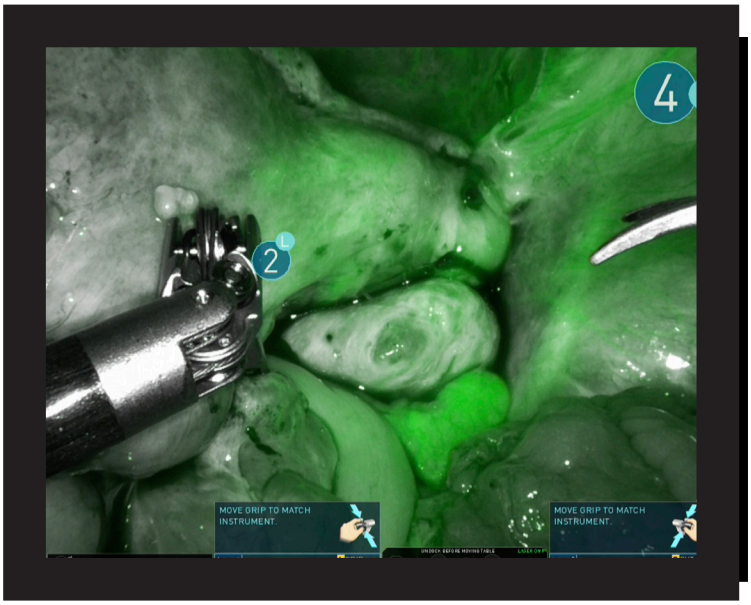
Endometriosis Update

Volume 3: 2021

Expert Commentary: Endometriosis of Ureter: A Silent Sinister



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Editors' Note

Dear Colleagues

Seasons greeting and a happy new year.

It gives us immense pleasure to present to you the third volume of endometriosis update. The concept of this update is to bring various aspects of management of endometriosis in a simplified manner to Gynaecological Practitioner. The update also aims to give insight into the research and the future directions. Diagnosis of endometriosis has always been a challenge and is dependent on visual identification of endometriotic lesion. The clinical review section gives an insight into how miRNA can be used to diagnose endometriosis in a blood sample. The clinical utility of this test can be a game changer in management of endometriosis especially in young women. Endometriosis is an enigmatous disease and the symptoms always do not match the severity. Infiltrative nature of this disease and subsequent fibrosis often involves the parametrium leading to involvement of ureter on one or both sides. It is not unusual to find patients with grade 3 or 4 endometriosis with ureteric obstruction and ipsilateral hydroureteronephrosis. Dr Das Mahapatra, founding secretary of the Endometriosis Society of India highlights this issue to prevent silent kidney loss. Infertility an artificial reproductive technology is a boon for patients of endometriosis who want to conceive. Dr Kanthi Bansal and Dr Anu Chawla discuss nuances of ART in cases with endometriosis. Dr. Gyana Shankar shares a surgical video describing the surgical techniques to manage severe endometriosis laparoscopically. The fact that endometriosis is becoming more or more medically managed disease, Dienogest is now one of the leading molecules which we used to treat endometriosis. We discuss Tips in your practice of how this molecule can be used to your patient's advantage for symptomatic relief as well as managing the disease in the long-term. Dr. Chandra Lula shares the ultrasonography images and how it can help in diagnosis of endometriosis. Dr. Vidya Thobbi highlights the role of alternate therapies that can help patients with endometriosis. Role of Vitamin D and influence of COVID-19 in the management of endometriosis is being reviewed by Dr Chitra. Quiz master Dr Chitra has compiled a MCQ that will be interesting for all of us to test our knowledge at the end of the reading this update.

We look forward to hearing from all of you regarding how you liked our previous three update. Please feel free to give suggestions of how we can improve and what would you like us to include in the forthcoming issues. You can contact with us on website address email address for number

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Expert Commentary

Endometriosis of ureter- A Silent Sinister

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Endometriosis is a disease mainly restricted within the pelvis. Nevertheless, extra pelvic locations are rarely found in lung, lymph nodes, scars, and, very rarely in the kidney1. Symptoms depend on the site of implantation. Chronic pelvic pain, painful periods, dyspareunia and dysuria are frequent manifestations.

These features are not unique for endometriosis and can also be present in other diseases. Extragenital endometriosis rarely involves the urinary tract with involvement of the bladder, ureter, kidney and urethra in 85, 10, 4, and 2%, respectively. The urinary system is the second most common site of extra pelvic endometriosis after the gastrointestinal tract.

The prevalence of UTE is estimated to range from 0.3 to 12% of all people affected by endometriosis. The close anatomical proximity of the distal ureter to the female reproductive organs makes it vulnerable for the development of extrinsic compression of the ureter. Association of ureteral endometriosis2 with renal obstruction is well recognized.

Ureteral endometriosis is either intrinsic (25%) and extrinsic (75%) and the ureter is usually involved below the pelvis brim3. In the extrinsic form ureteral endometriosis is localized to the adventitia or surrounding connective tissue of the ureter. While, in the intrinsic variety the endometrial lesion is present in the mucosa.

Involvement of ureter in both varieties may lead to urinary tract obstruction causing ureter hydronephrosis4. It is found mainly in deep endometriosis (20-52.6%) with extensive disease. However, the ureters may also be involved in minor cases acting as silent soldiers invading the innocent ureters. Involvement can be limited to a single ureter, more often the left one, or both ureters, particularly in patients with extensive pelvic endometriosis.

Ureteral endometriosis is usually found in women aged between 30 and 35 years. Hydroureter hydronephrosis, is associated with superimposed pyelonephritis in about one third of cases. As many as 25–50% of nephrons are lost when ureteral endometriosis is present. The true incidence of renal failure caused by endometriosis is completely unknown, although cases have been reported in the literature.

The diagnosis of ureteral endometriosis is difficult since the disease may be clinically silent or associated with non-specific symptoms. However, while renal imaging is useful in the cases of extrinsic endometriosis, the diagnosis of intrinsic endometriosis can only be ascertained after ureteroscopy.

The prognosis of ureteral endometriosis depends on the time of diagnosis. In many cases of bilateral obstruction, the patient is referred to the nephrologist because of an advanced, irreversible end-stage renal disease (ESRD).

The main problem is that bilateral ureteral endometriosis may be asymptomatic and many cases are discovered incidentally during laparoscopy for extensive endometriosis. On the other hand, while renal echography may show a pyelocaliceal dilatation in cases of extra ureteral endometriosis it is of little, if any, help for diagnosing patients with intrinsic ureteral endometriosis Ureteral endometriosis should be included in the differential diagnosis of obstructive ureteral lesions in women, particularly those involving the lower third of the left ureter.

Deep endometriosis5(DE) of the pelvis is often asymmetric and mainly involves the left pelvis: It may cause rectovaginal lesions and sometimes involve the bladder and ureters. The bladder lesion is usually situated in the posterior wall or at the dome; more rarely involves the bladder base.
Although some patients may benefit from progestin. Aromatase inhibitors are rarely effective. In most cases of ureteral endometriosis surgery is needed, laparoscopy surgery being preferred today to laparotomy.

The nature of invasive tissue may be confirmed by immune stains-6for cytokeratin-7 (CK7) and progesterone receptor (PR) which are positive in case of endometriosis, whereas immune stains for estrogen receptor (ER) are positive in 83% of cases and immune stains for CK20 are negative in all cases. CA125 immune stains are positive in 67% of cases. The stromal cells are positive for CD10, ER, and PR immunostaining
Recently I saw cases of Ureteral endometriosis with hydrouretero nephrosis in three young women who presented with different symptoms. It would be prudent, I thought, to share my experiences with you.

Case A
Miss M P 26 yrs. pursuing administrative job

Presentation:
This young lady consulted me (video) on 28.01.2021 for my opinion regarding her diagnosed advanced endometriosis with bilateral hydroureteronephrosis and DJ stents in both ureters. She had severe pain in lower abdomen during the periods in 2017 when USG showed bilateral hydronephrosis. Bilateral DJ stenting done on 08.01.2018. She had Inj. Depo-Provera every three months X two such. Creatinine level had increased. DJ stenting removed on 14.09.2018. USG on 07.06.2019 showed hydronephrosis in both kidneys left> right and bilateral polycystic ovarian morphology. Re-stenting was done in Aug '2019 and June 2020. She was treated with Dienogest intermittently for 6 months which reduced her symptoms and CA-125 level.

However, she then discontinued Dienogest. Menstrual cycle – K-10 years, was frequent and heavy with dysmenorrhea but without any dyskezia, Dysuria+. She had recurrent UTI treated with antibiotics. There was no other significant medical or surgical history or known drug allergy. She had no family history of Ca breast, ovary or colon or endometriosis.

There was no history of Neonatal vaginal Bleeding She had physical consultation on 22.03.2021 with Urologist, Colorectal Surgeon & myself. Steps of surgery, benefits and possible complications were explained by the board. Planned for laparoscopy followed by definitive surgery + Mirena insertion after routine pre-operative investigations and MRI.

Investigation:
USG on 22.01.2021- showed polycystic ovarian morphology. MRI on 08.02.2021 revealed presence of Deep Infiltrating Endometriosis and an endometriotic nodule in POD with bilateral ureteric involvement + Focal adenomyoma in the lower uterine segment. Hb -12.1 gm%, Blood Group-B positive, CA-125- 147.5 U/ml, reatinine - 1.55 mg/dl, Other preoperative investigations were normal. COVID - 19- Negative

Final Diagnosis: - Deep Infiltrating Endometriosis+ Bilateral ureteral Endometriosis + Early Adenomyosis

Counselling:
Patient and her relative were counselled pre-operatively about her problem of Endometriosis. It is very important to get the proper mapping of the extent of the disease before surgery by MRI & Diagnostic laparoscopy. They were also counselled that endometriosis is a progressive disease that causes painful periods and difficulty in conceiving. There is no effective medical treatment for permanent cure of this condition for which removal of uterus and ovaries is necessary. This is, however, not desirable in a young lady like her. Laparoscopic conservative surgery offers maximum benefit in terms of longer period of remission. Endometriosis is always likely to recur, the chance being 25% within 5 years. There is a 5% chance of persistence of pain. She has had bilateral ureteric obstruction with compromised renal function. Surgery to relieve the ureteric obstruction is advisable on an urgent basis. The operation will be long (6 to 8 hrs.), difficult and complicated. If necessary, the ureteric stenosis areas will be excised followed by re-anastomosis or implantation into the bladder. Post-operative stenting is necessary.

Rectal excision + end to end anastomosis + colostomy may be necessary. Post-operative medical therapy may be helpful. ICU admission may also be necessary in post-operative period. Involvement of Urologist and colorectal surgeon is essential. Any other surgical intervention if needed will be carried out also.

The advantages of laparoscopic surgery like, short stay, less morbidity, early return to work, less chance of hernia etc. were explained. She also explained that in case of difficulty, laparoscopic surgery might have to be converted to open surgery in about 2% cases. The complications of laparoscopic surgery like injury to nearby structure, infection, hemorrhage, DVT etc. were explained. They were also counselled about Mirena insertion. Mirena is not a permanent procedure. It reduces & delays the recurrence of the disease. Insertion of Mirena has a success rate of 90% in controlling her disease and period.

After insertion the Mirena period might be irregular for the first 3-6 months following which period would be lighter and she might become amenorrhoeic. Its efficacy lasts for 5 years and acts as a contraceptive as well. After explaining everything, informed consent was obtained for necessary operation.

Procedure:
Pre-anesthetic checkup was done by the Anesthetic team and the patient wheeled into the OT. Operation was done under General Anesthesia on 09.04.2021. Surgical team included a Gynecologist, Colorectal surgeon and Urologist. Laparoscopy showed the uterus was R/V, 6 weeks with early adenomyosis.

Both US ligaments are nodular & thick. Left adherent with ovary and fimbriae of left tube + rectum. Right sided nodule adherent with right US ligament & anterior rectal wall. Both ovaries were cystic, tube normal. Both ureters are densely adherent with endometriotic nodules of US ligament. POD – obliterated. Laparoscopic ureterolysis, enterolysis, nodule from anterior rectal wall sliced, R/V septum and both US ligaments partially excised by using LCS and bipolar. Dye test for rectal injury was negative. Hemostasis achieved. Both ureters dissected up to the lower end of the ureteric tunnel. Proximal ureter dilated bilaterally.

Decision for ureteric implantation taken as the long segment of the lower ureters were affected. Both ureters mobilized & divided, distal ureteric stump clipped, proximal ends spatulated. Bladder mobilized all-around. Both ureters reimplanted after Psoas hitching in a tension free modified LICH-GREGOIR fashion. 6/24 DJ stent placed. Drain inserted. Ports closed. Mirena introduced.

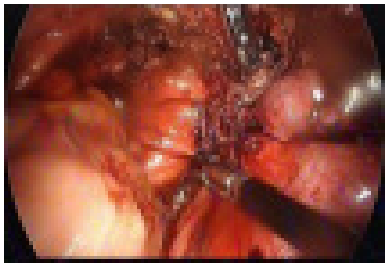
Duration of operation: 480 minutes.

Estimated blood loss: -300ml

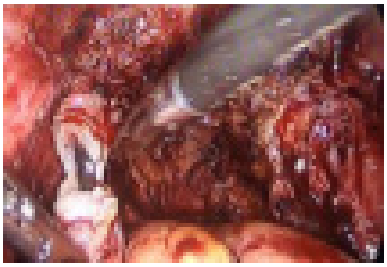
Post–Operative Period:
She was shifted to ITU for 48 hours. She recovered nicely. Drain & slice removed on 13.04.2021. Post-operative Hb% - 12.0 gm/dl. LMWH was administered. Continuous bladder drainage for 10 days. Patient had hematuria on 12.04.21 settled with Tab. Pause. IV Antibiotic continued for 5 days. No aminoglycoside given.

Plan:
Routine post- operative care – Foley's catheter removed on 19.04.2021. Post op follow up after 3 months showed she was happy and confident. There was no pelvic pain and period. DJ stent was removed after three months.

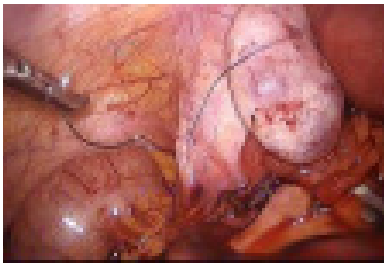
Can I say something?
The diagnosis of endometriosis was delayed by 10 years. Repeated UTI, a concern for a single sexually inactive young lady did not raise any alarm to initiate investigation much earlier. Involvement of ureters with endometriosis may be a silent process. Only a high index of suspicion and imaging technique may help to obtain an early diagnosis.
She is very intelligent and practical and decided not to tie the knot with anyone knowing her disease condition and the surgery she went through. I appreciate her clever decision. It is hard to imagine what her obstetric behavior if she ever decides to venture. Good luck to her.



Case A, fig. 1: Excision of deep endometriosis

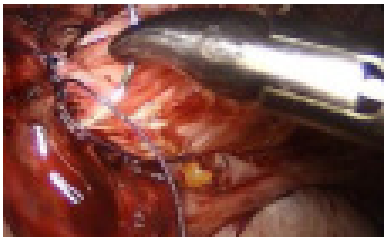


Case A, fig. 2: Dividing left ureter

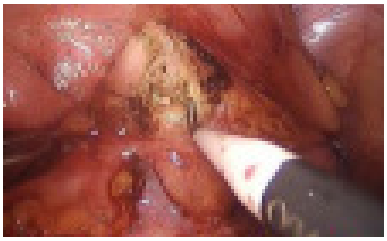


Case A, fig. 3: Clipping the distal end

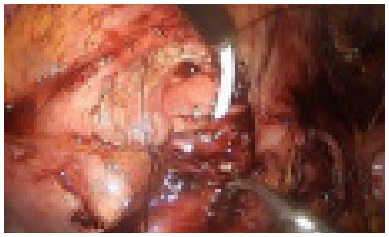
Case A, fig. 4: Hitching the bladder



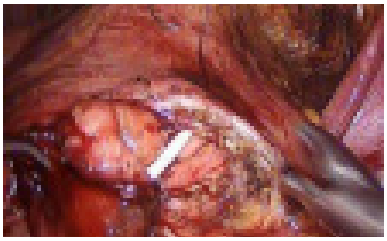
Case A, fig. 5: Opening the bladder



Case A, fig. 6: Fixing the ureter in the bladder wall



Case A, fig. 7: Placing the DJ stent



Case A, fig. 8: DJ stent in place

Case B

MS S D 30 yrs. A banker, married for two years, had irregular periods with clinical diagnosis of PCOS and was treated with OC for 5 yrs. She never had any symptoms of painful periods or any other suggesting endometriosis. OC was discontinued after marriage, though not trying for pregnancy. She had a severe painful and heavy period in one cycle only a year ago when she was treated with Tranexamic acid. Trans abdominal USG in April 2020 showed left hydro ureter with small left kidney and a stone in the lower part of left ureter.

However, no stone was found on Ureteroscopy. Instead, there was thickening and oedema of the lower part of the left ureter. RGP done. DJ stent was placed on 27.6.20 and replaced on 4.9.20. Stent removed on 1.1.21 for 50 days. Stent placed again on 22.2.21.

MRI on 11.8 21 showed 14 mm x 18 mm DIE in US ligament. Adhesion to the anterior mid rectal wall. RV septum and cul de sac fibrotic mass. Distal ureteral thickening involving the left ovary. stented ovaries are non endometriotic but a little poly cystic. J Z borderline at 7 mm early adenomyosis, left kidney small and shrunken with 20% function.

DTPA showed left kidney with18% function and right kidney 82%. on 13. 08.21.

Diagnosis -Deep endometriosis involving left ureter – stenosis – repeated stenting done. Pregnancy not yet attempted.
Counselling done and options were discussed.

Option I: - Medical therapy – is not expected to be effective for ureteric endometriosis

Option II: - Laparoscopic surgery with Ovariolysis, release of left ureteric endometriosis + ureteric stenting then tries for pregnancy. May not be successful in saving the left kidney function.

Option III: Laparoscopic excision of RV septum endometriosis and endometriosis of ureter followed by reimplantation of ureter into the bladder. Major and long operation (4-6 hours).

The procedure is expected to save the remaining function of the left kidney. Temporary bypass of colon may be necessary. 25% recurrence within 5 years, pregnancy chance is 50%. Surgery should be done by a team of doctors including Gynecologist, Colorectal surgeon and Urologist.

She is now confused and cannot decide what would be best for her. The couple has a plan to try for pregnancy probably after medical therapy or Option II: She is not keen to have any aggressive surgery at present.

My comments: I feel sorry for this young lady who had been under medical supervision so long without any symptoms of endometriosis. She had USG every six months showing PCOS features in addition to her infrequent periods.

Majority of gynecologists in the world recommend OC in the management of endometriosis. Voice has been raised recently that OC contains Estrogen and therefore we should be cautious to use it for an estrogen dependent disease.

Well, I acknowledge the beneficial effect on pain relief in endometriosis. But nevertheless, Estrogen probably has a role to initiate or to upstage the disease process. I believe OC masks the disease symptoms comparable to the popular saying "still water runs deep".

It is mandatory to take every effort including Laparoscopy to diagnose adolescent endometriosis at the earliest. It has been proved that diagnosis is delayed by clinical features only.

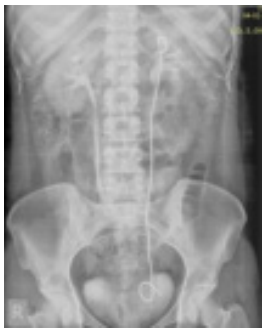
On ureteroscopy no stone but the lesion with stenosis was evident. A gynecologist should have been called for then and there to make the correct diagnosis earlier.

There are merits and demerits in both the options of less extensive conservative approach and extensive surgery by removing the DE and reimplantation of ureter. There is hardly anytime left, we need to save the remaining function of left small kidney at the earliest.

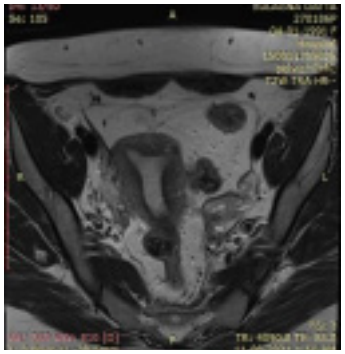
Case C

Miss A P 21 yrs. A postgraduate student consulted a gynecologist for frequent urinary tract infection. She was not sexually active. She has had severe painful periods for 5 yrs. There was history of hematuria 6 months ago and treated for recurrent UTI.

USG showed SOL in the bladder



Case B, fig. 1: Urogram showing right normal kidney and ureter and left DJ sent in situ



Case B, fig. 2: MRI with contrast showing deep endometriosis

at fundus and therefore referred to the Urologist. MRI with contrast showed a bladder lesion on the right bladder wall 2.4 cm x 2.8cm encroaching right ureteric orifice and bilateral hydro uretero nephrosis and deep endometriosis involving both US ligaments and anterior rectal wall.

Cystoscopy and biopsy of the mass done on 31.03.2021. Biopsy confirmed endometriosis. DTPA showed 75% bilateral renal function.

She was sent to me for counselling and discussion for definitive surgery. It was planned for partial cystectomy, excision of deep endometriosis and reimplantation of both ureters.

She came with her father for my opinion and counselling on 12.4.21. I tried to be sympathetic while counselling her regarding her disease, its extension, plan of management, the risks and outcome of surgery. I advised them to think over and assured me that I would definitely be happy to counsel them again if necessary.

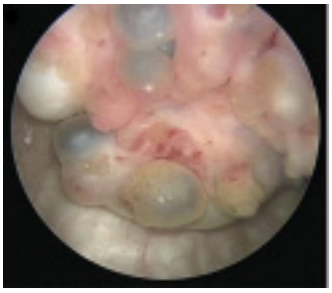
After two weeks her father called to say that they were going for alternative medical treatment as the doctor promised 100% cure within one year with minimum expenses. What could I say but" God bless her"?

Why did she decline the surgery?

I have been thinking what was the cause? My robust counselling or the money matters? Answer is- I do not know.

If it was my robust counseling, there was nothing I could do about it. It is absolutely necessary to give all the information regarding the disease, the treatment options and the outcome. In modern medicines sharing the information plays an important role. There is no place for denial.

Well, the other possibility of financial constraint pains me.
It is unfortunate that the public healthcare system perhaps hardly provides any expertise of that magnitude. Corporate healthcare is expensive, and there is very little in our hands. I suggest that ESI should raise funds to support economically deprived women's health. Do you all tune with my idea; my friends that this could be a solution?
I only hope, yes, only hope that she returns for the surgery.



Case C, fig. 1: Ms A P cystoscopy and biopsy

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Alternative medicine therapy in Endometriosis

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Endometriosis is a common gynecological condition among women of reproductive age group (10-15%), leading to chronic pelvic pain, severe dysmenorrhea and subfertility, which may affect a patient's quality of life.

In recent years, the complementary and alternative medical treatment (CAM) for endometriosis has become popular owing to the effectiveness at relieving dysmenorrhea , shrinking of adnexal masses , promoting pregnancy with few adverse effects when compared to other treatments.

The complementary and alternative treatment for endometriosis includes:

- Herbs (extract and patent)
- Acupuncture
- Microwave physiotherapy
- Chinese herb medicines

Herbal Products

They include the use of herbal formulae of two or more separate herbal ingredients selected that are prepared as a boiled decoction and then processed into as herbal extract, pills or capsules.

Many researchers have suggested the mechanism of these products on endometriosis is through:

1. Reducing the viscosity of blood, improving pelvic microcirculation
2. Inhibiting the expression of inflammatory factors, like, IL-1 and IL-6
3. Reducing the expression of prostaglandin E2, F2alpha and nerve growth factor
4. Inhibiting uterine smooth muscle activity and relieving uterine muscle spam

These can be evaluated by clinical parameters, such as:

1. Endometriotic lesion size measured by ultrasound examination
2. Pelvic pain, dysmenorrheal measured by clinical pain visual analogue scale (VAS)
3. Implanted endometrium size measured by weight and volume

Herbal extract therapies:

Herbal extracts commonly used include turmeric, reseratol, green tea , triterpenoid saponin , rhizoma zedoariae water decoction, etc.

These play an important role in endometriosis dysmenorrheal by affecting cell proliferation, apoptosis, angiogenesis, and the inflammatory microenvironment.

Resveratrol

It is a polyphenol extract from grapes, mulberry and other plants. Due to its antioxidant properties, it has shown to potentiate the effect of oral contraceptives in decreasing dysmenorrhea by inhibiting aromatase and COX-2 expression in endometrium in endometriosis patients. After use of Resveratrol, it was reported that the increased peritoneal levels of free oxygen radicals as seen in endometriosis were suppressed.

Epigallocatechin-3-gallate (EGCG):
It is an extract from green tea and possesses antiproliferative, antiangiogenic, pro-apoptotic effects and thereby can reduce the size and weight of lesions. Many studies reported that EGCG can suppress VEGF-C and VEGFR-2 in endothelial cells.
Various studies showed that EGCG could prevent fibrosis progression in endometriosis and also helps in inhibiting proliferation, migration and invasion of endometriotic cells.

Ginistein:
It is an isoflavone isolated from soy and possesses phytoestrogenic and antioxidant effects.
Various studies reported that this molecule decreases the surface of the endometriotic implants by its anti-angiogenic and anti-proliferative mechanisms. Genistein also decreases the expression of various pro-inflammatory factors, like, IL-6, TNF-alpha, COX2.

Rhizome Zedoariae Water Decoction:
It is derived from the dried tuber of Curcuma phaeocaulis valeton and helps in downregulation of JAK2, STAT3 phosphorylation, and protein overexpression and reduction of JAK2, STAT3 levels in ectopic endometrial tissues as seen in a rat model of Endometriosis.

Medicinal Plants:
Artemisia princeps
It belongs to family Asteraceae, and have been used for years in the management of infertility, dysmenorrhea.
It contains many bioactive compounds such as, flavonoids , sterolic acids and coumarins. Many studies reported that it has antitumor, antispasmodic , antioxidant properties.

Allium sativum
It is also known as Garlic, belongs to Liliaceae family. It possesses antioxidant effects . In a study, it was observed that diallyl trisulphide, a constituent of Garlic, inhibited angiogenesis in human endothelial cells.
It also suppresses the secretion of pro-inflammatory cytokines such as IL-2, IL-8, TNF-alpha, IFN-alpha and also enhanced the secretion of IL-10,which is an anti-inflammatory cytokine.

Curcuma longa
It is also known as Turmeric , a major bioactive compound represented by curcumin.
It increases the activity of IL-10-1082 A, an anti inflammatory cytokine gene promoter. In a recent study ,it was reported that ethanolic extract of C.longa in endometriosis rat models decreases oxidative stress.

Herbal Patent Medicine Therapies:
These are based on Chinese medicine theory using CHM as raw material , and include Guizhi fuling capsules (GFC), ELeng capsules (ELC), Dan Bie capsules (DBC), Sanjie Analgesic capsules (SAC), Dane fukang paste (DFP)

Guizhi fuling capsules (GFC)
It contains active ingredients that have anti-inflammatory, analgesic, and immune regulating effects.
Many clinical studies have shown that it can effectively reduce the levels of CA-125, CA-199 in endometriosis and can improve menstrual cycle and menstrual volume.
It also helps in blocking the signal transduction pathways between cells and inhibits the abnormal proliferation of endometrial cells.

ELeng capsules (ELC)
It can help reducing the promotion of vascular proliferation and adhesion formation by inhibition of expression of soluble intercellular molecule-1 (sICAM-1)
In an RCT, the total effective rate of dysmenorrhea was decreased from 84% to 48% with use of ELC in endometriosis patients.

Dan Bie capsules (DBC)
It can reduce the concentration of PGF2alpha and PGE2 , which can reduce pelvic stasis , improving the pelvic microvasculature and relieving pain.

Acupuncture:
It has attracted increasing attention as a safe and easy to perform treatment. It includes needling , auricular pointing and moxa-moxibustion. It can relieve pain in the central and peripheral regions by activating neurotransmitters , modulators including serotonin , norepinephrine and adenosine.

Various clinical and animal experiments concluded the different mechanisms of acupuncture treatment for dysmenorrhea that includes relaxation of the meridians and promotion of blood circulation, activation of various neurotransmitters, reduction of VEGF and regulation of abnormal prostaglandin

Moxibustion Treatment
In this technique, heat is applied to acupoints by burning compressed powdered herbal material, to stimulate them. Chinese medicine believes that this technique could warm meridians, relieve pain and promote blood circulation.

Acupuncture Combined with Moxibustion Treatment
It is a common practice and effectively stimulates the regulatory function of meridians and collaterals and thus improves local blood stasis. Warming needle moxibustion that combines acupuncture and moxibustion, involves wrapping moxa on the needle handle and igniting it during the needle retention process. The needle body transfers the heat into the acupoint to treat disease by warming the meridians and promoting blood circulation.

Auricular Acupoint Treatment
It is believed that acupuncture on the ear can reflect the general health of the human body.

This treatment is used for pain relief in inflammatory diseases, endocrine and metabolic disorders. It can be used as daily care treatment for endometriosis to improve a patient's quality of life.
One study showed that auricular acupressure could relieve uterine smooth muscle spasm by reducing the secretion of serum PGE2

Electroacupuncture
It is a modified form of acupuncture that uses electrical stimulation and can effectively improves blood circulation.

It blocks pain by activating various bioactive chemicals through peripheral , spinal and supraspinal mechanisms.

Fig. 1: EGCG

Fig. 2: Curcuma longa

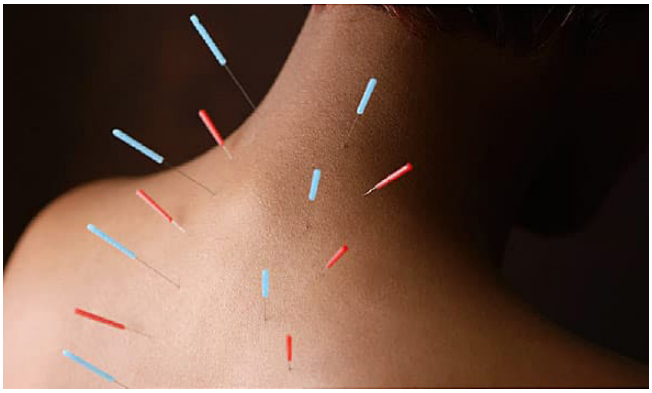

Fig. 3: Acupuncture

Fig. 4: Moxibustion

Chinese herb medicine enema (CHM enema)

CHM enema helps by inhibiting the activation of NF- Kb in cells, reducing the expression and secretion of regulated on activation in normal T-cell expressed , reducing inflammation and pain. Various studies showed decreased levels of serum CA-125and VEGF after treatment.

CHM Enema combined with microwave physiotherapy

The principle in using microwave's thermal effects is to expand local blood vessels, promote blood circulation and improve local nutrition.

Microwave therapy uses the magnetocaloric effect of microwaves on the tissues to stimulate different areas around the rectal wall.
It shrinks and soften the endometrial sac, increases blood circulation around the lesion, improves

Therapeutic approaches	Clinical indication	Specifications	Efficacy	Precautions
Herbal products	EM with chronic pelvic pain, dysmenorrhea, and infertility	According to TCM practitioners' judgment of the disease, propose appropriate TCM prescriptions	Alleviate dysmenorrhoea Shrink endometriotic lesion Promote pregnancy Reduce recurrence rate	Patients who are allergic to some foods and pollen should take the herbal products with caution
Acupuncture and Moxibustion	EM with chronic pelvic pain, dysmenorrhea, and infertility	Take the appropriate acupoints and choose needling, auricular point, or moxa-moxibustion therapy, according to the disease status of the patient. 30 min is a course of treatment for acupuncture (needling, auricular point); 40–50 min is a course of treatment for moxibustion	Alleviate dysmenorrhoea Promote pregnancy	Some patients may occur fainting condition
CHM enema	EM with chronic pelvic pain, dysmenorrhea, and infertility	Ask the patient to take the left lateral decubitus position. Put the boiled TCM herbal liquid into 20 mL syringe, with the temperature of 38~40°C. With a disposable catheter connection, slowly push TCM herbal liquid into the rectum. Tell the patient to relax and keep the TCM herbal liquid more than 2 hours	Alleviate dysmenorrhoea Shrink endometriotic lesion	Unfit for predominant irritable bowel syndrome patients
Microwave physiotherapy	Non acute phase of EM	Ask the patient to take supine position. Put the microwave physiotherapy instrument facing patient's lower abdomen, with the distance of 35–45 cm. 30 min is a course of treatment	Alleviate dysmenorrhoea Shrink endometriotic lesion	Attention to operating time, adjusting the distance of microwave physiotherapy equipment, so as not to scald patients

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CLINICAL REVIEW

Role of miRNA as a Non-Invasive Diagnostic modality for Endometriosis

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Trichy.

Endometriosis is the presence of endometrial glands and stroma outside the uterus, involving both genital and extra genital sites. 10 % of women of reproductive age group, 25 - 42 % of infertile women, 60 - 70 % of adolescent girls with dysmenorrhea have endometriosis. As per WHO 190 million women suffer from endometriosis world wide and 50 million women in India suffer from Endometriosis according to Endometriosis society of India. Endometriosis leads to severe pain and infertility which affects the quality of life. Laparoscopic surgery is the gold standard modality for confirmation of endometriosis.

There is always a diagnostic delay in this condition which may vary from 6-10 years, according to various data from many countries2. The cost of surgical procedure, morbidity, loss of economy incurred, health care providers are in a situation to start empirical treatment without the histological diagnosis, though it is the important criteria for definitive diagnosis of endometriosis. Meta-analysis of studies for diagnosis of endometriosis through biomarkers, imaging and physical examination are found to be inadequate to start the treatment3-5. Hence, we are in need of some modality for non-invasive diagnosis of endometriosis, which can replace laparoscopy.

However, no clinical marker of endometriosis either alone or in combination has provided adequate sensitivity or specificity for the diagnosis of endometriosis6-9. Hence there is an unmet need for diagnostic markers for endometriosis10. Recent advances in research have found several miRNAs as a valuable biomarker to diagnose endometriosis. If the biomarker in serum is positive, these patients could be initiated treatment. miRNA are short nucleotide sequences of non-coding RNA involved in regulatory pathways. They are single stranded RNA molecules 21 to 25 nucleotides in length that act as post transcriptional silencers of gene expression by degradation of their target RNAs11. miRNA expression profiles vary in different diseases like cancers, PCOD etc., so there is disparity between diseased and control groups12. Recent research has known, various miRNAs are either up-regulated or down-regulated in various diseases Vs controls.

They are present in the body fluids including blood, either contained in exomers or bound to protein complexes which makes them more stable and hence a better candidate marker13. There could be many shortcomings in picking up these mi RNAs levels because of the use of various techniques like RT-PCR, in situ hybridization, miRNA based micro arrays, next generation gene sequencing (NGS)and bioinformatics followed by validation of RT-PCR14 - 17.

NGS offers the advantage of screening samples for known, as well as novel miRNA in an unbiased manner. Recently NGS was used to screen miRNAs that are differentially expressed in the plasma and extracellular vesicles of women with endometriosis compared to control women. Recent study by Elahe et al showed plasma levels of 28 novel miRNAs and 41 miRNAs are differentially expressed in women with endometriosis compared to the control group.

This research work is an eye opener, to diagnose endometriosis using circulating bio-markers18. Multiple miRNA panels are better than using a single miRNA to confirm the diagnosis.

The prediction of endometriosis using miRNA has association with the pathophysiology of endometriosis such as epithelial- to- mesenchymal transition, neo- angiogenesis, cellular proliferation and invasion. Till today studies have shown poor sensitivity and specificity of miRNA suggesting limited role as a biomarker in diagnosis19,20.

Moreover, the phenotypes of endometriosis differ and there may be significant up-regulation and down-regulation of various phenotypes and control groups21. The mode of treatment is same for any phenotypes of endometriosis, either surgical or medical. There is no utility of testing specific types of mi RNA for various phenotypes and mi RNA in the serum can be utilized to identify the response to hormone therapy22. Clinical response is identified by improvement of symptoms. There is no correlation between symptoms to tissue level of response to therapy. A prospective study by Mustafa et al, showed that a set of 6 miRNAs were able to distinguish between endometriosis and other gynecological conditions, in 100 women who underwent laparoscopy for pelvic pain and/or infertility regardless of the current hormonal treatment or menstrual cycle phase23.

There are panels of miRNAs which are unique to endometriosis to predict the diagnosis of endometriosis among patients with pelvic pain and /or infertility. miRNA panels like miR-125 b, miR-342, miR-451, miR-3613, let-7b resulted in unparalleled specificity and sensitivity (difference 90 %). This serum miRNA testing has to go through several steps before being put up into clinical practice. Selected women who have undergone empirical treatment and presumed endometriosis patients and to predict the success or failure of hormonal treatment miRNA testing can be done.

Based on this, if there is failure of hormonal treatment, they can be recommended for surgery. There have been recent ongoing studies, where the same panel of miRNA has been tested among adolescent girls who are having symptoms suggestive of endometriosis (average age-17). These studies will aid adolescent girls to pick up the disease at an earlier stage and plan their treatment. Adolescent girls who had failed hormonal therapy can be changed to surgical management. Endometriosis is a condition where quality of life is reasonably affected because of lack of non-invasive testing and diagnosis is often delayed. Hence this non-invasive testing would be of great use in clinical practice. If studies are found to have promising results using these 6-miRNA panels, this will be a great boon in future to identify the disease earlier, so that they can be directed properly to manage the endometriosis which will improve the quality of life.

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Quiz

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1. Endometrial tissue comprises primarily
1. Only epithelial cells
2. Only stromal cells
3. Predominantly stromal cells
4. Predominantly epithelial cells

2. What is EAOC?
1. It is a type of classification
2. USG model for endometriosis
3. Risk assessment
4. Association with malignancies

3. Endometriotic lesion pathologically overexpress all except
1. ER - Beta estrogen receptor
2. StAR – steroidogenic acute regulatory protein
3. P450
4. 17 (OH) – dehydrogenase

4. Retrograde menstruation is proposed by
1. Bonney
2. Sampson
3. Sims
4. Novak

5. What is the most common extra-pelvic site of endometriosis?
1. CNS
2. Lung
3. Bladder
4. GIT

6. Life time risk of developing endometriosis in a woman with affected 1st degree relative is
1. 5%
2. 25%
3. 10%
4. 35%

7. KRAS mutation in EAOC is seen in
1. 5% of cases
2. 25-30% of cases
3. 10% of cases
4. 50% of cases

8. Long term complication of presacral neurectomy
1. Haemorrhage
2. Over active bladder
3. Constipation
4. Gluteal pain

9. What is accurate about presentation of endometriosis
1. Post menstrual pain
2. Pain directly proportional to lesion size
3. Mid line lesions more painful
4. Adhesions are less important

10. Apart from ovaries the next commonest site of endometriosis
1. Uterus
2. Distal ureter
3. Rectosigmoid colon
4. Posterior cul de sac

11. The best diagnostic modality for DIE is
1. TVS
2. CT
3. MRI
4. Barium studies

12. On USG visualisation of punctate echogenicity in the cystic wall
1. Suggest development of carcinoma
2. Adds to the specificity of diagnosis
3. Has no significance
4. Suggest calcification

13. The following statement regarding DIE is true
1. Commonest site is rectosigmoid colon
2. Does not respond to medical management
3. Is asymptomatic
4. Mass < 5mm deep to the peritoneum

14. Rupture of an endometrioma is associated with all except

1. Occurs in 25% of cases
2. Occurs during pregnancy
3. Causes severe pain
4. Associated with increased CA 125

15. Who identified endometriosis

1. Thomas cullen
2. Sampson
3. Rokitansky
4. Mayer

16. GnRH antagonist Elagolix causes

1. Progression of disease
2. Severe hot flushes
3. No effect on bone density
4. Excellent decrease in pain

17. Difference between ENZIAN and rASRM classification is

1. Includes bowel involvement
2. Includes DIE
3. Includes extra pelvic sites
4. Includes bladder involvement

18. Fertility is improved in

1. Cystectomy for cyst >4 cm
2. Laser destruction of cyst
3. Puncture of cyst
4. Cyst drainage and diathermy

19. EAOC is predominantly

1. Serous carcinoma
2. Mucinous carcinoma
3. Clear cell carcinoma
4. Granulosa cell tumour

20. Pain in endometriosis is due to

1. Fibrosis
2. Adhesions
3. Collection of blood
4. Increased density of innervation

21. The following is a risk factor for endometriosis

1. Pin point cervical os
2. Retroverted uterus
3. Late age of menarche
4. Long menstrual cycles

22. EFI predicts

1. Pain scoring
2. IVF pregnancy rate
3. Non IVF pregnancy rate
4. Stage of the disease

23. All are side effects of Danazol except

1. Weight loss
2. Hoarseness of voice
3. Emotional instability
4. Reduced Libido

24. Add back therapy is given to

1. Minimize cost
2. Prevent bone loss
3. Regularize cycles
4. Break through bleeding

25. Motto of endometriosis this year

1. Think endometriosis
2. Fight endometriosis
3. Early diagnosis of endometriosis
4. Think endometriosis & Fight endometriosis

True or false round

1. Endometriosis is more prone in birth weight<7lbs
2. Risk of endometriosis is 7times more common with 1st degree affected
3. Environmental pollution is linked with development of endometriosis
4. Dysmemorrhea is very severe if pt has only ovarian endometriosis
5. Danazol causes hepatocellular damage
6. Elagolix is administered nasally
7. miRNA is a promising diagnostic test
8. Danazol is available as pessary
9. Ca125 is an effective screening test
10. Norethindrone is the only approved FDA add back

Answers:

Multiple Choice Questions:

1. (3)
2. (4)
3. (4)
4. (2)
5. (4)
6. (3)
7. (1)
8. (3)
9. (3)
10. (4)
11. (3)
12. (2)
13. (1)
14. (1)
15. (1)
16. (4)
17. (2)
18. (1)
19. (3)
20. (4)
21. (1)
22. (3)
23. (1)
24. (2)
25. (4)

True or False:

1. True
2. True
3. True
4. False
5. True
6. False
7. True
8. True
9. False
10. True

Examining the Evidence

ART & Endometriosis – Outcome & Management

Dr. Anu Chawla, MS (obgyn), DNB, MRCOG, FMAS

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Endometriosis is a chronic gynecological disorder defined by the presence of endometrial glands and stroma outside the uterine cavity. The nature of endometriosis is heterogeneous in terms of the presentation of three phenotypes like Superficial peritoneal endometriosis, (SUP), Ovarian endometrioma (OMA) and deeply infiltrating endometriosis (DIE). Approximately, 5 – 10 % of reproductive age women are affected by endometriosis. One third of them are sub-fertile.

Main focus of the chapter is on the ***evidence- based review of literature*** published with regards to the ***outcome and management of the ART*** cycles performed in women with diagnosed endometriosis, the key recommendations and areas of future research in this direction.

Endometriosis and Subfertility:

i) Fecundity rates may be reduced in endometriosis potentially in relation to the severity of the disease, which is categorized, following the classifications as – i) Revised American Society for reproductive medicine classification] – (r ASRM)

ii) Revised American Fertility Society Classification:
Pregnancy rates among patients with endometriosis are related to the severity of endometriosis. Stage I-up to 55%, Stage III-up to 43% and Stage IV up to 32%.

The Potential mechanism that causes infertility in endometriosis are state of chronic information, dysregulated immune system, Peritoneal fluid with increased number of Immune Cells, Macrophages, Mast Cells, Natural Killer Cells, T Cells, Growth Factors, Chemokines, Cytokines, progesterone resistant, Elevated IL -16 and decreased Concentration of VEGF.

Impaired ovarian function will lead to Defective folliculogenesis, poor quality of Oocytes and poor fertilization. Oocytes have focal inflammation, Dark central granulation, Spindle abnormalities, Zona hardening and Mitochondrial content. This causes poor embryo quality affecting the results of ART. There is downregulation of HOX 1 gene leading to implantation failure.

Ovarian Reserve:
Presence of endometriomas, especially if bilateral can potentially affect the following:

1. Ovarian Reserve.
2. Ovarian response to gonadotropins during ART.

Kitajima et al's study reported a significant reduction in the primordial follicle cohort in affected ovaries.

Follicle depletion may potentially be secondary to one, or a combination of the following factors:

1. Inflammatory reaction----increased tissue oxidative stress-----FIBROSIS.
2. Free Iron, or other toxic agents diffusible through cyst wall of endometrioma
3. Mechanical stretching of ovarian cortex.
4. Ovarian surgery, especially if repetitive.

Effect of endometriomas on IVF outcome

Review of studies, about the impact of an endometrioma on ovarian response during IVF concludes that the ***evidence is equivocal.***

Systematic reviews of controlled studies report similar ovarian responses to controls with no evidence of endometriosis, and in women with a unilateral ovarian endometrioma compared to contralateral normal ovaries.

In one systematic review, there was a lower ovarian response, with lower number of oocytes retrieved. Mean difference (-0.23, 95% CI 0.37 -0.1) and a higher cancellation rate (OR 2.83; 95% CI 1.32-6.06) in women with an endometrioma, although the total dose of gonadotropins used for stimulation was comparable.

However, the following rates were similar in women with an endometrioma compared to women with no endometrioma.

1. Live birth (OR 0.98; 95% CI 0.71-1.36)
2. Pregnancy Rate (OR 1.17; 95% CI 0.87-1.58)
3. Miscarriage Rate (OR 1.7; 95% CI 0.86 -3.35)

Also, women with peritoneal endometriosis with no endometrioma, when compared to those with an endometrioma, were found to have similar IVF outcome with regards to:-

1. Live birth rate
2. Pregnancy rate
3. Miscarriage rate
4. Cycle cancellation rate
5. Mean Number of oocytes retrieved

Risks of surgery before IVF versus Risks of IVF before surgery Donnez et al (fertility sterility 2018)

Table provided below

S.No	Risks of surgery prior to IVF	Risks of IVF prior to surgery
1.	Depends on surgeon skill	Progression of disease
2.	Costs	Increase in inflammatory reaction
3.	Possible surgical complications	Difficult oocyte retrieval
4.	Impact to ovarian reserve risk of premature ovarian failure	Risk of cycle cancellation
5.	Incomplete surgery and recurrence	Follicular fluid contamination
6.	May delay ART	• Endometrioma infection • Undiagnosed occult malignancy • Risk of rupture with subsequent chemical • Peritonitis • Pregnancy related complications

Risks of surgery before IVF versus Risks of IVF before surgery Donnez et al (fertility sterility 2018)

Surgical Treatment before IVF:

A Cochrane review that incorporates two randomized controlled trials, reports similar pregnancy rates for surgical and expectant management. Here, the surgical management refers to the cystectomy or aspiration. ESHRE guidelines group concluded that a cystectomy for an endometrioma larger than 3cm, prior to an ART can be considered for the management of:

1. Endometriosis – Associated pain
2. Increasing the accessibility of follicles during oocyte retrieval procedures
3. To ameliorate any concern for malignancy

Important clinical recommendations regarding the surgical treatment prior to IVF:

1. Appropriate counselling about following 2 risks:
- Reduced ovarian function following the surgery
- Possible risk of an oophorectomy

2. Various prognostic factors that influence the ART outcome to be taken into consideration while deciding for surgical intervention:

- Age
- Ovarian reserve
- Unilaterality/ bilaterality of disease
- Number and size of cysts
- Symptoms
- Presence or absence of suspicious radiological features
- Extent of extra ovarian disease
- History of previous ovarian surgery
- Postoperative adhesions
- Potential delay of ART
- Importance of histological confirmation
- Cyst complications
- Symptom alleviation can vary to different extents

3. The following group of women may benefit from proceeding directly with IVF, as surgery may reduce the ovarian function and further delay the start of treatment:
- Asymptomatic women
- Women of advanced reproductive age
- Women with reduced ovarian reserve
- Bilateral endometriosis
- History of prior ovarian surgery

4. Surgery may be considered as the first line in the following set of women:
- Highly symptomatic women
- Those with intact ovarian reserve
- Women with unilateral, large cysts
- Cyst with suspicious radiological and clinical features.

5. Reproductive outcomes have not been shown to be improved by the excision of DIE,

6. A direct temporal causal relationship has not been well established between endometriomas and reduced monthly fecundity rates.

7. Management decisions should be based on individual circumstances, such as the patient's choice, age, ovarian reserve and associated symptoms.

8. Endometriosis associated infertility:

Role of Assisted Conception:

1. Minimal to mild endometriosis with patent fallopian tubes, Intrauterine insemination with controlled ovarian stimulation is an effective option and it increases the live birth rate. (Tummon et al 1997 Costello 2001). But the key hazard is multiple pregnancy.

2. IVF/ART is commonly the first line for: -
- Severe endometriosis.
- Associated impaired tubal function
- Advanced female age
- Reduced sperm quality

3. IVF does not appear to increase the risk of recurrence of endometriosis (D'Hooghe et al 2006)

4. In women with endometrioma, clinicians may use antibiotic prophylaxis at the time of the oocyte retrieval although the risk of ovarian abscess following follicle aspiration is low (Benaglia et al 2008)

5. In selected cases, GnRH agonists can be prescribed for 3-6 months prior to treatment with ART, to improve clinical pregnancy rates in infertile women with endometriosis. (Sallam et al 2006)

Key recommendations based on level A or B evidence for the management of women with endometriosis – Scheedorn et al 2016

Section of diagnosis

1. Perform transvaginal sonography to diagnose or exclude an ovarian endometrioma– Moore et al 2002

Section of pain management

2. Use hormonal treatment (OCP/ Progestogens/ anti progestogen) or GnRH agonist as one of the options (Vercellini et al 1993, Brown et al 2010, 2012)

3. Prescribe hormonal add back therapy to coincide with the start of GnRH agonist therapy, to prevent bone loss and hypoestrogenic symptoms. (Makarainer et al 1996, Bergqvist et al 1997, Taskin et al 1997, Moghissi et al 1998)

4. Surgically treat endometriosis when identified at laparoscopy i.e. "See & Treat" as it is effective in reducing endometriosis associated pain (Jacobson et al 2009)

Complementary and Alternative management Strategies for infertility associated with Endometriosis

1. Acupuncture (Gerhard & Postreek, 1992)
2. Antioxidant therapy (Agarwal et all 2005)
3. Chinese herbal medicine (Burks wicks et al, 2009)
4. Manual physical therapy (Wurn et al 2008)

No Evidence was found by ESHRE Guideline group, for the beneficial effects. However, women often use these therapies in an attempt to improve quality of life and to cope with the disease.

Epidemiology Environment BMI Diet Genetic Studies	**Diagnosis** Biomarkers Imaging **Classification & Prognosis** Clinical staging phenotype symptoms **Clinical trials, treatment and outcomes** Multi Centre RCTs outcome measures Pelvic Pain Novel Treatment	**Patho physiology** Immuno-modulators Inflammatory Mediators Stem cells mi RNA and Transgenic models Progestins & SPRMs Ovary and Microbiome

Table: Key sections addressed in defining future direction for endometriosis research

Study	Type of Study	Pregnancy Outcome
Fernando et al 2009	Retrospective	Preterm birth risk increased with OR 1.98, SGA baby risk increased with OR 1.95
Bengalia et al	Retrospective	No associations
Kuvasaari – Pirinen et al 2012	Retrospective	Preterm birth risk increased with OR 3.25
Takemura et al 2013	Retrospective	Placenta previa OR 15.1

Table: Endometriosis and adenomyosis – Pregnancy / Neonatal outcomes:
Risk of miscarriage in women with endometriosis – is not increased.
However, there is controversial evidence due to adenomyosis as a common confounder in many studies (P.Yang, CMa et al (2019 Fertility Sterility), Marta leonardi et al (2016 Fertility Sterility).

Review of literature

1. Mireia – Gonzalez Comadarn et al Reproductive outcomes among women undergoing IVF, diagnosed with endometriosis – associated infertility do not differ significantly from women without the disease. Although women with endometriosis generate fewer oocytes, fertilization rate is not impaired and the likelihood of achieving a live birth is also not affected.
2. Removal of endometriomas before in vitro fertilization does not improve fertility outcomes Case controlled study by Juan A Garcia Velasco et al (Fertility sterility 2004)
3. Endometriosis does not seem to have a negative impact on endometrial receptivity of recipients in donor oocyte IVF cycles.
4. Presence of ovarian endometrioma is associated with a reduced responsiveness to gonadotropins (Edgardo Somigliana et al, Italy) Fertil steril 2006
5. The impact of ovarian cystectomy on ovarian response to stimulation during in Vitro fertilization cycles (G. Nargund et al Human Reproduction)
6. Infertile women with endometrioma larger than 3 cm, there is no evidence that cystectomy prior to treatment with assisted reproductive technologies improves pregnancy rates. Benschop et al 2010, Donnez et al 2001, Hart et al 2018
7. In women with endometrioma larger than 3 cm, it is only recommended to consider cystectomy prior to ART, to improve endometriosis associated pain or the accessibility to follicles.
8. Suppression of ovarian function (by means of danazol, GnRH analogues, and Oral contraceptive pills) to improve fertility in minimal to mild endometriosis is not effective and should not be offered for this indication alone – (Hughes E, Brown J et all)
9. Infertile women with AFS/ASRM stage I/II endometriosis, it is recommended to perform operative laparoscopy including adhesiolysis, rather than performing only diagnostic laparoscopy only, to promote ongoing pregnancy rates.
10. Excision of endometrioma capsule, instead of only drainage & electro coagulation of endometrioma wall, helps to achieve higher spontaneous pregnancy rates (Hart et al 2008)
11. Endometrial Immunostaining for Bcl 6 is correlated with the fertility status. Of those fertile women had low level of Bcl 6. High Bcl 6 immunostaining strongly predicted the presence of endometriosis or occasionally hydrosalpinges. D. Slizewski etal (2015)
12. Second live birth after undergoing ART in women operated on, for endometriosis. (Jeremy Boujenah)Endometriosis fertility index (EFI), as a predictive factor for a spontaneous pregnancy in fertility management. (Fertil Steril-2016)
13. Among frozen cycles, pregnancy outcomes were comparable between women with and without endometriosis. These results suggest that women with endometriosis may benefit from the low levels of hormonal exposure in frozen embryo transfer setting. (Hamdan Metal-2015, Harb HM, Chue tal-2013)
14. The percentage of endometriosis associated ART cycles has decreased overtime. As compared with male factor infertility, endometriosis is associated with increased cancellation and decreased hyperstimulation risks. (Fertil Steril 2015)
15. Population based studies suggest a possible association of endometriosis with preterm birth and placenta previa (Fertil Steril 2015)
16. Effect of Elagolix on endometrium. When Elagolix is used for endometriosis associated pain, it suppressed endometrial proliferation in a dose dependent manner after 6 months treatment.
17. Women affected by endometriosis have an independently elevated risk of placenta previa in pregnancy. (Innie Chen et al) (FertilSteril-2018, 2019)
18. Mitochondrial dysfunction in cumulus cells from subjects undergoing IVF/ICSI with known endometriosis. (Albert L Hsn et al -2015) (Reflected by decreased ATP production)
19. MicroRNAs seem to be involved in peritoneal alterations in endometriosis. They might serve as biomarkers for fertility outcome prediction. Joseph Mari Alexander et al spain; (Fertil Steril-2017)
20. LAROSE, A randomized controlled trial - No difference in outcomes between robotic and conventional laparoscopy for endometriosis. (Enrique soto et al) (Fertil Steril-2017)

21. Role of pioglitazone to reduce TNF a and 1L-6 levels in COS cycles in stage iii/iv endometriosis undergoing ART. (CH Kim et al korea, Fertil Steril- October 2012)
22. should endometriosis be an indication for ICSI in fresh IVF cycles. (J. Lekovich et al NYC)

- To increase higher proportion of normal fertilization,
- Higher number of day 5 transfers,
- Clinical pregnancy rate and d) live birth rate when compared to standard insemination cycles - (Fertil Steril - September 2015)

23. Endometriosis probably has no effect on ART Results after ICSI procedure- K. Sakhel et al 2004)
24. Whole genome sequencing of 137 endometriosis patients with a common ancestor- Gene TNFRSF6B and SEPT10- likely to be responsible
25. Atosiban treatment before embryo transfer in endometriosis is effective in priming of the uterus, suitable for embryo implantation. (Ye He, Huan Wu et al; Fertil Steril-2016)
A recent paper worth a special mention - Gone with the wind -- Paul patriceo , fertility sterility feb 2021

The conclusion described in the above paper is as follows – Outcome of ART cycles are the same as male factor ART patients as long as the euploid embryo is transferred.
To summarize, the following take home messages are crucial
1. Early diagnosis, suppressive therapy
2. Cystectomy, Donnez technique
3. Fertility preservation, Ana coboay FS 2021
4. FET
5. PPOS Progesterone primed ovarian stimulation
6. Outcome of ART cycles are likely to be the same as male factor ART patients as long as the euploid embryo is transferred.

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IVF or ICSI in women with endometriosis
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In Endometriosis
Free Radicals impair fertility as it changes the composition of peritoneal environment

Reproductive BioMedicine Online; www.rbmonline.com/Article/2291,Vol 13. No 1. 2006 126–134, on web 8 May 2006

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Heavy Menstrual Bleeding[1]

- Czech & Poland studies along with two multicenter studies achieved decrease in the intensity and duration of bleeding[1]
- Duration of bleeding was shortened from 5.4 at baseline to 4 days during treatment[2]

Cycle Control[1]

- Evidences have shown good cycle control with DNG/EE[1]
- Spotting and break-through bleeding occurs usually during the 1st administration cycle but the incidence decreases over the course of the treatment[2]

Dysmenorrhea[1,2]

- In a study over 2000 women showed that incidence of dys-menorrhea was reduced from 28.8% before treatment to near 0 in the 6th cycle[1]
- Incidence of dys-menorrhea decreased from 35% to 10% from cycle 3 onwards[2]

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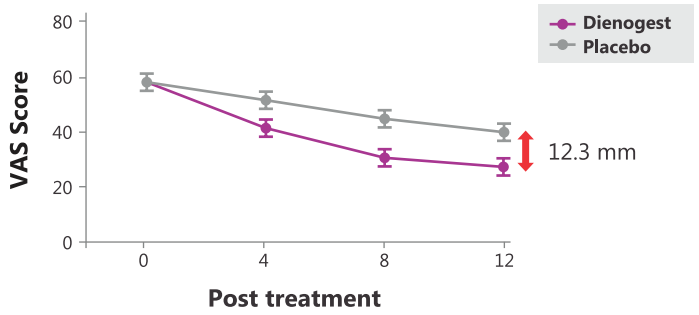
Dienogest at a dose of 2 mg daily for 12 weeks was significantly more effective than placebo for reducing EAPP (endometriosis-associated pelvic pain)

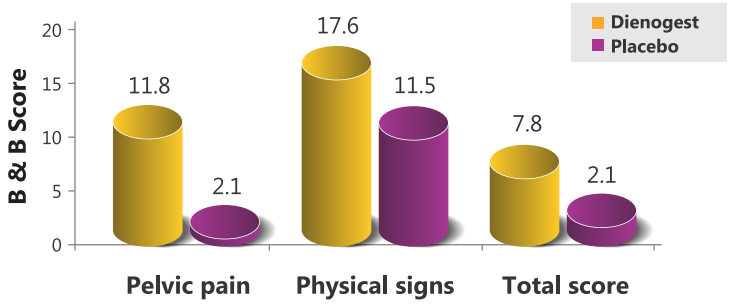
Reduces VAS score:



VAS score significantly lower in dienogest compared to placebo in 12 weeks (difference = 12.3 mm; p<0.0001)

Strowitzki T, et al. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2010; 151: 193-198.

Improvement in B&B score:



% of patients showing NONE category at end of 12 weeks

B&B scale (Biberoglu & Behrman) - for symptoms (pelvic pain, dysmenorrhea & dyspareunia) & signs (pelvic tenderness & induration)

B&B scoring : None, mild, moderate & severe.
VAS score : Where 0 mm represents absence of pain and 100 mm indicates unbearable pain

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Images in Endometriosis

Ultrasonography in Endometriosis

Dr. Chander Lulla
CONSULTANT SONOLOGIST AND FETAL MEDICINE SPECIALIST
Academic Qualifications:MD,DMRD
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Endometriosis is a common, chronic gynecological condition defined as the presence of functional endometrial glands and stroma-like lesions outside the uterus.

It manifests in three ways:

1. Superficial (peritoneal) disease
2. Cystic ovarian disease (endometriomas)
3. Deep infiltrating endometriosis, which is the most complex and surgically challenging form.

Adenomyosis is a manifestation of the same process as endometrioses (in which endometrial tissue is confined to the uterine musculature).
The disease involvement is highly variable, ranging from microscopic endometriotic implants to large cysts (endometriomas) and nodules.

Epidemiology
Young women, with a mean age of 25-29 years , and occasionally adolescent girls. 5% of cases may be diagnosed in postmenopausal women.
Potential risk factors include family history and short menstrual cycles. Racial predisposition is controversial .

In women who underwent laparoscopy for various reasons, the prevalence was as follows:

1. Asymptomatic women (laparoscopy for tubal ligation): 1-7%
2. Primary infertility: 17-50%
3. Pelvic pain: 5-21%

Pathology
The pathogenesis of endometriosis remains unclear; potential mechanisms include:

- **Metastatic theory:** transplantation of endometrial cells (via retrograde menstruation, lymphatic or vascular dissemination, iatrogenic implantation) with probable immune/hormonal/inflammatory mediators ; In support of this theory up to 90% of women have bloody peritoneal fluid during the perimenstrual period.

- **Metaplastic theory:** retroperitoneal deep endometriosis may originate from metaplasia of Müllerian remnants located in the rectovaginal septum

- **Induction theory:** whereby shed endometrium releases substances that induce undifferentiated mesenchyme to form endometriotic tissue.

Location: Common by frequency are

1. Ovaries
2. Pelvic peritoneum.
3. Less common locations include C-section scars (scar Endometriosis), deep subperitoneal tissues, GI tract, ,Bladder chest, and subcutaneous tissues.

The most common pelvic sites of involvement are the Pouch of Douglas, Uterosacral Ligament and Torus Uterinus.

Deep pelvic endometriosis is divided into:

1. anterior cul-de-sac
- Detrusor muscle of the Urinary bladder
- Vesicovaginal septal involvement

2. posterior cul-de-sac
- retroperitoneal lesions and dependent intraperitoneal locations that may result in infiltrating lesions
- adhesions between the anterior rectal wall and posterior vaginal fornix
- rectovaginal septal involvement

3. pelvic sidewall
- including ureteral lesions

4. gastrointestinal tract
- rarely proximal to the terminal ileum , Usually Rectosigmoid. Appendix, Cecum, Terminal Illeum

5. urinary tract
- bladder > distal Ureter

Extra-abdominal locations include:

1. chest
- uncommon
- almost exclusively right-sided
- usually in the setting of long-standing (>5 years) pelvic endometriosis

2. cutaneous disease
- scars (scar Endometrioses)
- abdominal wall and recesses (e.g. / umbilical region – umbilical endometrioses/Inguinal hernias)
- cervix: associated with cone biopsy
- labia/ Vulva (via the round ligament)
- Canal of Nuck
- inguinal region

Imaging features

Although laparoscopy continues to be the gold standard for the diagnosis of endometriosis, both ultrasound and MRI are increasingly being used, especially to evaluate deep disease. MRI has high sensitivity (90%) and specificity (91%) . Ultrasound has been shown to have sensitivities and specificity above 90% for deep endometriosis, depending on location 31.

Ultrasound

Transabdominal ultrasound has classically been described as a very limited technique for assessing endometriosis beyond the detection of ovarian endometriomas.
Transvaginal ultrasound is the preferred method of examination unless declined by the patient.
It is however not able to reliably detect superficial disease. It has been shown to have sensitivity over 90% 31 in detecting deep infiltrating endometriosis (DIE) when extended beyond imaging the uterus and ovaries and to include an assessment of the anterior and posterior compartments.

If DIE is found the kidneys need to be assessed for Hydronephrosis Soft Markers: Transvaginal ultrasound can dynamically assess mobility and site-specific tenderness, known as 'soft markers' for endometriosis, suggestive of superficial disease and pelvic adhesions 32. The loss of the Sliding sign on transvaginal ultrasound assessment indicates obliteration of the POD , which is important for surgical planning.
Nodules of endometriosis tend to appear sonographically as solid, hypoechoic, irregular masses. They may show little or no blood flow on color Doppler.

In 2016, the consensus opinion from the International Deep Endometriosis Analysis (IDEA) group 32 was published, which clearly and systematically identifies the features of endometriosis by ultrasound:

Uterus: anteverted-retroflexed uterus ('s sign', or 'question mark sign') is seen with severe posterior compartment DIE and adenomyosis (Fig.1)

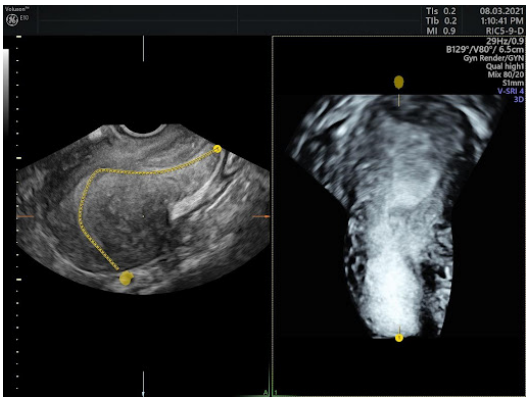


Fig. 1: Uterus: anteverted-retroflexed uterus ('s sign', or 'question mark sign') is seen with severe posterior compartment DIE and adenomyosis

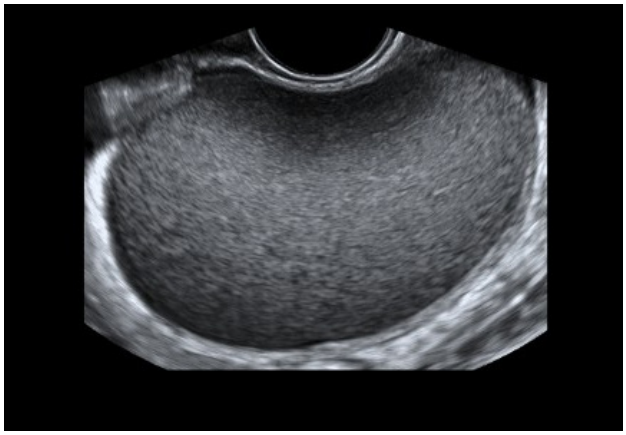


Fig. 2: Ovarian endometriomas
Typical : Unilocular cystic lesions containing uniform low-level echoes (ground glass appearance)

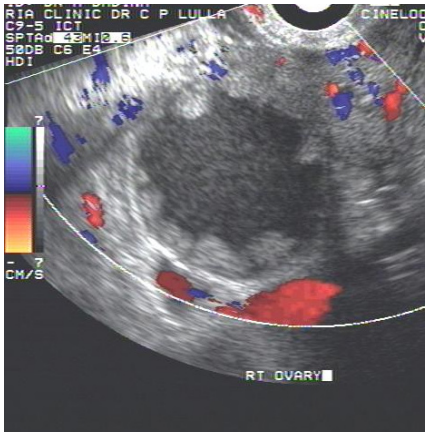


Fig. 3: No blood flow on color Doppler (color score 1)

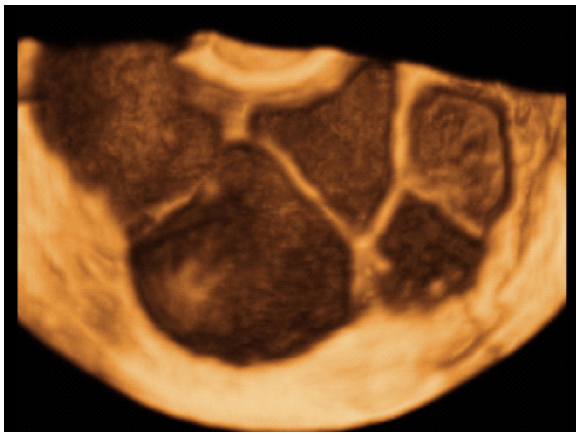


Fig. 4: Cysts maybe single or multiple

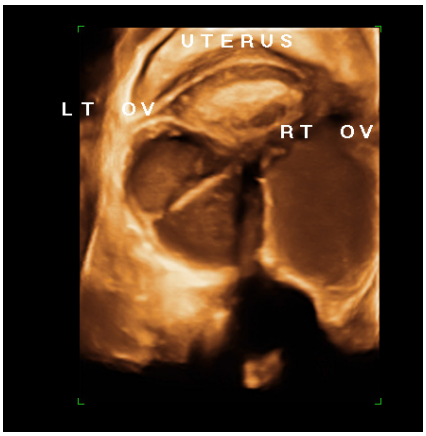
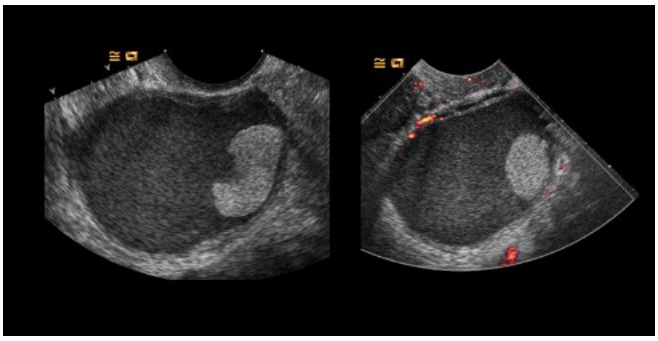
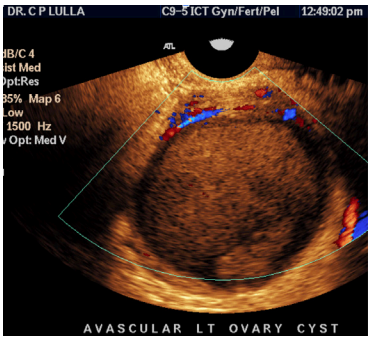


Fig. 5: 'kissing' ovaries sign describes ovaries that are adherent to one another posterior to the uterus and is frequently seen with bilateral endometriomas.

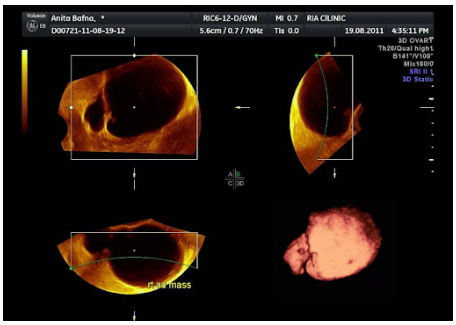
Atypical appearances: multiple locations and papillary projection





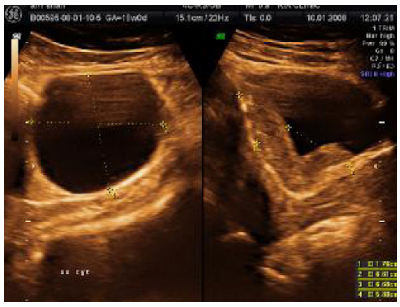
Endometriomas may undergo alteration(decidualization) in pregnancy and can be confused with an ovarian neoplasia

Fallopian tubes: may show hydrosalpinx

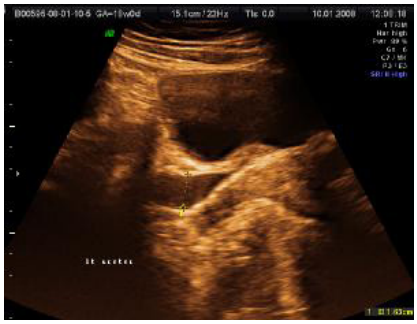


Urinary bladder

- DIE occurs more frequently in the bladder base and bladder dome
- Involvement can be varied, including hypoechoic linear or spherical lesions, with or without regular contours involving the muscularis (most common) or (sub)mucosa of the bladder

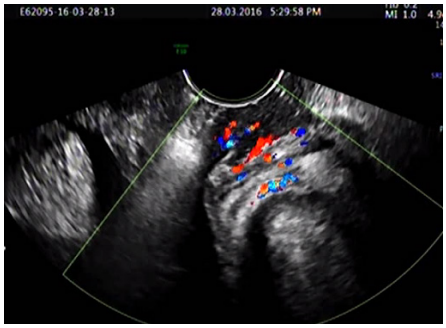


Ureters: may appear dilated with DIE and this can best be seen with transvaginal ultrasound. Dilatation of the ureter caused by endometriosis is due to a stricture (from either extrinsic compression or intrinsic infiltration)



Rectovaginal septum

- DIE nodule on transvaginal ultrasound in the rectovaginal space below the lower border of the posterior lip of the cervix
- DIE in the rectovaginal septum is very rare

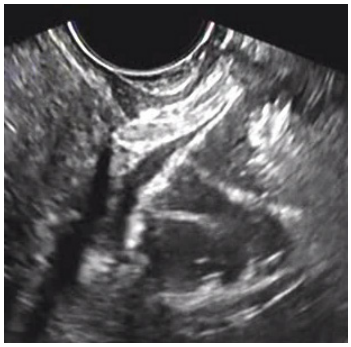


Posterior vaginal wall/ posterior vaginal fornix

- Thickening of the vaginal wall
- Discrete hypoechoic nodule in the vaginal wall which may be homogeneous or inhomogeneous, with or without large cystic areas

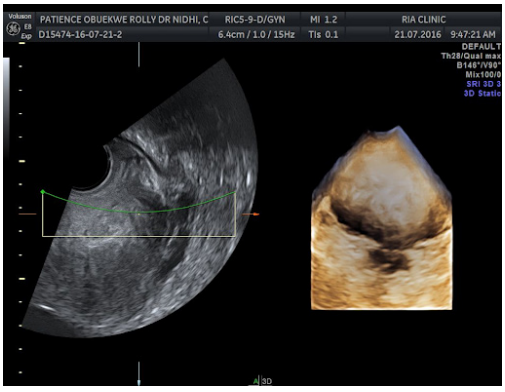
Uterosacral ligaments

- Regular or irregular hypoechoic nodules are seen within the peritoneal fat surrounding the uterosacral ligament. The lesion may be isolated or may be part of a larger nodule extending into the vagina or into other surrounding structures
- Thickening of the white line of the uterosacral ligaments (>5.8mm) has been shown to have a strong association with endometriosis



Rectosigmoid colon: Nodules can be single or multifocal and hypoechoic. A second rectal lesions has been demonstrated to occur in 54.6% of cases. They cause Retraction and adhesion of the bowel wall , resulting in the so-called 'Indian headdress' or 'moose antler' sign

Pouch of Douglas: The pouch of Douglas is considered obliterated if the sliding sign is negative (ie. if the rectum and uterus do not slide apart). Obliteration can be partial or complete (Frozen Pelvis)



Ureterovesical region

- can be obliterated due to adhesions. Should be assessed with the sliding sign (like the pouch of Douglas)
- up to 1/3 of women with a previous caesarean section will have adhesions in this region

Occasionally acute hemorrhage may be seen in endometriomas (<10%), such as layering blood products or a retractile thrombus . Unlike many other ovarian cysts , endometriomas do not commonly resolve over time

Contrast-enhanced ultrasound (CEUS)

Ultrasound contrast agents (sulphur hexafluoride microbubbles) are purely intravascular (unlike iodine or gadolinium-based contrasts, which have an interstitial phase), so an enhancing lesion in the CEUS reflects a vascularized lesion. Thus, the fibrotic and haemorhhagic areas will not present contrast enhancement. Endometriotic implants present a variable contrast enhancement and can appear as lesions with homogeneous or heterogeneous enhancement with a non-enhanced center, depending on the associated fibrotic/ haemorhhagic component.

The use of CEUS in deep pelvic endometriosis can be useful to define the extension and morphology of the implant, assess the preservation of structure of the intestinal wall (differentiating it from intestinal neoplasia), and to assess an extraurinary origin in cases of ureteric involvement (differentiating it from urothelial neoplasia)

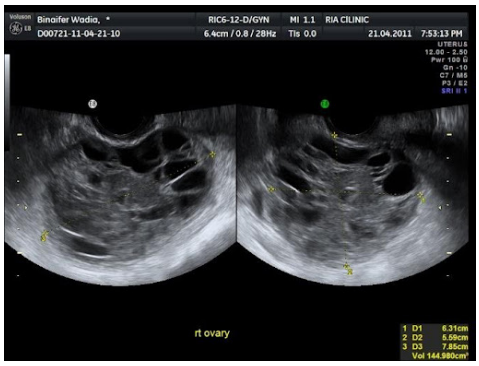
Complications

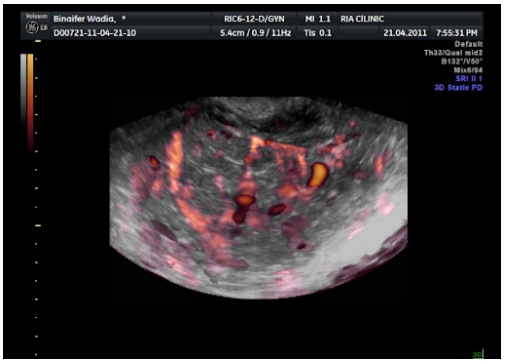
Malignant transformation of an endometrioma has been documented, but is rare, occurring in <1% of cases. . Thus, annual ultrasound examinations of endometriomas have been advocated . One needs to look for atypical findings and increased vascularity(-color score 3-4) as seen in images below.

Differential diagnosis

Differential considerations for endometriomas include:

- Dermoid cysts
- Hemorrhagic ovarian cysts:
- Mucinous lesions: e.g. ovarian mucinous tumors





Journal Scan

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FIRST ARTICLE

Endometriosis and the Coronavirus (COVID-19) Pandemic: Clinical Advice and Future Considerations.

Leonardi, Mathew, et al. "Endometriosis and the Coronavirus (COVID-19) Pandemic: Clinical Advice and Future Considerations." *Frontiers in Reproductive Health 2 (2020): 5.*

ABSTRACT

Endometriosis is an inflammatory disease with endometrium like tissue outside the uterine cavity. It causes pain and infertility. During the Covid - 19, pandemic times, health centers were temporarily closed down for outpatient facilities, diagnostic imaging centers did not function, elective surgeries were cancelled and fertility treatments were postponed. This created an insecurity and built more anxiety and stress among women with symptomatic endometriosis. Health care providers were on the lookout for improved facility with recommended restrictions due to Covid-19 to contact the patients.

Effect of endometriosis on Covid-19:

There is no evidence to say, women with endometriosis are at increased risk for Covid-19. But those with thoracic endometriosis had a severe Covid-19 disease.

Effect of Covid-19 on endometriosis:

Though Covid- 19 directly does not hasten the progression or development of endometriosis, delay in diagnosis and management of endometriosis due to suspension of many facilities in the health care sectors were common.

Management of endometriosis during Covid -19 pandemic:

1. Tele consultations were instituted to help people who needed assessment of the disease. As diagnostic modalities like Imaging and Laparoscopy were unavailable, clinical diagnosis was accepted.
2. Those who had been diagnosed with endometriosis and on treatment were called for discussion. Those comfortable with their present treatment were encouraged to continue the same. On the other hand, who were not relieved of symptoms, were called for further evaluation.
3. Diagnostic modalities like imaging were offered only when it was safe to do so.
4. Laparoscopy – was deferred until it was absolutely required to surgically treat the disease.

Parallelly, all patients on NSAIDs were allowed to continue the same, despite Covid – 19 pandemic. Multidisciplinary management of endometriosis was continued focusing on their problems, modifications of their routine and emotional support were offered through tele consultation. Acute exacerbations of pain warranting emergency medical attention, were advised to reach the hospital during emergency situations.

Resuming – pre-pandemic regular care

Though endometriosis is a non-malignant disease, it needs to be treated with priority. It has a huge impact on quality of life. So once we resume regular care, previously cancelled surgeries should be scheduled first.

Appropriate preoperative Covid – 19 testing is important. Minimal invasive surgical approach should be followed, as it reduces blood loss, post-operative pain and minimizes the hospital stay. Attention should be to minimize the use of electrocautery as aerosolization of virus can occur.

Reviewer's View

Endometriosis has an impact on the quality of life. Covid – 19 did cause a huge stress and apprehension to the women who were diagnosed with endometriosis. Different treatment plans like surgical management / ART were delayed for them. Wherever possible with the new avenue of tele consultations many were offered the treatment they required. Surgical procedures were taken up, when there was an acute illness with necessary precautions. Of course the incidence of the disease did not increase or those with the disease were more affected with Covid – 19.

SECOND ARTICLE

Is There a Role of 25-Hydroxy Vitamin D in the Pathogenesis of Mild and Moderate-to-Severe Endometriosis?

Tuten N, Acikgoz S, Mammadov Z, Malik E, Tuten A, Guralp O. Is There a Role of 25-Hydroxy Vitamin D in the Pathogenesis of Mild and Moderate-to-Severe Endometriosis?. Gynecol Obstet Reprod Med [Internet]. 2021Aug.2 [cited 2021Nov.9];27(2):132-7. Available from: https://gorm.com.tr/index.php/GORM/article/view/949

ABSTRACT

Endometriosis causes pelvic pain and infertility and affects 10% of women of reproductive age group. It mimics autoimmune disease and malignancy which has aberrations in lymphocyte activity, neo-angiogenesis and invasion. Recent studies have shown inflammatory, immunological, genetic and environmental factors play a role in pathogenesis of endometriosis.

Malfunction of the immune system can lead to chronic inflammation causing endometriosis. There is reduction of T-cell cytotoxicity, functional inadequacy of natural killer (NK) cells and activated macrophages in peritoneal fluid, which triggers cytokines and angiogenic factors.

There has been an association between vitamin D and PCOS, cancer breast and cancer ovary. Vitamin D plays a role in regulation of normal cell growth and immune regulatory effects upon chronic inflammatory responses. It increases anti-inflammatory cytokines and reduces pro-inflammatory cytokines. It also induces apoptosis and suppresses neo-angiogenesis.

AIMS AND OBJECTIVES

This study evaluates the association between serum 25 hydroxy vitamin D (25-OH-D) levels, clinical and laboratory parameters in endometriosis. 53 women with endometriosis and 37 women without endometriosis as control group were included in this study between May 2012 to July 2013 from Istanbul university, Cerrahpasa School of Medicine hospital. Informed consent and ethical committee approval were obtained.

Inclusion criteria were women between 15-40 years with histologically proven endometriosis.

Exclusion criteria included recent vitamin D intake (within last 6 months), current use of UV tanning lamps, systemic diseases, known malignancy, menopause, HRT and COCs.

Control group included proven non endometriosis patients through laparoscopy. Indications for laparoscopy included ovarian cyst, infertility, chronic pelvic pain of menstrual and non-menstrual origin. Age, BMI, obstetric history, VAS score for chronic pelvic pain and dysmenorrhoea were noted (0 – 10 score was noted).

Questionaries regarding sun exposure in the past and present were documented. r-ASRM classification was used to evaluate the severity of endometriosis (stage 1 and 2) were graded as mild, (n=28) and (stage 3&4) were graded as moderate / severe) (n=25). Serum was obtained prior to surgery and C-reactive protein, WBC, CA 125, parathormone, calcium, phosphorous, and 25-OH-D were measured. Chemiluminescence immunoassay was done to estimate 25-OH-D level and parathormone and CA 125 were measured with electro chemiluminescence technique.

RESULTS

Statistical analysis was done by SPSS software version 18.0. Students' t test or ANOVA and Pearson correlation test were used to evaluate the possible correlation. P value of < 0.05 was accepted as statistically significant.

No difference was seen among clinical, demographic and obstetric parameters in both groups. Dysmenorrhoea was higher in the endometriosis group (p=0.003) C-reactive protein and WBC were comparable in both groups.

Serum CA 125 was elevated in women with endometriosis compared to controls (p=0.001). 25-OH-D was decreased in mild, moderate and severe endometriosis compared to the control group(p=0.001). There was no significant difference in mild, moderate and severe endometriosis.

Study group had unilateral or bilateral endometrioma, Douglas pouch obliteration, peritoneal and deep infiltrating endometriosis. Women with bilateral endometrioma had decreased 25-OH-D than unilateral endometrioma. Serum 25-OH-D had no correlation with infertility, DIE, POD obliteration, dysmenorrhoea and VAS score. Serum 25-OH-D was reduced in all stages of endometriosis compared to the control group. There was no difference between stage I and II Vs Stage III and IV. Increased milk consumption and higher 1, 25-OH-D vitamin 3 levels were associated with reduction in endometriosis risk.

Polymorphism in VDBP (GC2) is seen in endometriosis patients, which leads to inadequate phagocytosis of macrophages. VDR and 1 α hydroxy less expression was higher in healthy tissue. Contradictory findings were reported by Somigliana. Bugglio et al reported 25-OH-D3 levels were comparable in both groups. Miyashita's study suggested vitamin D level was dependent on severity of endometriosis which was not so in this study. A possible hypothesis is consumption of vitamin D by endometriosis or endometrioma as metabolism is active in the reproductive tract.

Vitamin D is an anti-inflammatory agent and tries to reduce inflammation in the endometriosis and endometrioma. Ciavattini found a linear correlation between 25-OH-D3 and diameter of endometrioma. In this study bilateral endometrioma patients had much lower 25-OH-D3 than in unilateral endometrioma. Since endometrioma has more endometriotic foci than superficial or DIE, the levels are lower in the endometrioma group. Considering various factors like vitamin D, receptor status, gene polymorphism and immunological status which will influence endometriosis, no single mechanism can explain the effects of vitamin D and endometriosis.

CONCLUSION

25-OH-D levels are reduced in all stages of endometriosis compared to healthy women. No difference between stage I and II Vs Stage III and IV. For 25-OH-D had no correlation with infertility, DIE or POD obliteration. Women with bilateral endometrioma had lower levels of 25-OH-D than unilateral endometrioma. 25-OH-D in women with or without dysmenorrhoea were not different from each other in endometriosis or non- endometriosis sub groups. 25-OH-D levels had no correlation with dysmenorrhoea – VAS score.

REVIEWER'S COMMENTS

Endometriosis mimics auto-immune disease and malignancy. Recent studies have shown inflammatory, immunological, genetic and environmental factors play a role in pathogenesis of endometriosis. Chronic inflammation causes endometriosis and there is reduction of T-cell cytotoxicity, functional in-adequacy of natural killer (NK) cells and activated macrophages in the peritoneal fluid, which triggers cytokines and angiogenic factors.

Vitamin D plays a role in regulation of normal cell growth and immune regulatory effects upon chronic inflammatory responses which increases anti-inflammatory cytokines and reduces proinflammatory cytokines. 25-OH-D3 was decreased in all stages of endometriosis compared to the control group. Vitamin D3 level was decreased in bilateral endometrioma than unilateral endometrioma.

A possible hypothesis of lower vitamin D3 level is due to active metabolism in the reproductive tract. Vitamin D3 is an anti-inflammatory agent and tries to reduce the inflammation in endometriosis. Considering various factors like vitamin D, receptor status, gene polymorphism and immunological status which will influence endometriosis. No single mechanism can explain the effects of vitamin D and endometriosis.

Tips for Practice
When & How to use Dienogest?

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1. Patient selection

A) Endometriosis associated pelvic pain:

Effective in reducing pelvic pain associated with endometriosis when used continuously for one year and the effect is persistent (1) for at least 24 weeks after cessation of treatment. The reduction in pelvic pain while using dienogest is superior to placebo management and is equally effective to leuprolide acetate 3.75 mg given every four weeks or intranasal buserelin acetate 900 mg/day when used for 24 weeks. Postoperative administration of dienogest shows a significant reduction in pelvic pain than the expectant management upto 24 months of follow-up and is as effective as GnRha.(2) Dienogest plus estradiol valerate is found to be more effective than levonorgestrel-releasing intrauterine device in reducing pelvic pain after surgery for endometriosis.(3)

Practice tip: Dienogest is very effective in reducing pelvic pain both preoperatively and postoperatively when given for at least 24 weeks.

B) Ovarian Endometriomas:

Effective reduction in size of endometrioma (upto 30%) when dienogest was used for 12 months both as primary treatment as well as in recurrent endometrioma.

C) Deep infltrating endometriosis (DIE):

Dienogest can be used as primary therapy for pain secondary to DIE. It is as effective as surgical treatment in relieving pain in more than 90% of women with DIE at one year follow-up and when given for 12 months was effective to control pain even without surgically reducing the lesions. Postoperative administration of dienogest significantly reduced the endometriosis-related pain in patients with DIE.(4)

Practice tip: Dienogest is effective in relieving pain in patients with DIE even without surgical management.

D) Extragenital Endometriosis:

Dienogest proved to reduce the size of the lesion and pain relief in patients with colon endometriosis over 6 months treatment and in bladder endometriosis over 12 months.(5)

Practice tip: Dienogest has proven efficacy in treating extragenital endometriosis.

E) Scar Endometriosis:

Smaller lesions may respond to dienogest. It can reduce the symptoms but not the size of the lesion. Dienogest may help to prevent the recurrence of lesions and also improves the Quality of life of the patient.

2. In patient's looking for fertility- Where does it feature?

On dienogest there is complete ovulation inhibition at a daily dose of 2 mg but ovarian activity resumes rapidly (range 1–43 days) after cessation of dienogest. Return of fertility is seen on an average of 30 days after cessation including cases of successful pregnancies in the duration upto 1 years after stopping therapy.

Precycle medical intervention with dienogest was beneficial in women with ovarian forms of endometriosis undergoing IVF.(6) Dienogest pre-treatment led to 2.5 times higher clinical pregnancy rate and three times higher delivery rate compared to GnRha.

Practice tip: Dienogest is effective and safe for women on treatment for infertility and planning for IVF compared to GnRha.

3. Is it safe for adolescents- Recommendation for this age group?

A 52 week multicentre study was done involving 6 European countries, VISADO study : The VISanne Study to Assess Safety in ADOlescents)(7), in which Dienogest 2 mg was given daily in the Treatment of Adolescents with Clinically Suspected Endometriosis. They concluded that 2 mg dienogest once daily for 52 weeks was associated with a decrease in lumbar spine BMD, followed by partial recovery after treatment discontinuation.

Practice tip: As bone accreditation is critical in adolescents, dienogest 2 mg tailored treatment can be given in adolescents if benefits outweigh the risks.

4. What dose and duration can be safely used?

Dienogest 2 mg showed significant reduction in VAS score for pelvic pain when given upto 52 weeks and Dienogest 2 mg for 12 months showed reduction in nodule size. Dienogest 1 mg, is associated with irregular vaginal bleeding that led to discontinuation. In both 2- and 4-mg groups, statistically significant and equivalent reduction in clinical symptoms (dyspareunia, pelvic pain, dysmenorrhea) with remarkable improvement in quality of life and revised ASRM score was seen. Both 2 and 4 mg were associated with irregular vaginal bleeding, which improved over time.
Lowest effective dose is 2 mg/d.
When compared to Triptorelin 3.75 mg given i.m., hot flushes were more with triptorelin and when compared with NETA 2.5mg/day, side effects at high with NETA than Dienogest: weight gain (32% vs. 16%), spotting (22% vs. 13%), and decreased libido (14% vs. 9%).
There was a greater loss in BMD with Leuprolide acetate 3.75mg/month and Buserelin acetate 900mg/day intranasally than with Dienogest. (8)

Practice tip: A dose of 2 mg once daily is recommended upto 52 weeks with a beneficial profile and lesser side effects.

5. How to monitor while on Dienogest?

- Do not give Dienogest if there is:
- Undiagnosed vaginal bleeding
- Pregnancy and lactation
- Active thromboembolic disorder
- History of cardiovascular disease
- Diabetes
- Severe hepatic disease
- History of liver tumors or sex hormone dependant malinancies

Immediately stop continuation of Dienogest if a patient develops cholestatic jaundice or pruritus. There are no clear trials if Dienogest affected Bone Mineral Density, so consider monitoring BMD, if the treatment continues past 6 months.

As dienogest is completely metabolized mainly by cytochrome P450(CYP) 3A4, the inducers of this cytochrome like rifampicin and St John's-wort can decrease its plasma concentration and inhibitors like fluoxetine, ketoconazole or erythromycin can increase dienogest concentration. Like with the contraceptive pill, vomiting and diarrhoea can reduce the efficacy of dienogest.

Dienogest is recommended to be started on day1 of the menstrual cycle and is to be taken every day without interruption. If a tablet is missed, the next one is to be taken as soon as possible and to be continued as normal from the next day.(9)

6. What side effects to expect and how to manage?

Dienogest being a newer generation progesterone tends to have greater specificity in binding to progesterone receptors. The side effects associated with dienogest are due to potent progestogenic effects related to the high circulating levels of the unbound molecule, such as weight gain, increased blood pressure, breast tenderness, and nausea. It produces no androgenic side effects and has little effect on metabolic and lipid parameters.

In one observational study, all patients treated with dienogest experienced some side effects, such as vaginal bleeding, headache, constipation, nausea, and hot flashes, headache, pain in the back, and tenderness in the breast.

Most of the symptoms can be treated symptomatically, but severe symptoms should be kept in mind if the patient presents with leg pain, Any unusual sudden cough, breathlessness, etc. A regimen which includes initiation of treatment with a gonadotropin-releasing hormone followed by long-term dienogest therapy may reduce initial irregular bleeding.

Also, initiation of dienogest 2 mg at the onset of menses may also decrease initial bleeding. Bleeding that occurs with long-term treatment is typically spotting. If endometrium thickness is low on ultrasonography, management can include a break in the treatment for 5–7 days allowing recovery of the atrophied endometrium, or a short-term application of 1 mg oral or transdermal estradiol (5–7 days) can be done.

The occurrence of persistent abnormal uterine bleeding may require further investigation, such as ultrasound examination.(10)

7. What counselling should be done before starting the therapy?

Before initiating the treatment, patients should be counseled on what to expect when on treatment with dienogest. Women should be reassured and counselled that bleeding with dienogest 2 mg is not a sign of a lack of efficacy of the drug or recurrence of disease. Two patterns of bleeding irregularities may occur due to dienogest 2 mg treatment: initial abnormal uterine bleeding during the first few months which typically lasts for 8-10 days, and bleeding/spotting with longer-term use.

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Update

Stimulation Protocols in Endometriosis

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Endometriosis is a progressive disease with 20-40% incidence. The estimated overall prevalence of endometriosis in population-based studies varies from 0.8% to 6% (1–3); however, in subfertile women the prevalence seems to be considerably higher, ranging from 20% to 50%, but with significant variation over time periods and the age of patients (4,5).

In a large cohort study on women of reproductive age, the risk of infertility was increased two-fold in women <35 years with endometriosis compared with women without endometriosis (6). Endometriosis is therefore a frequent cause of infertility, either by itself or in conjunction with other fertility-reducing factors.

Endometriosis with infertility is thought to be multifactorial and impairs fertility directly by destroying the normal anatomy of the fallopian tube and ovary or indirectly through inflammatory reaction and oxidative damage to degrade the quality of oocytes.
In endometriosis, intrauterine insemination (IUI) is best suited for patients with Grade I & grade II endometriosis. The outcomes are better when IUI is combined with ovarian stimulation with Letrozole, Clomiphene citrate or Gonadotropins. Best results are when controlled ovarian stimulation with Gonadotropins, triggering with HCG along with monitoring is performed after conservative surgery or medical treatment (5).

When the above approaches fail, in vitro fertilization (IVF) offers an alternative treatment and it may also enhance reproductive outcome by removing gametes and zygotes from an immunologically hostile peritoneal environment (15,16) for these patients (6–14). With the development of assisted reproductive technology, IVF-ET has gradually become an important treatment for patients with infertility from endometriosis.

Pituitary down-regulation is a key link in the IVF-ET process. Gonadotropin-releasing hormone agonist (GnRH-a) can play a competitive role in the pituitary gland and block its release of GnRH, thereby inhibiting the secretion of related hormones in the ovary and achieving the effect of pituitary down-regulation.

In addition, GnRH-a can effectively prevent premature luteinization of follicles and improve the synchronization of follicular growth and development [7]. Furthermore, it can reduce the degree of inflammatory reaction, improve the pelvic microenvironment, and obtain high-quality eggs and embryos.
Infertile women with endometriosis had substantially lower success with IVF compared with tubal factor infertility, including lower ovarian response, reduced implantation rate and pregnancy rate. In addition, a more advanced disease is related to an increasingly inferior outcome. The patients of endometriosis are poor responders to gonadotropin stimulation. The stimulation protocols need to be optimally planned to achieve good pregnancy rates.

The controlled ovarian stimulation in these cases is done in an extremely judicious manner and the best option would be to perform tailor made stimulation or individualized stimulation protocol (17).

In two more recent meta-analyses on outcome of IVF in endometriosis, live birth rate was found to be similar in minimal/mild endometriosis and other indications for IVF, whereas in patients with moderate/severe endometriosis, the results were inferior, including fewer oocytes retrieved, lower implantation rate, and lower birth rate.

In vitro fertilization is performed using GnRh analogues, agonists or antagonists. It's observed that the average number of oocytes retrieved was higher in the agonist group compared to the antagonist group; there is a higher pregnancy rate and number of embryos in the antagonist group compared to the agonist group in the low AMH group. IVF gives encouraging results in endometriosis and is one of the best options for infertility, in selected cases. Several studies on use of GnRH agonists in IVF shows that with pretreatment of GnRH agonists for 3 to 6 months, the rate of implantation was high compared to the group without down regulation. (13).

A retrospective analysis showed a tendency for a higher cumulative conception rate in patients with endometriosis treated with a long GnRH agonist protocol and gonadotropins as compared to patients with endometriosis treated with gonadotropins and/or clomiphene citrate (CC) without downregulation .(19,20)

Types of protocol:
Agonist protocol:
Ultra Short Protocol: In the short protocol, GnRH analog is commenced in the early follicular phase, usually on day 2 of the cycle, followed by gonadotropins 1 day later. In the ultrashort agonist protocol the agonist is administered on days 2, 3 and 4 and gonadotropins are given from day 3 of the cycle until the day of hCG administration (18).

Long Protocol:
The "long protocol" used to be the most commonly used IVF protocol .It provides same success rates with low rich of ovarian hyperstimulation (OHSS) and also less use of gonadotrophins.
In this protocol, prolong down regulation is achieved using GnRH agonist depot prior to stimulation. Prolonged use of GnRH agonists in women with endometriosis aims at inactivating or neutralizing the endometriotic activity present, as GnRH agonists are known to interfere with paracrine and endocrine factors involved in endometriosis (21).

In theory, women with endometriosis following prolonged downregulation with GnRH agonists are probably starting an IVF cycle with the disease under control and perhaps with an increased chance of pregnancy (22). Both retrospective and prospective studies have examined the value of prolonged downregulation in patients with endometriosis undergoing IVF stage III or IV endometriosis undergoing IVF, following a 6-month period of hormonal suppression with a GnRH agonist. No pregnancies were achieved previously in these patients after IVF without the use of prolonged downregulation.

Modified super long down regulation protocol:
OCPs are started from 2 to 5 of the previous cycle for 21 successive days.
The downregulation is achieved by administration with long-acting agonist depot 1.5 to 1.875 mg on days 14 to 19 after OCP. This procedure was repeated after 4 weeks till E2 <30 pg/mL and LH levels <2 mIU/mL.
On days 14 to 20 after pituitary-ovarian suppression, hMG was injected at a daily dose of 112.5 to 375 U until the day of hCG administration.

Super-long down regulation protocol:
Long acting agonist depot at a dose of 2.5 to 3.75 mg is administered on days 2 to 5 of the cycle. This is followed after 4 weeks by IM of FSH /HMG at a daily dose of 150 to 300 IU until the day of hCG.

Antagonist protocol:
In this protocol, GnRH agonists for 3 to 6 months are given to patients before starting the IVF. On the 2nd day of menses, FSH/HMG is started based on the age, BMI, AMH & AFC of the patient and is individualized. From day 7th or follicle size reaches 12-14 mm, antagonist 0.35 mg is started till the date of HCG along with FSH/HMG.

Conclusion:

In conclusion, despite less well ovarian response, reduced embryo quality, and impaired implantation in moderate/severe cases, endometriosis patients obtained comparable IVF/ICSI success to patients with tubal factors infertility. Combination effect of aggressive COH, appropriate pituitary suppression, and efficient surgery before IVF seemed to be crucial in IVF/ICSI success of patients with endometriosis. Therefore, IVF/ICSI can be considered as an effective approach for managing endometriosis-associated infertility. Individual patient factors play the most crucial role in the final outcome. Treatment choice depends upon the patient's age, duration of infertility, disease level of progression and wish for childbearing.

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Video Corner

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