Endometriosis has still remained an enigma for us all. The disease has increased its prevalence over time & has defied all attempts at unraveling the mystery about its origin, progression & its impact on a woman’s reproductive life. Epidemiological studies estimate a prevalence of 6-10%, and it may be much higher if milder forms of the disease, which are under diagnosed, are included. Many women have been rendered infertile & many more have led a painful life afflicted by this pervasive & insidious disease. The problem is not only its detection, which requires a laparoscopy - an invasive procedure – but the therapy is equally frustrating and fascinating for all of us who deal with this amazing disease.

As our current knowledge about this disease guides us, we have reached following consensus in dealing with women suffering with endometriosis;

1. The accurate diagnosis is made with laparoscopy, unless there is an endometriotic cyst (detected on ultrasonography) or when there is a visible vaginal nodule on inspection.
2. Laparoscopy is ‘Gold Standard’ diagnostic procedure for all forms of endometriosis
3. A visual inspection of the lesion is adequate for a diagnosis of endometriosis, but histological confirmation of at least one lesion is ideal.
4. Positive histology confirms the diagnosis, but negative does not exclude it
5. Histological examination fails to detect endometrium in about 50% of visible endometriosis.
6. Medical therapy alone has no role in women desirous of childbearing.
7. Medical therapy is a useful option for women desirous of pain relief only.
8. All medical therapy like COC, Progesterones, Danazol, GnRHA have almost similar efficacy.
9. When the patient is given antiestrogen therapy (eg. Progesterones, GnRHA) it should be covered with calcium and vitamin D to prevent osteoporosis.
10. Medical therapy is not effective in pain symptom of recto-vaginal endometriosis & removal of recto-vaginal nodule is necessary for alleviation of pain symptoms.
11. Destruction or excision of endometriotic implants in all stages & all forms of disease improves pregnancy outcomes as well as reduces pain
12. In case of endometriotic cyst a cystectomy reduces the chances of recurrence & improves chances of pregnancy.
13. There is still a lack of clarity about the optimum role of medical therapy before or after the surgery for endometriosis.

Upon this background I am trying to share with you some exciting & promising developments taking place in diagnosis as well as in the therapy of endometriosis.

Diagnosis of endometriosis

As we all know, the only reliable & accurate method of diagnosis is by visual inspection of peritoneal cavity & locating the lesion or a histo-pathological confirmation of a biopsy obtained at a laparoscopy (or a laparotomy). Naturally the procedure is not a first line diagnostic tool. As it requires anesthesia and as the procedure has significant morbidity – both, the patients as well as the doctors are reluctant to undertake the procedure quickly. This has led to a delay of average 9 years in diagnosis.

A recent survey among 7025 women respondents with endometriosis (European Endometriosis Alliance, 2006) demonstrated that 65% of the women with endometriosis were first misdiagnosed with another condition, and 46% had to see five doctors or more before they were correctly diagnosed, resulting in an average delay of 8 years between the onset of symptoms and the diagnosis of endometriosis (Zondervan et al., 1999; Ballard et al., 2006).
Currently used non-invasive approaches for the diagnosis like USG, MRI or blood tests (CA-125) have not been accurate enough for the diagnosis of endometriosis. (Chen et al., 1998; Zondervan et al.,1999; Harada et al., 2002; Somigliana et al., 2004; Kennedy et al., 2005; Ballard et al., 2006, Mol et al., 1998).

A subfertile woman with a history of menstrual pain and normal clinical examination in absence of positive USG for endometriotic cysts provides a dilemma for most gynaecologists. The advice for a laparoscopy is not confident enough & patient’s reluctance for invasive procedure in absence of firm recommendation delays the diagnosis. From a clinical perspective, it is unlikely that these women will have moderate-to-severe endometriosis, but up to 50% of them (Meuleman et al., 2009) may have mild peritoneal endometriosis with or without adhesions associated with subfertility and possibly pain. A non-invasive diagnostic test would be useful to rule out endometriosis in this group of women and may benefit them for a more precise management of subfertility therapy. (D’Hooghe et al., 2003, 2006; Kennedy et al., 2005).

With this limitation in mind there has been extensive research for a simpler diagnostic tool & few papers published recently have shown great promise. Two main evolving methods of diagnosis are biochemical methods & histological evaluation of uterine endometrium.

Biochemical methods: A recent study published in Human Reproduction (Mihalyi, Gevaert et al 2009, 2010) has shown great promise in making accurate diagnosis of endometriosis. The study involves a combined analysis of 6 biomarkers using stepwise logistic regression analysis and least squares support vector machines (LSSVMs). The study shows that it is possible to diagnose minimal–mild endometriosis using plasma analysis of multiple biomarkers combined with advanced statistical analysis with a high sensitivity (87–92%) and an acceptable specificity (60–71%) during the secretory phase and the menstrual phase.

This case–control study was conducted in 294 infertile women, consisting of 93 women with a normal pelvis and 201 women with endometriosis. They measured plasma concentrations of:

1. interleukin IL-6 (0.71 vs 0.34 pg/ml) 4. Cancer antigen CA 19-9
2. interleukin IL-8(1.77 vs 0.88 pg/ml), 5. Tumour necrosis factor-α (TNF-α) (0.03 vs 0.44 pg/ml)
3. Cancer antigen CA 125 (22.0 vs 13.0 U/ml) 6. High-sensitivity C-reactive protein (hsCRP) (1.35 vs 0.64 mg/l)

Compared with controls, both women with minimal–mild and moderate–severe endometriosis had higher plasma levels of IL-6, IL-8 and CA-125 and lower levels of TNF-alpha regardless of cycle phase. In addition, women with moderate–severe endometriosis had significantly higher hsCRP levels than controls Using stepwise logistic regression, moderate–severe endometriosis was diagnosed with a sensitivity of 100% (specificity 84%) during the secretory phase. Using LSSVM analysis, minimal–mild endometriosis was diagnosed with a sensitivity of 94% (specificity 61%) during the secretory phase and during the menstrual phase.

Another study published (Gajbiyeh, Sonawani et al 2011) very recently use a proteomic approach to identify novel endometrial antigens using sera from endometriosis patients and healthy controls, with evaluation of biomarkers for non-invasive diagnosis of endometriosis. They conducted a cross-sectional study to identify specific endometrial antigens in women with early endometriosis (n = 17), advanced endometriosis (n = 23) and without endometriosis (n = 30). The study identified 3 endometrial antigens: tropomyosin 3 (TPM3), stomatin-like protein 2 (SLP2), and tropomodulin 3 (TMOD3). Serum levels of antibodies against the proteins TPM3, SLP2 and TMOD3 were significantly elevated in endometriosis patients when compared with controls. The sensitivity and specificity of serum antibodies were calculated to,

→ anti-TPM3a-Ab (61%, 93%), anti-TPM3c-Ab (44%, 93%), anti-TPM3d-Ab (78%, 89%),
→ anti-SLP2a-Ab (50%, 96%), anti-SLP2c-Ab (61%, 93%),
→ anti-TMOD3b-Ab (61%, 96%), anti-TMOD3c-Ab (78%, 93%), anti-TMOD3d-Ab (78%, 96%)

The authors concluded that serum levels of antibodies against the proteins TPM3, SLP2 and TMOD3 were better than those of serum CA125 levels (21%, 89%) in the detection of early stages of endometriosis. The high specificity shown in this study (90%+ in all markers) suggest that the accuracy is of high order & the false negative diagnosis will be very low.
I believe that we are on threshold of an accurate & useful blood test to make an easy & early diagnosis of endometriosis. This will be a great step forward in managing this curious scourge of women. These tests sound familiar in the connotation of ‘six markers’ & ‘three markers’!

**Endometrial Histology:** In the search for a non-invasive diagnostic test scientists have found multiple-sensory small-diameter nerve fibres in a higher density in endometrium from patients with endometriosis compared to women with a normal pelvis. This fact has enabled a development of a semi-invasive diagnostic test for minimal–mild endometriosis.

In a classical study titled ‘Density of small diameter sensory nerve fibres in endometrium: a semi-invasive diagnostic test for minimal to mild endometriosis’ published in Human Reproduction, (Bokor, Kyama et al) from university of Leuven, Belgium collected secretory phase endometrium samples (n 40), obtained from women with laparoscopically/ histologically confirmed minimal-mild endometriosis (n 20) and from women with a normal pelvis (n 20). Immunohistochemistry was performed to localize neural markers for sensory nerve fibres in the functional layer of the endometrium. Sections were immunostained with anti-human protein gene product 9.5 (PGP 9.5), anti-neurofilament protein, anti-substance P (SP), anti-vasoactive intestinal peptide (VIP), anti-neuropeptide Y and anti-calcitonine gene-related polypeptide. The density of small nerve fibres was approximately 14 times higher in endometrium from patients with minimal-mild endometriosis (1.96 +/- 2.73) when compared with women with a normal pelvis (0.14 +/- 0.46). The combined analysis of neural markers PGP9.5, VIP and SP could predict the presence of minimal-mild endometriosis with 95% sensitivity, 100% specificity and 97.5% accuracy.

Another prospective & equally classical study ‘Diagnosis of endometriosis by detection of nerve fibres in an endometrial biopsy: a double blind study’ published in Human Reproduction by (Al-Jefout, Dezarnaulds et al) showed in a double-blind comparison with expert diagnostic laparoscopy a high presence of nerve fibres in endometrium. Endometrial biopsies, with immunohistochemical nerve fibre detection using protein gene product 9.5 as marker, taken from 99 consecutive women presenting with pelvic pain and/or infertility undergoing diagnostic laparoscopy by experienced gynaecologic laparoscopists, were compared with surgical diagnosis.

In women with laparoscopic diagnosis of endometriosis (n 64) the mean nerve fibre density in the functional layer of the endometrial biopsy was 2.7 nerve fibres/mm². Only one woman with endometriosis had no detectable nerve fibres. Six women had endometrial nerve fibres but no active endometriosis seen at laparoscopy. The specificity and sensitivity were 83 and 98%, respectively, positive predictive value was 91% and negative predictive value was 96%. Nerve fibre density did not differ between different menstrual cycle phases. Women with endometriosis and pain symptoms had significantly higher nerve fibre density in comparison with women with infertility but no pain (2.3 and 0.8 nerve fibre/mm², respectively.

This study clearly shows that an endometrial biopsy, with detection of nerve fibres, provides a reliability of diagnosis of endometriosis which is close to the accuracy of laparoscopic assessment. Although semi-invasive in nature it obviates all the complications attached to a laparoscopy.

**Therapy for endometriosis**

Although there is a loose consensus on therapeutic principles for both, pain & infertility associated with endometriosis, I would like to share some fresh developments which chart a new course.

**Antiestrogen therapies: COC, Progesterones, Danazol, Gestrinone:** Suppression of ovarian hormones to induce amenorrhea is the basis for most medical treatments in endometriosis. Combined OC pills (COC) with estrogen & progestrone combination (E+P) suppress ovarian folliculogenesis and steroid secretion, and induce amenorrhea of so-called pseudopregnancy in the management of endometriosis. Progestogens alone have a similar though less consistent effect. Due to a direct stimulatory effect on the endometriotic tissue E+P is often sub-optimal in providing symptom relief if dysmenorrhea is the major complaint. Danazol was the first compound that could effectively suppress ovarian function without a direct effect on the endometrium. One of the interesting properties of danazol is its effect on the immune system. However, its androgenic side effects made it less attractive to patients and physicians. Danazol vaginal delivery systems & Danazol-releasing IUD
are under development in a bid to avert the systemic side effects. LNG – IUD (‘Mirena’), once a week COC skin patch & the COC vaginal ring are also tried for long term pain relief in endometriosis to avoid the systemic side effects.

**Gonadotropin-releasing Hormone Agonists (GnRHA):** This has been one of the most effective and popular option in the postoperative treatment of endometriosis. These compounds profusely suppress ovarian function and induce endometrial atrophy and amenorrhea after the initial stimulatory flare up effect. Agonists are currently available only for parenteral use as depot intramuscular (IM) injections, subcutaneous depot implants/injections, or intranasal sprays. The daily release dose of agonist is adjusted in such a way that complete pituitary suppression is induced. FSH and LH levels are undetectable and estradiol remains <20pg/ml. This profound ovarian suppression results in amenorrhea, symptomatic improvement, and regression of endometriotic lesions. However, at the same time a majority of women develop menopausal symptoms, hypoestrogenic changes, and bone loss. In order to reduce the severity of menopausal symptoms and to prevent bone loss, various estrogen/progestogen add-back regimens have been recommended.

It has been theorized by (Barbieri 1998) that estradiol levels between 30-50pg/ml are effective in inducing endometrial atrophy but the levels leading to bone loss is much lower (<20 pg). Thus, a therapeutic window of estradiol levels adequate for suppression of endometriosis without untoward side effects is available.

Agonists are not suitable in patients with PCO due to its inconsistent suppressive effect & have significant side effect profile during the initial flare-up. Peptide Gonadotropin-releasing Hormone Antagonists structurally resemble native GnRH and GnRH agonists. Unlike agonists, antagonists competitively block GnRH receptors and produce an immediate suppressive effect on the pituitary, leading to quick reduction in serum FSH and LH levels. GnRH antagonists had troublesome side effects like injection-site reactions and allergic/anaphylactic reactions related to histamine release from mast cells. Cetrorelix, a peptide GnRH antagonist, is approved for suppression of LH surge in women undergoing in vitro fertilization (IVF). In clinical trials Cetrorelix was found effective in controlling pelvic pain and in inducing regression of endometriosis on post-treatment laparoscopy (Finas, Hornung et al 2006). The effect was immediate, without flare-up, and the course of treatment was shorter than that with GnRH agonists.

Peptide GnRH analogs, both agonists and antagonists, require parenteral administration in the form of long-acting depots. This is associated with prolonged effect and inability to rapidly terminate the treatment when necessary. Recently several non-peptide small-molecule GnRH antagonists have been developed which are orally active. This improves patient acceptability, facilitates dosing and allows rapid discontinuation if necessary. We can also plan dose adjustment to vary the level of pituitary suppression and the circulating estradiol levels in the therapeutic window. This may facilitate long-term treatment without the need for add-back therapy.

**Oral GnRH Antagonists:** Elagolix (NBI-56418) is a small non-peptide GnRH Antagonist molecule that binds reversibly with high affinity to the human GnRH receptor. Elagolix has recently completed phase II clinical trials in women with pelvic pain associated with endometriosis. The drug is rapidly absorbed from the GI tract, reach maximum plasma concentration within 30-60 minutes after ingestion, followed by a rapid decline in blood levels. Elagolix induces dose-dependent FSH, LH, and estradiol suppression without detectable flare effect. At a dose of 100–150mg/day, serum estradiol concentrations remained between 20-50 pg/ml, which seems to be the optimal range (Dmowski 2008.Struthers et al 2009).

Elagolix seems to be well tolerated in comparison with placebo. The most common side effects reported were headaches, nausea, and dizziness. The reporting of hot flashes with doses ranging from 50 to 200mg was 49.3% compared with 42.6% in the placebo groups. None of the women receiving elagolix reported severe vasomotor or hypoestrogenic symptoms. There was no increase in serum N-telopeptide concentrations, a biomarker for bone resorption. There was improvement in the composite pelvic signs and symptoms score (CPSSS) and the visual analog scale (VAS) for pelvic pain scores, which was most pronounced at doses of 150mg once daily and 100mg twice daily. Return of regular ovulatory cycles, as evidenced by urinary pregnanediol measurements, was rapid in most patients. Availability of oral therapy which can be titrated to individual needs is one of the most exciting developments in the field of endometriosis management.
**Diet, Habitus & alternative therapies:** There are by now adequate studies to establish relationship between diet, body habitus, mental stress & endometriosis. Alternative therapies become an attractive option under these situations. Various forms of nutritional therapy, dietary modifications, exercise plans, homeopathy medicines & immune therapy have been proposed with observational reports.

Lending credence to the current fad of lean figure & increasing incidence of endometriosis in young adolescents, in a very interesting study published recently, women diagnosed with endometriosis were taller, thinner, and had a significantly lower BMI. They were late matures (menarche ≥ 14 y) and late to initiate sexual activity (≥ 21 y). For every unit increase in BMI (kg/ m²), there was an approximate 12–14% decrease in the likelihood of being diagnosed with endometriosis. BMI was 21.3 for women with endometriosis, compared with 23.2 for the controls, a difference over all ages of –1.9. This is a consistent difference of about 10 lb at every age, assuming an average height of about 64.5 in. The authors concluded that women diagnosed with endometriosis may have a consistently lean physique during adolescence and young adulthood with a supposition that there might be an in utero or early childhood origin for endometriosis (Hediger et al 2005).

**Chinese herbal Medicines (CHM):** A recent Cochrane review on Chinese herbal medicines has shown promising results. Two Chinese RCTs involving 158 women were included in this review. Both these trials described adequate methodology.

CHM vs Gestrinone: There was no evidence of a significant difference in rates of symptomatic relief between CHM and gestrinone administered subsequent to laparoscopic surgery (95.65% vs 93.87%). The intention-to-treat analysis also showed no significant difference between the groups. There was no significant difference between the CHM and gestrinone groups with regard to the total pregnancy rate (69.6% vs 59.1%, one RCT).

CHM vs Danazol: CHM was administered orally and then in conjunction with a herbal enema resulted in a greater proportion of women obtaining symptomatic relief than with danazol. Overall, 100% of women in all the groups showed some improvement in their symptoms. Oral plus enema administration of CHM showed a greater reduction in average dysmenorrhea pain scores than did danazol. Combined oral and enema administration of CHM showed a greater improvement, measured as the disappearance or shrinkage of adnexal masses, than with danazol. For lumbosacral pain, rectal discomfort, or vaginal nodules tenderness, there was no significant difference either between CHM and danazol.

The authors went on to conclude that post-surgical administration of CHM may have comparable benefits to gestrinone but with fewer side effects. Oral CHM may have a better overall treatment effect than danazol; it may be more effective in relieving dysmenorrhea and shrinking adnexal masses when used in conjunction with a CHM enema. However, more rigorous research may confirm the potential role of CHM in treating endometriosis (Flower et al 2009).

**Aromatase inhibitors:** An interesting publication (Ailawadi, Bulun et al 2004) showed marked benefits of Letrozole in clearing up endometriosis within 6 months of therapy in cases with pain. Letrozole 2.5 mg + Progestin 2.5 mg + Vit D 800 iu + Calcium 1.25 gm were given for 6 months & a 2nd look laparoscopy & biopsy was performed. In all cases the endometriosis disappeared! A few subsequent studies have also confirmed these findings. Aromataze enzymes are found in 3 places; ovaries, adipose tissues & endometriotic implants. Conventional therapy (GnRH agonists, Danazol, Progestins) suppresses the ovarian tissues, but do not have a major effect on other tissues, & hence their effects are transitory. Aromataze inhibitors suppress all three locations & hence their superiority.

Aromatase P450 is the key enzyme for estrogen biosynthesis, catalyzing the conversion of androstenedione and testosterone to estrone and estradiol. Although the normal endometrium contains no detectable levels of aromatase activity, this enzyme is active with high levels in endometriotic tissue and increase local estrogen production. Aromatase inhibitors target this enzyme to decrease local estrogen synthesis and thus to inhibit the growth of endometriotic implants. However, this treatment also would reduce ovarian estrogen production and may therefore require estrogen add-back therapy to protect bones. This usage should be limited to the small number of severe cases of women with pelvic endometriosis causing intractable pain. Long-term therapy should of course be monitored with bone density scans and low-dose add-back hormone replacement therapy (HRT). We can offer very little, other than radical pelvic surgery with its potential risks, to a women with intractable...
endometriosis related pelvic pain. Aromatase inhibitor therapy may be justified in these cases, despite a limited evidence base.

**Lipiodol Flushing:** An interesting study published in ‘Fertility Society of Australia, Neil Jhonson, uni. of Auckland, Nov 2003’ used the oil based dye to flush the fallopian tubes as done at HSG. This flushes out debris from tubes that is not actually blocking but which in some ways is hindering pregnancy. This also reduces the stickiness of fimbria & in some way reduces the embryotoxicity of tubal milieu. The study was carried out on 158 patients with 5+ yrs of infertility, & there was 4.5 times rise in pregnancy rate over next 6 months!

**Photodynamic Therapy (PDT):** Photodynamic therapy is based on the selective destruction of growing tissue resulting from interaction between photosensitizer, light & oxygen. Primarily used in cancer cases this therapy has shown great initial potential. In last decade there have been 20+ publications about the use of this technology for endometriosis treatment.

**SERMs & SPRMs:** Selective Estrogen Receptor Modulators are dubbed “designer estrogens” because they mimic the action of estrogen where it’s wanted, such as in the cardiovascular and skeletal systems, but avoid estrogenic action where it’s not; i.e. breast and uterine tissue. SERMs have been shown in animal studies to prevent bone loss and estrogenic proliferation; In one study on rhesus monkeys with Endometriosis, treatment with SERMs resulted in decreased uterine size and significant decreases in lesion size. There are several SERM studies underway, including one at the National Institutes of Health on the use of raloxifine in patients with Endometriosis.

**Terbutaline:** currently used to prevent premature labor, studies are underway to determine the efficacy of this drug as potential treatment for Endometriosis pain. Terbutaline relaxes the uterine muscles and can be helpful in easing menstrual pain related to the disease.

**Mifepristone (RU-486):** the controversial so-called abortion drug may have implications in treating Endometriosis. RU-486, an anti-progestin, binds itself to progesterone receptors on the wall of the uterus and blocks the effect of the woman's natural progesterone. In addition to its anti-progestin and anti-glucocorticoid properties, RU-486 is also a non-competitive anti-estrogen. As such, RU-486 blocks the capacity of the endometrial tissue to grow in response to estrogen, making Mifepristone a possible hormonal treatment for Endometriosis.

**Angiogenesis (stopping the lesion at it's source):** Angiogenesis holds that ectopic tissue requires blood supply, regardless of size, location or theory of implantation. Without blood vessel development, hormone impact can be negated. Hence, Endometriosis lesions can be potentially destroyed by cutting off their blood supply. Angiogenesis has interesting implications on the prevention of adhesion formation as well. It may be shown through further studies that this highly complex and unique technique holds real opportunity for treatment in Endometriosis, whether alone or as an adjunct therapy.

**Endocrine Disrupters:** cleaning up our act (and our environment) Dioxins are one such pollutant.

Endocrine disrupters are chemicals present in our environment that, by virtue of their ability to interact with the endocrine system, are causing a variety of adverse health effects in humans and animals. Because the endocrine system plays such a critical role in normal growth, development and reproduction, even small disturbances in function may have profound and lasting effects. (Rier S., Foster W. 2002)

The US Environmental Protection Agency clearly describes dioxin as a serious public health threat. The EPA report states, there is no “safe” level of exposure to dioxin - even trace amounts are a risk. Further, the EPA report confirmed that “dioxin is a cancer hazard to people; that exposure to dioxin can also cause severe reproductive and developmental problems (at levels 100 times lower than those associated with its cancer causing effects); and that dioxin can cause immune system damage and interfere with regulatory hormones.”
Evidence of dioxin as a catalyst for Endometriosis has been well documented. In a 1996 Environmental Protection Agency study, dioxin exposure was linked with increased risks for Endometriosis, as well as the increased risks of pelvic inflammatory disease, reduction of fertility, and interference with normal fetal and childhood development. According to a February 2000 report from the Food & Drug Administration, tampons and feminine hygiene products currently sold in the U.S. are made of cotton, rayon, or blends of rayon and cotton. Even though these products are now produced using elemental chlorine free or totally chlorine free bleaching processes, these methods can still generate dioxins at "trace levels." Thus, there may be low amounts of dioxin present from environmental sources in cotton, rayon, or rayon/cotton tampons and feminine hygiene products. Using safe products will go a long way in preventing endometriosis.

**Iron chelators:** In a path breaking review titled ‘Potential involvement of iron in the pathogenesis of peritoneal endometriosis’, (Defre’re, Donnez et al) suggest that in endometriosis patients, iron overload has been demonstrated in the different components of the peritoneal cavity (peritoneal fluid, endometriotic lesions, peritoneum and macrophages). Animal models suggest that this may originate from erythrocytes carried into the pelvic cavity mainly by retrograde menstruation. Peritoneal macrophages play an important role in the degradation of these erythrocytes and in subsequent peritoneal iron metabolism. Iron overload could affect a wide range of mechanisms involved in endometriosis development, such as oxidative stress or lesion proliferation. They concluded that excess iron accumulation can result in toxicity and may be one of the factors contributing to the development of endometriosis. Treatment with an iron chelator could thus be beneficial in endometriosis patients to prevent iron overload in the pelvic cavity, thereby diminishing its deleterious effect.

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