therapies could offer **cure & safety:**

Anti-Angiogenesis factors

Statins

TNF-α Blockers

Peroxisome proliferator activated-receptor gamma ligand (PPAR-ϒ)

Pentoxifylline with fewer side effects

ANTI-ANGIOGENESIS FACTORS

A **network of capillaries** surrounds endometriotic lesions and **angiogenesis** is a crucial event in the growth and survival of the lesions

Lesions secrete angiogenic factors like **vascular endothelial growth factor (VEGF)** and the peritoneal fluid is rich in angiogenic factors

Dopamine receptor 2 agonists

Cabergoline

Quinagolide

Shown to reduce angiogenesis by dephosphorylation of VEGF2

Safely used in humans for the treatment of **hyper-prolactinemia** and **lactation**

STATINS

Cholesterol lowering agents effective in the treatment of *hypercholesterolemia* and *cardiovascular diseases*

- **Anti-Inflammatory**
- **Antiangiogenic**
- **Antioxidant**

Other useful actions of STATINS

Beneficial effect of Statins therapy is related to **cholesterol-independent actions** including **modulation** of signal transduction pathways involved in regulation of **cell proliferation** and **apoptosis** and **antioxidant** activity which may also affect cell growth and function

STATINS

It is associated with potential risk of **teratogenicity and these drugs are listed as category X medications**.

Drugs tested in invitro tissue cultures and animal models of endometriosis:

Caplostatin

Endostatin

Atorvastatin

Simvastatin

Mevastatin

Lovastatin

Alamaniokaini et al, 2013

STATINS - ADVANTAGES

Inhibition of the mevalonate pathway by Statins as their intrinsic **antioxidant** properties have several beneficial effects on endometriosis

Decreased endometrial stromal cell

- Adhesiveness
- Invasiveness
- Proliferation
- Angiogenesis
- Inflammation
- Oxidative Stress

Statins alone or in combination with other therapeutic options **inhibit the initiation** and **progression** of endometriosis

Evaluation of statins as a potential novel treatment of endometriosis is still in the **early stages**

NON-HORMONE IMMUNOMODULATORS TNF-α

Is a **pro-inflammatory cytokine** and elevated levels are found in the peritoneal fluid of women with endometriosis with a direct correlation with the stage of the disease

Actively studied for the treatment of Endometriosis

Infliximab – A monoclonal antibody against TNF-α

Etanercept – A fusion protein with the ability to neutralize **TNFα**

Non-Hormone Immunomodulators

PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR GAMMA LIGANDS (PPAR-Ɣ)

Have **anti-inflammatory properties** and reduce estrogen biosynthesis by **inhibiting** aromatase enzyme

PPAR-γ agonists – **Pioglitazone** found effective in treating endometriosis induced in baboons, with these ligands down regulating growth and angiogenesis by down regulation of macrophages, as well as inhibiting E2 production by inhibiting aromatase cytochtome P450

Telmesartan – Partial agonist of PPAR-γ with antiatherogenic properties along with angiotensin 1 receptor (AT1R) blocker-in animal studies up regulated PPAR gamma while down regulating AT1Rproteins in endometriotic lesions, associated with decreased CD31 positive micro vessel reduced number and holds promise as a new treatment with currently being used in humans as an antihypertensive drug.

ELAGOLIX

Produce a dose dependent **hypestrogenic environment** by direct pituitary gonadotropin suppression

Inhibits endometriotic cell proliferation and invasion thus by maintaining sufficient circulating e2, vaginal atrophy and bone demineralization

ADVANTAGES

Orally Administered

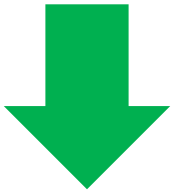
Short Half Life (6h)

Rapid Elimination

(if the treatment is interrupted by any reason)

ADJUVANT MEDICAL TREATMENT

Medical Treatment + Laparoscopic Procedures



Preoperatively or Postoperatively

ADVANTAGES BEFORE SURGERY

Reduced Inflammation & Vascularization

Reduced Shrinkage of Implants

Reduced Recurrence of Endometriosis

RISK FACTORS – CLINICAL RECURRENCE

Endometriosis has distinctive tendency to **recur** after **conservative surgery**

1. **Previous history of endometriosis**
2. **Stage IV revised classification of the AFS**
3. **Score rAFS *(Total, adhesions and implants score)***

Other 2 main factors for reintervention are **Endometrioma size** and **Total rAFS score**

ASSISTED REPRODUCTION IN ENDOMETRIOSIS

Mild to Moderate Endometriosis

Mobile fallopian tubes and ovaries,
Intrauterine insemination with or without hyperstimulation
(may be considered)

Ovarian hyperstimulation plays a crucial role in determining success in IVF

IVF TREATMENT RECOMMENDED IF

Tubal function is compromised

Male factor infertility

Prolonged treatment with a GnRHa before IVF

MANAGEMENT OF OVARIAN ENDOMETRIOMA BEFORE IVF

Does the presence of the Endometrioma impair the results of IVF?

Should we or should we not operate on endometriomas in patients scheduled for ART?

6 CONCLUSION

CONCLUSION

Empirical treatment of pain

It is common practice for **laparoscopy** to be performed if the patient does not react favorably to the prescribed **medical or hormonal pain treatment**, to exclude or **diagnose endometriosis**

The GDG recommends clinicians to counsel women with symptoms presumed to be due to endometriosis thoroughly, and to empirically treat them with **adequate analgesia, combined hormonal contraceptives or progestagens.**

Clinicians are recommended to prescribe **hormonal treatment** [hormonal **contraceptives** (level B), **progestagens** (level A), **anti-progestagens** (level A), or **GnRH agonists** (level A)] as one of the options, as it reduces endometriosis-associated pain (Vercellini, et al., 1993, Brown, et al., 2012, Brown, et al., 2010).

CONCLUSION

The GDG recommends that clinicians take **patient preferences, side effects, efficacy, costs and availability into consideration** when choosing **hormonal treatment** for endometriosis-associated pain.

Clinicians can consider prescribing a **combined hormonal contraceptive**, as it reduces endometriosis-associated dyspareunia, dysmenorrhea and non-menstrual pain (Vercellini, et al., 1993).

Clinicians may consider the continuous use of a **combined oral contraceptive pill** in women suffering from endometriosis-associated dysmenorrhea (Vercellini, et al., 2003).

CONCLUSION

The GDG recommends clinicians to give careful consideration to the use of **GnRH agonists in young women and adolescents**, since these women may **not have reached maximum bone density.**

In women with pain from **rectovaginal endometriosis refractory** to other medical or surgical treatment, clinicians can consider prescribing **aromatase inhibitors** in **combination with oral contraceptive pills, progestagens, or GnRH analogues, as they reduce endometriosis-associated pain** (Ferrero, et al., 2011, Nawathe, et al., 2008).

The GDG recommends that clinicians should consider **NSAIDs** or **other analgesics** to reduce **endometriosis-associated pain**.

CONCLUSION

Clinicians can consider prescribing a **levonorgestrel-releasing intrauterine system** as one of the **options to reduce endometriosis-associated pain** (Ferreira, et al., 2010, Gomes, et al., 2007, Petta, et al., 2005).

Clinicians are recommended to use **GnRH agonists** (**nafarelin, leuprolide, buserelin, goserelin or triptorelin**), as one of the options for reducing endometriosis-associated pain, although evidence is limited regarding dosage or duration of treatment (Brown, et al., 2010).

Clinicians are recommended to prescribe **hormonal add-back therapy** to coincide with the start **of GnRH agonist therapy**, to prevent **bone loss and hypoestrogenic symptoms during treatment.** This is not known to reduce the effect of treatment on pain relief (Bergqvist, et al., 1997, Makarainen, et al., 1996, Moghissi, et al., 1998, Taskin, et al., 1997).

CONCLUSION

Clinicians may consider the use of a **vaginal contraceptive ring or a transdermal** (**estrogen/progestin**) patch to reduce endometriosis-associated dysmenorrhea, dyspareunia and chronic pelvic pain (Vercellini, et al., 2010).

Clinicians are recommended to use **progestagens** [**medroxyprogesterone acetate (oral or depot), dienogest, cyproterone acetate, norethisterone acetate or danazol**] or **anti-progestagens (gestrinone**) as one of the options, to reduce endometriosis-associated pain (Brown, et al., 2012).

The GDG recommends that clinicians take the different side-effect profiles of **progestagens and anti-progestagens** into account when prescribing these drugs, especially irreversible side effects (e.g**. thrombosis, androgenic side effects**).

LIMITATIONS OF CURRENT ENDOMETRIOSIS-TREATMENT MODALITIES

Almost all currently available treatments of endometriosis are **suppressive, not curative**

On treatment discontinuation, recurrence of symptoms is a **Rule**
After medical treatment or conservative treatment, the was estimated to be
21.5% at 2 years
40-50% at 5 years

Recurrence rate of clinically detectable endometriosis tends to be **higher in older women** with **advanced stages of the disease** and **lower in women with infertility**

LIMITATIONS OF CURRENT ENDOMETRIOSIS-TREATMENT MODALITIES

Contraceptive rather than **fertility promoting therapy**

Endometrioma: Lack of effective medical treatment and hazardous surgical options

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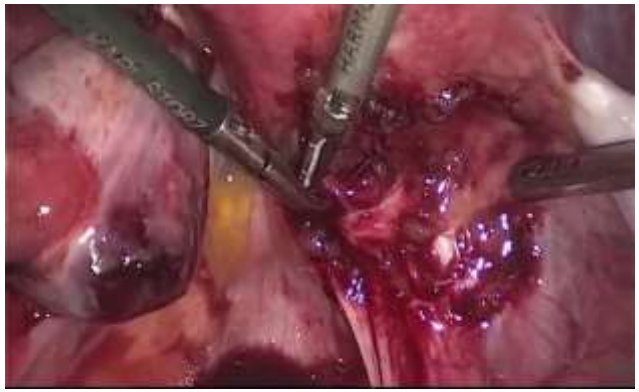
Limited Medical options for Deep infiltrating Endometriosis and Extrapelvic disease



TAKE HOME MESSAGE

Be aware that endometriosis can be **a long- term condition** can have significant physical, sexual, psychological and social impact. Women may have complex needs and may require long-term support

Offer initial management with a **short trial** (for eg,3 months) **of paracetamol or non steroidal anti-inflammatory drug alone or in combination**

If **fertility** is apriority, the management of endometriosis- related subfertility should have **multidisciplinary team involvement** with input from **a fertility specialist**. This should include recommended **diagnostic fertility tests or preoperative tests and other fertility** treatments such as **assisted reproduction**

THANK YOU

Etiopathogenesis

Endometriosis is thought to be a polygenically inherited disease with a complex, multifactorial etiology

Estrogen-dependent disorder that tends to regress after estrogen deprivation

Gonadotropin-releasing hormone analogues strongly reduce the estrogenic pattern in patients with endometriosis.

Etiopathogenesis

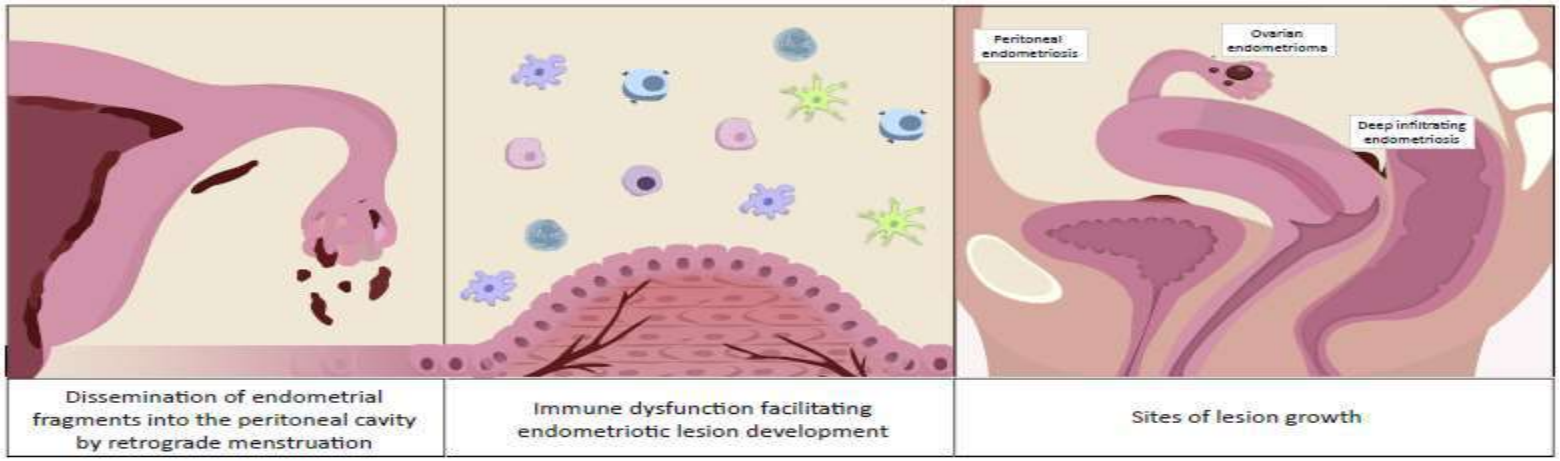
The greatest difficulty is obtaining scientific evidence that may justify its pathogenesis with special reference to both genetic and environmental predisposing factors

The most recognized etiopathogenic hypotheses are three

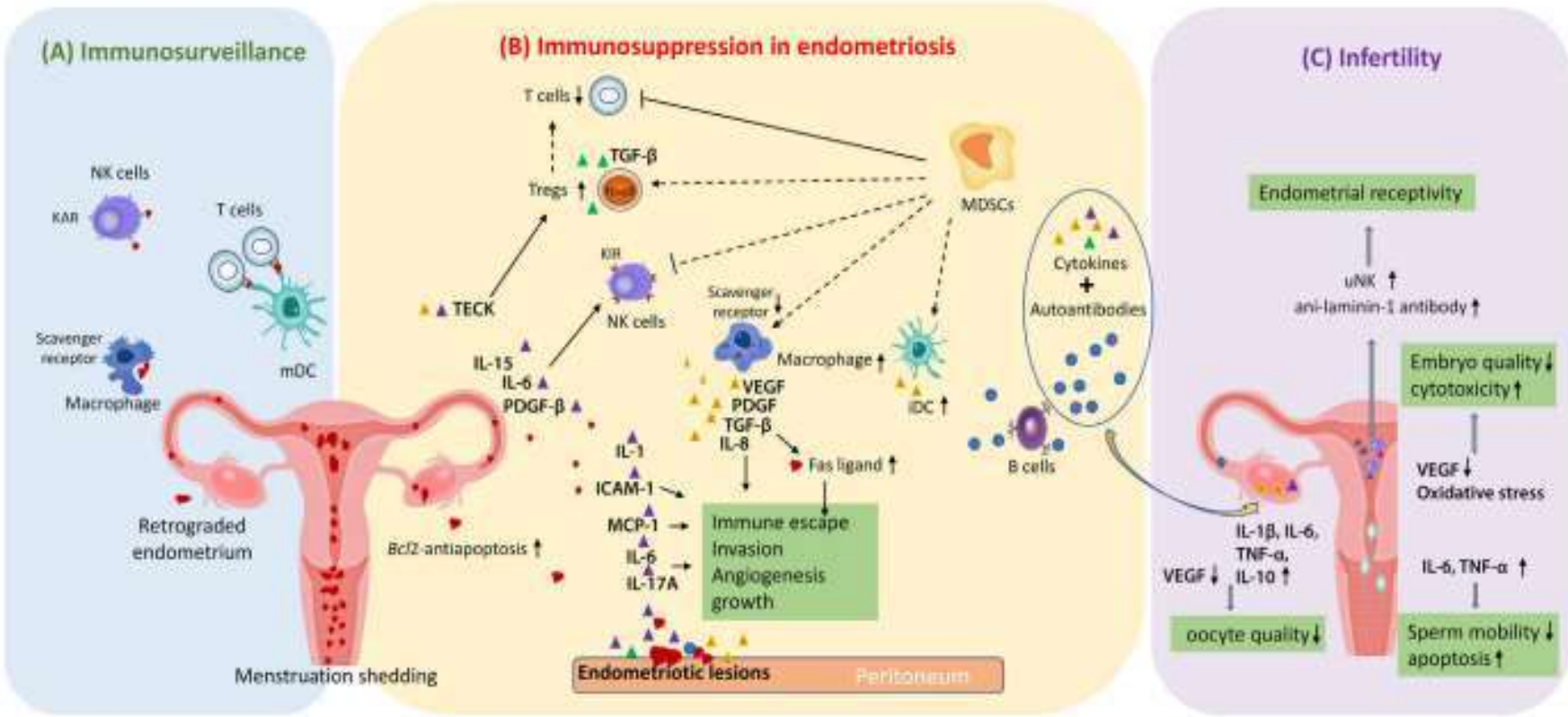
1.possible retrograde menstrual flow causing the dispersion of endometrial cells through the tubes and into the peritoneal cavity

2.possible metaplastic process of the coelomic epithelium [] Signorile P.G et al 2012]

3. possible lymphatic or haematogenous spread of endometrial cells [Donnez J et al . 2002].



Endometriosis, still incurable and common disease, that impacts the quality of life, represents a unique immunological scenario. The aberrant changes in cellular immune response and its cytokines are found to be related to the pathophysiology ie (immune escape, adhesion, invasion, angiogenesis and proliferation



Schematic representation of the complex pathophysiology of endometriosis with immunity. Endometrium flow through fallopian tube into peritoneal cavity during menstruation. (A) Retrograded endometrium can usually be cleared by peritoneal immune cells in normal healthy individuals. (B) However, once an endometriotic fragment bypassed the immunosurveillance and adhere onto the peritoneum wall, a cascade of cytokines regulation will begin. (C) The changes of cellular and hormonal immune response in peritoneal cavity, follicular fluid and endometrium lead to decreased fecundity, even infertility by reducing endometrial receptivity, oocyte quality, sperm mobility and embryo cytotoxicity.

Pioneer Work

[Frontiers in Bioscience, Elite, 5, 748-754, January 1, 2013]

Association of VEGF +405G>C polymorphism with endometriosis

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VEGF +405G>C Polymorphism endometriosis

Table 1. Genotype frequencies of VEGF polymorphisms in Healthy Control Women, Endometriosis patients and each clinical subgroup of endometriosis patients

	+405GC Genotype Polymorphism				
Total No: of patients:626	GG	GC	CC	X^2-Value	P-Value[2]
Healthy control [1]women n=324(%)	134	167	23		
Patients with endometriosis n=302 (%)	178	101	23	21.713	< 0.0001
Re-AFS stage I+II mild n=122(%)	77	36	9	18.332	0.0001
Re-AFS stage II+III severe n=180(%)	101	65	14	11.461	0.0032
With adenomyosis and/or leiomyomas n= 191 (%)	116	57	18	23.118	< 0.0001
Without adenomyosis and/or leiomyomas n= 111 (%)	62	44	5	7.136	0.0282
With chocolate cysts n=225(%)	132	75	18	18.344	0.0001
Without chocolate cysts n=77(%)	46	26	5	8.801	0.0123

[1] The Control group was used as the reference group, [2] $P < 0.05$ considered as statistically significant

A significant difference of the VEGF +405G>C polymorphism genotypes was found between patients with endometriosis and in each clinical subgroup of endometriosis patients.

VEGF +405G>C Polymorphism endometriosis

Table 2. Allele distributions of *VEGF* +405G>C polymorphism in Healthy Control Women, Endometriosis patients and each clinical subgroup of endometriosis patients

Total No: of patients:626	GC Allele Polymorphism				
	G	C	X^2-Value	P-Value[2]	Odds Ratio[3] (95% CI[4])
Healthy control[1] women n=324(%)	435	213			
Patients with endometriosis n=302 (%)	457	147	10.697	0.0011	0.66 (0.51- 0.84)
Re-AFS stage I+II mild n=122(%)	190	54	9.242	0.0024	0.58 (0.41- 0.82)
Re-AFS stage II+III severe n=180(%)	267	93	5.093	0.0240	0.71 (0.53-0.95)
With adenomyosis and/or leiomyomas n= 191 (%)	289	93	7.960	0.0048	0.66 (0.49 -0.87)
Without adenomyosis and/or leiomyomas n= 111%	168	54	5.283	0.0215	0.66 (0.46 - 0.93)
With chocolate cysts n=225(%)	339	111	8.203	0.0042	0.66 (0.51 - 0.87)
Without chocolate cysts n=77%	118	36	4.805	0.0284	0.62 (0.41- 0.93)

[1]The Control group was used as the reference group, [2]P< 0.05 considered as statistically significant, [3]OR = odds ratio, [4]CI = confidence interval

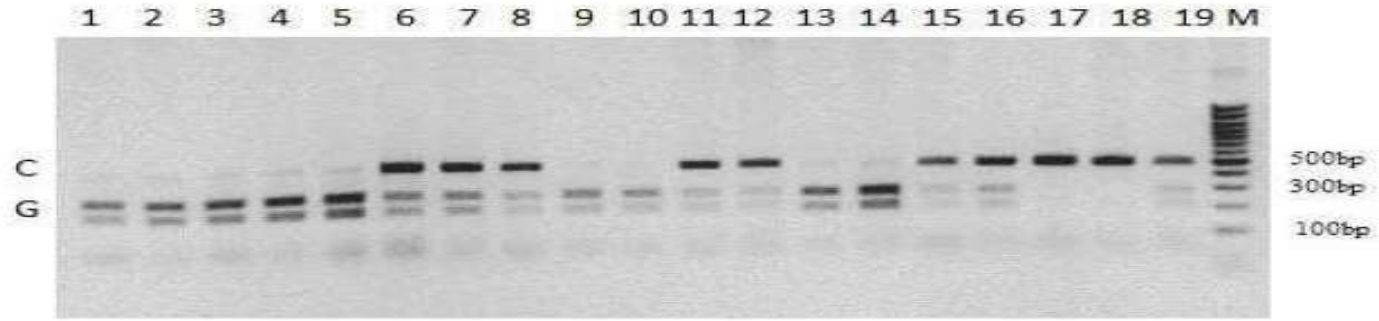

Figure 1. The +405G allele was cut into two fragments of 273 and 196 bp, while the +405C allele remained uncut (469 bp).

The allele frequencies in all the patients with endometriosis and in each clinical subgroup of endometriosis patients were found to be significantly different from those of the control women. The significant differences in allele frequencies were found to be as a result of an increased proportion of homozygote GG genotype carriers and were not due to heterozygote GC carriers.

Table 3. Distribution of genotypes and allele frequencies for the *VEGF* +405G>C polymorphism between the clinical subgroups of patients with endometriosis

	Genotype	X^2-Value	P-Value	AlleleG	AlleleC	X^2-Value	P-Value[1]		
	GG	GC	CC						
Re-AFS[2] stage I+II mild n=122	77	36	9	------	------	190	54	------	------
Re-AFS stage II+III severe n=180	101	65	14	------	------	267	93	------	------
Significance: mild versus severe	----------	------	-----	1.568	0.4565	---------	---------	0.891	0.3453
With adenomyosis n= 191	116	57	18	------	------	289	93	------	------
Without adenomyosis n=111	62	44	5	------	------	168	54	------	------
Significance: with versus without	----------	------	------	4.529	0.1039	---------	---------	0.009	0.9263
With chocolate cysts n=225	132	75	18	------	------	339	111	------	------
Without chocolate cysts n=77a	46	26	5	------	------	118	36	------	------
Significance with versus without	----------	------	------	0.185	0.9115	---------	---------	0.045	0.8311

[1]P< 0.05 considered as statistically significant, [2]Re-AFS = Revised American Fertility Society, The P-value was evaluated by X^2 test with a 2 X 3 contingency table for genotypes frequencies and 2 X 2 table for allele frequencies

No significant difference was observed in the genotype and allele frequencies of VEGF +405G/C polymorphism between the groups with Re-AFS stage I+II (mild endometriosis) and Re- AFS stage III+IV (severe endometriosis), with and without chocolate cysts and with and without adenomyosis.

Table 4. Demographic and clinical characteristics of cases and controls

Characteristics	Study Group Cases/Controls	Cases[1] (n=302)	Controls[1] (n=324)
Age (yrs)	302/324	27.4 ± 5.2	28.9 ± 4.9
BMI (kg/ m^2)	302/324	22.7 ± 3.0	23.1 ± 3.4
Age at Menarche (yrs)	302/324	13.4 ± 1.3	12.5 ± 2.3
Menstrual Cycles	302/324		
Regular		283 (94%)	314 (97%)
Irregular		19(6%)	10 (3%)
Type of Infertility	302/324		
Primary		238 (79%)	-----
Secondary		64 (21%)	-----
Duration of Infertility	302/324	5.2 ± 2.8	

[1]Values are given as the mean ± SD or n (%)

The demographic and clinical characteristics of the cases and controls

THE JOURNAL OF
Obstetrics and Gynaecology Research

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Genetic contribution of the interferon gamma dinucleotide-repeat polymorphism in South Indian women with endometriosis

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Abstract

Aim: To investigate whether the interferon-γ (IFNG) gene dinucleotide (CA)-repeat polymorphism is responsible in part for genetic susceptibility to endometriosis in South Indian women.

Methods: Following extraction of genomic DNA, genotyping of interferon-γ CA-repeat polymorphism was performed using genescan technology.

Results: The global IFNG allele frequencies in all patients with endometriosis were significantly different from those in the control women ($\chi^2 = 37.062$; 6 degrees of freedom; $P \leq 0.0001$). Significant difference was observed in global allele frequencies between the control women and each clinical subgroup of patients with endometriosis except for patients suffering from endometriosis associated with adenomyosis. The difference was due to an increase in a12 (112 bp) allele in the patients with endometriosis and each clinical subgroup of patients with endometriosis.

The distribution of the IFNG a12 genotypes was significantly different between patients with endometriosis and the control women. ($\chi^2 = 10.635$; 2 degrees of freedom; $P = 0.0049$). A significant difference in the IFNG a12 genotypes was found only among the three clinical subgroups.

Conclusion: These results suggest that the IFNG gene CA-repeat polymorphism is associated with susceptibility to endometriosis in South Indian women.

Key words: endometriosis, endoscopy, hysteroscopy, laparoscopy, pelvic pain.

Table 1 Frequency of interferon-γ alleles in healthy control women and patients with endometriosis

Allele size (bp) Number of CA repeats	108 10	110 11	112 12	114 13	116 14	118 15	120 16	χ^2	*P*-value
Healthy control women $n = 324$	9	201	248	33	100	35	22		
Patients with endometriosis $n = 302$	8	151	304	34	75	32	0	37.062	<0.0001
Re-AFS stage I+II mild $n = 122$	2	56	117	12	33	24	0	22.526	0.0010
Re-AFS stage II+III severe $n = 180$	6	95	187	22	42	8	0	32.309	<0.0001
Without adenomyosis and/or leiomyomas $n = 111$	4	54	99	17	37	11	0	14.027	0.0293
With adenomyosis and/or leiomyomas $n = 191$	4	97	205	17	38	21	0	34.372	<0.0001
Without chocolate cysts $n = 77$	3	40	55	20	26	10	0	18.923	0.0043
With chocolate cysts $n = 225$	5	111	249	14	49	22	0	42.899	<0.0001

The global distribution of alleles between the control subjects and the patients groups was evaluated with χ^2-test with a 2×7 table. The control group was used as the reference group. $P < 0.05$ is considered statistically significant. CA, dinucleotide; Re-AFS, revised American Fertility Society.

Table 2 Distribution of genotypes and allele frequencies for the a12 of interferon-γ gene dinucleotide-repeat polymorphism in healthy control women and patients with endometriosis

	Genotype a12: +/+	a12: +/−	a12: −/−	χ^2-value	*P*-value	Allele a12	Others	χ^2-value	*P*-value	OR (95%CI)
Healthy control women $n = 324$	74	138	112	–	–	248	400	–	–	–
Patients with endometriosis $n = 302$	101	124	77	10.635	0.0049	304	300	17.957	<0.0001	0.61 (0.49–0.77)
Re-AFS stage I+II mild $n = 122$	37	55	30	4.895	0.0865	117	127	6.475	0.0109	0.67 (0.5–0.9)
Re-AFS stage II+III severe $n = 180$	64	69	47	9.968	0.0068	187	173	17.084	<0.0001	0.57 (0.44–0.74)
Without adenomyosis $n = 111$	33	51	27	4.525	0.1041	99	123	2.500	0.1139	0.77 (0.57–1.05)
With adenomyosis $n = 191$	68	73	50	10.348	0.0057	205	177	22.493	<0.0001	0.35 (0.27–0.47)
Without chocolate cysts $n = 77$	22	39	16	5.474	0.0647	40	114	7.651	0.0057	1.77 (1.19–2.67)
With chocolate cysts $n = 225$	79	85	61	10.276	0.0059	111	339	21.724	<0.0001	1.89 (1.45–2.47)

The control group was used as the reference group. $P < 0.005$ was considered statistically significant. The *P*-value was evaluated using the χ^2-test with a 2×3 contingency table for genotypes frequencies and 2×2 table for allele frequencies versus control women. Significance was evaluated using the χ^2-test with a 2×3 contingency table (with a 2×3 contingency table for genotypes frequencies and 2×2 table for allele frequencies). CI, confidence interval; OR, odds ratio; Re-AFS, revised American Fertility Society.

Table 3 Distribution of genotypes and allele frequencies for the a12 of interferon-γ gene dinucleotide-repeat polymorphism between the clinical subgroups of patients with endometriosis

	Genotype			χ^2-value	*P*-value	Allele	Others	χ^2-value	*P*-value	OR
	a12: +/+	a12: +/−	a12: −/−			a12				(95%CI)
Re-AFS stage I+II mild $n = 122$	37	55	30	–	–	117	127	–	–	–
Re-AFS stage II+III severe $n = 180$	64	69	47	–	–	187	173	–	–	–
Significance: mild versus severe	–	–	–	1.467	0.4803	–	–	0.775	0.3787	–
Without adenomyosis $n = 111$	33	51	27	–	–	99	123	2.500	–	–
With adenomyosis $n = 191$	68	73	50	–	–	205	177	22.493	–	–
Significance: with versus without	–	–	–	1.839	0.3987	–	–	4.265	0.0389	–
Without chocolate cysts $n = 77$	22	39	16	–	–	40	114	7.651	–	–
With chocolate cysts $n = 225$	79	85	61	–	–	111	339	–	–	–
Significance with versus without	–	–	–	3.951	0.1387	–	–	0.046	0.8293	–

$P < 0.005$ considered statistically significant. The *P*-value was evaluated using the χ^2-test with a 2×3 contingency table for genotypes frequencies and 2×2 table for allele frequencies. Significance was evaluated using the χ^2-test with a 2×3 contingency table (with a 2×3 contingency table for genotypes frequencies and 2×2 table for allele frequencies). CI, confidence interval; OR, odds ratio; Re-AFS, revised American Fertility Society.

The global IFNG allele frequencies in all patients with endometriosis were significantly different from those in the control women (c2 = 37.062; 6 degrees of freedom; *P 0.0001).*

Significant difference was observed **in global allele frequencies between the control women and each clinical subgroup of patients with endometriosis except for patients suffering from endometriosis associated with adenomyosis.**

The difference was due to an increase in a12 (112 bp) allele in the patients with endometriosis and each clinical subgroup of patients with endometriosis.

The distribution of the IFNG a12 genotypes was significantly different between patients with endometriosis and the control women. (c2 = 10.635; 2 degrees of freedom; *P = 0.0049).A significant difference in the IFNG a12* **genotypes was found only among the three clinical subgroups.**

IFNG gene CA-repeat polymorphism is associated with susceptibility to endometriosis in South Indian women.

Indian J Med Res 129, April 2009, pp 395-400

Possible aggravating impact of gene polymorphism in women with endometriosis

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Table I. Comparison of socio-demographic and reproductive history among cases and controls

Characteristics	Endometriosis group (n=97)	Control group (n=102)
Age (yr)	28.5 ± 6.5	28.4 ± 4.8
Body mass index (kg/m²)	23.7 ± 2.0	23.6 ± 1.7
Age at menarche (yr)	12.6 ± 1.3	12.5 ± 1.1
Duration of infertility (yr)	5.5 ± 4.0	3.9 ± 4.2
Primary infertility [n (%)]	74 (76.2)	59 (57.8)
Secondary infertility [n (%)]	23 (23.7)	10 (9.8)
Proven fertility [n (%)]	NR	33 (32.3)
Dyspareunia [n (%)]	33 (34)	17 (16.6)
Dysmenorrhoea		
Mild [n (%)]	29 (29.8)	26 (25.4)
Moderate [n (%)]	4 (4.1)	5 (4.9)
Severe [n (%)]	4 (4.1)	1 (0.9)
No dyspareunia & dysmenorrhoea [n (%)]	27 (27.8)	53 (51.9)

Data are presented as mean ± SD
NR, not reported

Table II. PCBs concentrations in different stages of endometriosis and control group

Congener	Endometriosis (n=86)				Control group (n=91)	(r) correlation coefficient	*P* value
	Stage I (µg/ml)	Stage II (µg/ml)	Stage III (µg/ml)	Stage IV (µg/ml)			
PCB-1(co-planar)*	0.23 ± 0.26	0.42 ± 0.28	0.60 ± 0.27	0.84 ± 0.56	0.05 ± 0.14	+0.5388	<0.0001
PCB-5 (co-planar)*	0.10 ± 0.12	0.24 ± 0.21	0.62 ± 0.39	0.75 ± 0.43	0.01 ± 0.06	+0.6753	<0.0001
PCB-29 (co-planar)*	0.13 ± 0.15	0.29 ± 0.31	0.50 ± 0.34	0.99 ± 0.54	0.02 ± 0.08	+0.6471	<0.0001
PCB-98 ((Non-coplanar)*	0.03 ± 0.10	0.11 ± 0.18	0.34 ± 0.32	0.26 ± 0.31	0.00 ± 0.03	+0.4357	<0.0001

Data are represented as mean ± SD. $P<0.05$

Table III. Frequencies of GSTM1 null gene polymorphism in women with and without endometriosis

Gene	Endometriosis					Controls (n=102)	OR	95% CI
GSTM1	Stage 1 (n=37)	Stage II (n=33)	Stage III (n=16)	Stage IV (n=11)	Total (n=97)			
Null (%)	4 (10.8)	6 (18.1)	8 (50)	8 (72.7)	26 (26.8)	15 (14.7)	2.12	1.045-4.314 (P=0.03)*
Non-null (%)	33 (89.1)	27 (81.8)	8 (50)	3 (27.2)	71 (73.1)	87 (85.2)		

*$P<0.05$. Two-tailed Fishers exact test

Results: Women with endometriosis showed significantly higher concentrations of PCBs compared with **control group.**

The study results suggested that women having higher concentration of PCBs and GSTM1 null (*0/*0) polymorphism might have an increased susceptibility of endometriosis. The findings need to be confirmed in a larger sample.

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MALE FACTOR

Role of environmental estrogens in the deterioration of male factor fertility

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Objective: To evaluate the role of the environmental estrogens polychlorinated biphenyls (PCBs) and phthalate esters (PEs) as potential environmental hazards in the deterioration of semen parameters in infertile men without an obvious etiology.

Design: Randomized controlled study.

Setting: Tertiary care referral infertility clinic and academic research center.

Patient(s): Twenty-one infertile men with sperm counts <20 million/mL and/or rapid progressive motility <25% and/or <30% normal forms without evidence of an obvious etiology and 32 control men with normal semen analyses and evidence of conception.

Intervention(s): Semen and blood samples were obtained as part of the treatment protocol.

Main Outcome Measure(s): Evaluation of semen parameters such as ejaculate volume, sperm count, motility, morphology, vitality, osmoregulatory capacity, sperm chromatin stability, and sperm nuclear DNA integrity.

Result(s): PCBs were detected in the seminal plasma of infertile men but not in controls, and the concentration of PEs was significantly higher in infertile men compared with controls. Ejaculate volume, sperm count, progressive motility, normal morphology, and fertilizing capacity were significantly lower in infertile men compared with controls. The highest average PCB and PE concentrations were found in urban fish eaters, followed by rural fish eaters, urban vegetarians, and rural vegetarians. The total motile sperm counts in infertile men were inversely proportional to their xenoestrogen concentrations and were significantly lower than those in the respective controls.

Conclusion(s): PCBs and PEs may be instrumental in the deterioration of semen quality in infertile men without an obvious etiology. (Fertil Steril® 2002;78:1187–94. ©2002 by American Society for Reproductive Medicine.)

Received February 22, 2001; revised and

TABLE 1

Seminal xenoestrogens and semen parameters in infertile men and controls.

Characteristics	Controls (n = 32)	Infertile men (n = 21)	t
Age	32.5 ± 4.86	33.7 ± 3.45	0.98
PCB concentration (μg/mL)	0	7.63 ± 5.35	
PE concentration (μg/mL)	0.06 ± 0.02	2.03 ± 0.214	51.92*
Ejaculate volume (mL)	3.5 ± 1.38	2.5 ± 1.0	2.86*
Sperm count (×10⁶/mL)	72.75 ± 17.61	17.04 ± 15.73	11.73*
Rapid linear progressive motility (grade A) (%)	53.0 ± 5.77	39.0 ± 34.08	2.28*
Total progressive motility (grade A+B) (%)	70.0 ± 18.98	52.0 ± 45.08	2.01*
Normal morphology (%)	63.46 ± 12.52	38.67 ± 23.86	4.94*
Head defects (%)	18.35 ± 1.23	35.67 ± 20.43	4.81*
Midpiece defects (%)	15.0 ± 10.61	23.33 ± 21.94	1.85
Tail defects (%)	3.0 ± 2.48	2.33 ± 1.15	1.16
Sperm vitality	79.48 ± 18.56	54.79 ± 26.97	3.95*
Sperm hypo-osmotic swelling test (%)	74.0 ± 13.39	53.98 ± 16.67	4.82*
Sperm nuclear chromatin decondensation (%)	19.58 ± 4.12	17.48 ± 1.95	2.17*
Single-stranded DNA (%)	4.3 ± 2.02	15.92 ± 6.02	10.10*

Note: Values represent mean ± SD.

* $P<.05$.

Rozati. Environmental estrogens and male factor infertility. Fertil Steril 2002.

TABLE 2

Correlation of environmental estrogens and semen parameters in infertile men.

Semen parameters	Polychlorinated biphenyls (n = 21)		Phthalate esters (n = 21)	
	r	t	r	t
Ejaculate volume	−0.682	4.066*	−0.198	0.877
Sperm count	−0.022	0.099	−0.221	0.985
Rapid linear progressive motility (grade A)	−0.403	1.902	−0.046	0.199
Total progressive motility (grade A+B)	−0.477	2.357*	−0.142	0.624
Normal morphology	0.124	0.429	−0.769	5.36*
Head defects	−0.111	0.379	−0.436	2.11*
Vitality	−0.791	4.33*	−0.125	0.55
Sperm osmoregulatory capacity (%)	−0.754	5.02*	−0.165	0.73
Sperm nuclear chromatin decondensation (%)	−0.076	0.331	0.04	0.18
Single-stranded DNA (%)	0.564	2.787*	0.855	7.72*

* $P<.05$.

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TABLE 3

Xenoestrogen concentrations and semen quality in different categories of infertile men.

Patient characteristics	n	Mean polychlorinated biphenyl concentrations (μg/mL)	Mean phthalate ester concentrations (μg/mL)	Mean total motile sperm counts ($\times 10^6$/mL)
Control 1	13	0.0	0.064	25.11
Control 2	19	0.0	0.059	30.28
Urban dwellers	15	9.38	2.61	0.66
Rural dwellers	6	3.27	0.59	4.21
Fish eaters	15	9.44	2.65	0.59
Non–fish eaters	6	3.1	0.48	4.37
Urban fish eaters	12	10.49	3.13	0.51
Urban vegetarians	3	4.92	0.57	1.24
Rural fish eaters	3	5.26	0.77	0.92
Rural vegetarians	3	1.28	0.39	7.5

Note: Control 1: fertile men from urban areas with a mixed diet (excluding fish). Control 2: fertile men from rural areas with a mixed diet (excluding fish).

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TABLE 4

Kolmogorov-Smirnov test values for the difference in total motile sperm counts between infertile men and controls.

Groups	Values
Control 1 vs. control 2	0.115
Urban dwellers vs. control 1	0.68[a]
Rural dwellers vs. control 2	0.93[a]
Urban vs. rural dwellers	0.32[a]
Fish eaters vs. non–fish eaters	0.35[a]
Fish-eating urban dwellers vs. control 1	0.742[a]
Urban vegetarians vs. control 1	0.967[a]
Fish-eating rural dwellers vs. control 2	0.9[a]
Rural vegetarians vs. control 2	0.9[a]

Note: Control 1: fertile men from urban areas with a mixed diet (excluding fish). Control 2: fertile men from rural areas with a mixed diet (excluding fish).

[a] $P<.05$.

Rozati. Environmental estrogens and male factor infertility. Fertil Steril 2002.

There was a significant deterioration in semen parameters (decreased ejaculate volume, sperm count, rapid and total progressive motility, normal morphology, vitality, sperm osmoregulatory capacity, nuclear chromatin decondensation, and sperm nuclear chromatin integrity) in infertile men without an obvious etiology when compared with controls.

PCBs were detected in the seminal plasma of infertile men but not in that of controls.

PE concentrations were significantly higher in the seminal plasma of infertile men than in that of controls

PCB and PE concentrations were the highest in infertile urban fish eaters, followed by infertile rural fish eaters, infertile urban vegetarians, and infertile rural vegetarians