MEDICAL MANAGEMENT OF ENDOMETRIOSIS-
New Concepts

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MEDICAL MANAGEMENT OF ENDOMETRIOSIS (New Concepts)

Presentation Overview

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2. PREVALENCE
3. TYPES, DIAGNOSIS & STAGING SYSTEM
4. MEDICAL TREATMENT
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1 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
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**
Summarizing the affects of Endometriosis:

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

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

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

**PITUITARY**
- Altered pituitary-ovarian axis
- Altered LH surge

**PREIMPLANTATION EMBRYO**
- Poor embryo quality
- Early embryo arrest

**IMPLANTATION**
- Reduced uterine receptivity
- Altered hormone regulation

**PREGNANCY**
- Increased pre-term loss
- Recurrent miscarriages
PREVALENCE
1 in 10 women of reproductive age* suffer from Endometriosis


176 million women in the world suffer from Endometriosis
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)
TYPES, DIAGNOSIS & STAGING SYSTEM OF ENDOMETRIOSIS
There are three types of endometriosis:

1. **Superficial** Endometriosis
2. **Ovarian** Endometrioma
3. **Deep Infiltration** Endometriosis (DIE)
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.
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**
Laparoscopic visualization of ovarian endometriomas has a sensitivity of 97% (unilocular) & 95% (bilocular).

Ovarian Biopsy is required rarely.
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
Laparoscopy is required for definitive diagnosis of endometriosis

Disease severity is assessed by simply describing the findings at surgery or quantitatively using ASRM
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
‘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 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**)
MEDICAL TREATMENT
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.
In case of **moderate to severe** endometriosis-associated **infertility**, this combined approach should be considered as the ‘**First Line Therapy**’

Operative Laparoscopy + GnRH Agonist
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
Removal or reduction of ectopic endometrial implants

Restoration of normal anatomy

Reducing Disease Progression

Alleviation of Symptoms

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

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

Daily oral combined **oral contraceptives** can be used safely for **long term**
1. Combined Oral Contraceptives
2. Oral Contraceptive Pills
3. NSAIDs
5. Selective Progesterone Receptor Modulators (SPRMS)
6. Selective Estrogen Receptor Modulators (SERMS)
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
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**
Used as a **first line agents** in the management of endometriosis related **pain** and dysmenorrhea

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

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 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
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

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

2 to 4 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)

20 mg DAILY
**CRYPTERONE ACETATE**

**Antiandrogen** with weak progestational activity

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

10-12.5 mg DAILY

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
104 mg subcutaneously

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

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

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

0.2 mg DAILY

Gestrinone

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

Side effects relate to both androgenic and antiestrogenic effects.

Gestrinone was shown to be as effective as danazol and GnRH analogues.
ETONOgestrel implant offers *contraceptive* benefit for 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)*.
Progestosterone 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

1. Mifepristone
   - Predominant progesterone antagonist effect, has been used for Medical Abortions

2. Ulipristal Acetate
   - Used for Contraceptive Emergency
SELECTIVE ESTROGEN RECEPTOR MODULATORS (SERMS)

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

![Diagram of SERMS categories]

1. Triphenylethylene Derivatives
   - Tamoxifen

2. Non-Steroidal Compounds
   - Raloxifene
   - *(A Benzothiophene Derivative)*

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

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

Leuprolide Acetate

- 3.75 mg Monthly Injection
- 11.5 mg Three Monthly

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

**Goserelin** and **Nafarelin** are the most commonly used preparation
GONADOTROPIN RELEASING HORMONE AGONIST (GnRH Agonist)

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

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

- **Steroid Precursors** → **Aromatase Enzyme** → **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

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


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

- Decreased endometrial stromal cell Adhesiveness
- Decreased endometrial stromal cell Invasiveness
- Decreased endometrial stromal cell Proliferation
- Decreased endometrial stromal cell Angiogenesis
- Decreased endometrial stromal cell Inflammation
- Decreased endometrial stromal cell 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-γ)

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 cytochrome 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
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?
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).
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**).
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

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 a priority, 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.
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.
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 i.e. (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.
Association of VEGF +405G>C polymorphism with endometriosis

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

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<tr>
<th>Characteristics</th>
<th>Study Group Cases/Controls</th>
<th>Cases(^1) (n=302)</th>
<th>Controls(^1) (n=324)</th>
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<td>Age (yrs)</td>
<td>302/324</td>
<td>27.4 ± 5.2</td>
<td>28.9 ± 4.9</td>
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<td>BMI (kg/ m(^2))</td>
<td>302/324</td>
<td>22.7 ± 3.0</td>
<td>23.1 ± 3.4</td>
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<td>Age at Menarche (yrs)</td>
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<td>Menstrual Cycles</td>
<td>302/324</td>
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<td>Regular</td>
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<td>283 (94%)</td>
<td>314 (97%)</td>
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<tr>
<td>Irregular</td>
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<td>19 (6%)</td>
<td>10 (3%)</td>
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<td>Type of Infertility</td>
<td>302/324</td>
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<td>Primary</td>
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<td>238 (79%)</td>
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<tr>
<td>Secondary</td>
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<td>64 (21%)</td>
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<td>Duration of Infertility</td>
<td>302/324</td>
<td>5.2 ± 2.8</td>
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</tr>
</tbody>
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\(^1\)Values are given as the mean ± SD or n (%)
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; $P = 0.0001$). 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.
Interferon-γ (CA) repeats polymorphism

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

<table>
<thead>
<tr>
<th>Allele size (bp)</th>
<th>108</th>
<th>110</th>
<th>112</th>
<th>114</th>
<th>116</th>
<th>118</th>
<th>120</th>
<th>χ²</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of CA repeats</td>
<td>10</td>
<td>11</td>
<td>12</td>
<td>13</td>
<td>14</td>
<td>15</td>
<td>16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Healthy control women n = 324</td>
<td>9</td>
<td>201</td>
<td>248</td>
<td>33</td>
<td>100</td>
<td>35</td>
<td>22</td>
<td>37.062</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Patients with endometriosis n = 302</td>
<td>8</td>
<td>151</td>
<td>304</td>
<td>34</td>
<td>75</td>
<td>32</td>
<td>0</td>
<td>22.526</td>
<td>0.0010</td>
</tr>
<tr>
<td>Re-AFS stage I+II mild n = 122</td>
<td>2</td>
<td>56</td>
<td>117</td>
<td>12</td>
<td>33</td>
<td>24</td>
<td>0</td>
<td>32.309</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Re-AFS stage II+III severe n = 180</td>
<td>6</td>
<td>95</td>
<td>187</td>
<td>22</td>
<td>42</td>
<td>8</td>
<td>0</td>
<td>14.027</td>
<td>0.0293</td>
</tr>
<tr>
<td>Without adenomyosis and/or leiomyomas n = 111</td>
<td>4</td>
<td>54</td>
<td>99</td>
<td>17</td>
<td>37</td>
<td>11</td>
<td>0</td>
<td>34.372</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>With adenomyosis and/or leiomyomas n = 191</td>
<td>4</td>
<td>97</td>
<td>205</td>
<td>17</td>
<td>38</td>
<td>21</td>
<td>0</td>
<td>18.923</td>
<td>0.0043</td>
</tr>
<tr>
<td>Without chocolate cysts n = 77</td>
<td>3</td>
<td>40</td>
<td>55</td>
<td>20</td>
<td>26</td>
<td>10</td>
<td>0</td>
<td>42.899</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>With chocolate cysts n = 225</td>
<td>5</td>
<td>111</td>
<td>249</td>
<td>14</td>
<td>49</td>
<td>22</td>
<td>0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The global distribution of alleles between the control subjects and the patients groups was evaluated with χ²-test with a 2 x 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

<table>
<thead>
<tr>
<th>a12: +/+</th>
<th>Genotype</th>
<th>a12: +/−</th>
<th>a12: −/−</th>
<th>χ²-value</th>
<th>P-value</th>
<th>Allele a12</th>
<th>Others</th>
<th>χ²-value</th>
<th>P-value</th>
<th>OR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy control women n = 324</td>
<td>74</td>
<td>138</td>
<td>112</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>108.635</td>
<td>0.0049</td>
<td>304</td>
</tr>
<tr>
<td>Patients with endometriosis n = 302</td>
<td>101</td>
<td>124</td>
<td>77</td>
<td>10.635</td>
<td>0.0049</td>
<td>304</td>
<td>300</td>
<td>17.957</td>
<td>&lt;0.0001</td>
<td>0.61 (0.49–0.77)</td>
</tr>
<tr>
<td>Re-AFS stage I+II mild n = 122</td>
<td>37</td>
<td>55</td>
<td>30</td>
<td>4.895</td>
<td>0.0865</td>
<td>117</td>
<td>127</td>
<td>6.475</td>
<td>0.0109</td>
<td>0.57 (0.57–1.05)</td>
</tr>
<tr>
<td>Re-AFS stage II+III severe n = 180</td>
<td>64</td>
<td>69</td>
<td>47</td>
<td>9.968</td>
<td>0.0068</td>
<td>187</td>
<td>173</td>
<td>17.084</td>
<td>&lt;0.0001</td>
<td>0.44 (0.44–0.74)</td>
</tr>
<tr>
<td>Without adenomyosis n = 111</td>
<td>33</td>
<td>51</td>
<td>27</td>
<td>4.525</td>
<td>0.1041</td>
<td>99</td>
<td>123</td>
<td>2.500</td>
<td>0.1139</td>
<td>0.77 (0.77–1.52)</td>
</tr>
<tr>
<td>With adenomyosis n = 191</td>
<td>68</td>
<td>73</td>
<td>50</td>
<td>10.348</td>
<td>0.0057</td>
<td>205</td>
<td>177</td>
<td>22.493</td>
<td>&lt;0.0001</td>
<td>0.35 (0.27–0.47)</td>
</tr>
<tr>
<td>Without chocolate cysts n = 77</td>
<td>22</td>
<td>39</td>
<td>16</td>
<td>5.474</td>
<td>0.0647</td>
<td>40</td>
<td>114</td>
<td>7.651</td>
<td>0.0057</td>
<td>1.77 (1.19–2.67)</td>
</tr>
<tr>
<td>With chocolate cysts n = 225</td>
<td>79</td>
<td>85</td>
<td>61</td>
<td>10.276</td>
<td>0.0059</td>
<td>111</td>
<td>339</td>
<td>21.724</td>
<td>&lt;0.0001</td>
<td>1.89 (1.45–2.47)</td>
</tr>
</tbody>
</table>

The control group was used as the reference group. P < 0.005 was considered statistically significant. The P-value was evaluated using the χ²-test with a 2 x 3 contingency table for genotypes frequencies and 2 x 2 table for allele frequencies versus control women. Significance was evaluated using the χ²-test with a 2 x 3 contingency table (with a 2 x 3 contingency table for genotypes frequencies and 2 x 2 table for allele frequencies). CI, confidence interval; OR, odds ratio; Re-AFS, revised American Fertility Society.
<table>
<thead>
<tr>
<th>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</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype</td>
</tr>
<tr>
<td>Re-AFS stage I+II mild n = 122</td>
</tr>
<tr>
<td>Re-AFS stage II+III severe n = 180</td>
</tr>
<tr>
<td>Significance: mild versus severe</td>
</tr>
<tr>
<td>Without adenomyosis n = 111</td>
</tr>
<tr>
<td>With adenomyosis n = 191</td>
</tr>
<tr>
<td>Significance: with versus without</td>
</tr>
<tr>
<td>Without chocolate cysts n = 77</td>
</tr>
<tr>
<td>With chocolate cysts n = 225</td>
</tr>
</tbody>
</table>

P < 0.005 considered statistically significant. The P-value was evaluated using the χ²-test with a 2 × 2 contingency table for genotypes frequencies and 2 × 2 table for allele frequencies. Significance was evaluated using the χ²-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 ($c^2 = 37.062; 6$ 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. ($c^2 = 10.635; 2$ degrees of freedom; $P = 0.0049$). A *significant difference in the IFNG $a12$ genotypes* was found only among the three clinical subgroups.

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

Rozati Roya, Giragalla Simha Baludu* & B. Satyanarayana Reddy*

Department of Obstetrics & Gynaecology, Owaisi Hospital & Research Centre & *Department of Reproductive Medicine, Maternal Health & Research Trust, Hyderabad, India

Table 1. Comparison of socio-demographic and reproductive history among cases and controls

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

Data are presented as mean ± SD
NR, not reported
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.
Role of environmental estrogens in the deterioration of male factor fertility

Roya Rozati, M.D., a P. P. Reddy, Ph.D., b P. Reddanna, Ph.D., c and Rubina Mujtaba, Ph.D. a

Mahavir Hospital and Research Center and University of Hyderabad, Hyderabad, India

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.)
## TABLE 1

Seminal xenoestrogens and semen parameters in infertile men and controls.

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

*Note: Values represent mean ± SD.*

* P<.05.


## TABLE 2

Correlation of environmental estrogens and semen parameters in infertile men.

<table>
<thead>
<tr>
<th>Semen parameters</th>
<th>Polychlorinated biphenyls (n = 21)</th>
<th>Phthalate esters (n = 21)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
<td>t</td>
</tr>
<tr>
<td>Ejaculate volume</td>
<td>-0.682</td>
<td>4.066*</td>
</tr>
<tr>
<td>Sperm count</td>
<td>-0.022</td>
<td>0.099</td>
</tr>
<tr>
<td>Rapid linear progressive motility (grade A)</td>
<td>-0.403</td>
<td>1.902</td>
</tr>
<tr>
<td>Total progressive motility (grade A+B)</td>
<td>-0.477</td>
<td>2.357*</td>
</tr>
<tr>
<td>Normal morphology</td>
<td>0.124</td>
<td>0.429</td>
</tr>
<tr>
<td>Head defects</td>
<td>-0.111</td>
<td>0.379</td>
</tr>
<tr>
<td>Vitality</td>
<td>-0.791</td>
<td>4.33*</td>
</tr>
<tr>
<td>Sperm osmoregulatory capacity (%)</td>
<td>-0.754</td>
<td>5.02*</td>
</tr>
<tr>
<td>Sperm nuclear chromatin decondensation (%)</td>
<td>-0.076</td>
<td>0.331</td>
</tr>
<tr>
<td>Single-stranded DNA (%)</td>
<td>0.564</td>
<td>2.787*</td>
</tr>
</tbody>
</table>

* P<.05.

### TABLE 3

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>n</th>
<th>Mean polychlorinated biphenyl concentrations (µg/mL)</th>
<th>Mean phthalate ester concentrations (µg/mL)</th>
<th>Mean total motile sperm counts (×10⁶/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control 1</td>
<td>13</td>
<td>0.0</td>
<td>0.064</td>
<td>25.11</td>
</tr>
<tr>
<td>Control 2</td>
<td>19</td>
<td>0.0</td>
<td>0.059</td>
<td>30.28</td>
</tr>
<tr>
<td>Urban dwellers</td>
<td>15</td>
<td>9.38</td>
<td>2.61</td>
<td>0.66</td>
</tr>
<tr>
<td>Rural dwellers</td>
<td>6</td>
<td>3.27</td>
<td>0.59</td>
<td>4.21</td>
</tr>
<tr>
<td>Fish eaters</td>
<td>15</td>
<td>9.44</td>
<td>2.65</td>
<td>0.59</td>
</tr>
<tr>
<td>Non–fish eaters</td>
<td>6</td>
<td>3.1</td>
<td>0.48</td>
<td>4.37</td>
</tr>
<tr>
<td>Urban fish eaters</td>
<td>12</td>
<td>10.49</td>
<td>3.13</td>
<td>0.51</td>
</tr>
<tr>
<td>Urban vegetarians</td>
<td>3</td>
<td>4.92</td>
<td>0.57</td>
<td>1.24</td>
</tr>
<tr>
<td>Rural fish eaters</td>
<td>3</td>
<td>5.26</td>
<td>0.77</td>
<td>0.92</td>
</tr>
<tr>
<td>Rural vegetarians</td>
<td>3</td>
<td>1.28</td>
<td>0.39</td>
<td>7.5</td>
</tr>
</tbody>
</table>

*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).


### TABLE 4

<table>
<thead>
<tr>
<th>Groups</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control 1 vs. control 2</td>
<td>0.115</td>
</tr>
<tr>
<td>Urban dwellers vs. control 1</td>
<td>0.68*</td>
</tr>
<tr>
<td>Rural dwellers vs. control 2</td>
<td>0.93*</td>
</tr>
<tr>
<td>Urban vs. rural dwellers</td>
<td>0.37*</td>
</tr>
<tr>
<td>Fish eaters vs. non–fish eaters</td>
<td>0.35*</td>
</tr>
<tr>
<td>Fish-eating urban dwellers vs. control 1</td>
<td>0.742*</td>
</tr>
<tr>
<td>Urban vegetarians vs. control 1</td>
<td>0.967*</td>
</tr>
<tr>
<td>Fish-eating rural dwellers vs. control 2</td>
<td>0.9*</td>
</tr>
<tr>
<td>Rural vegetarians vs. control 2</td>
<td>0.9*</td>
</tr>
</tbody>
</table>

*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).

*P* < 0.05.

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.