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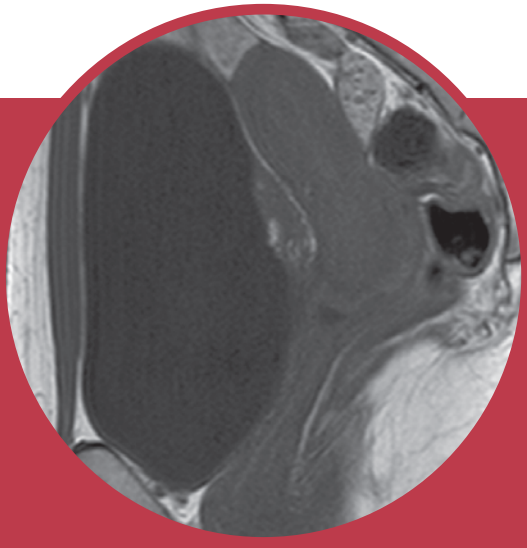
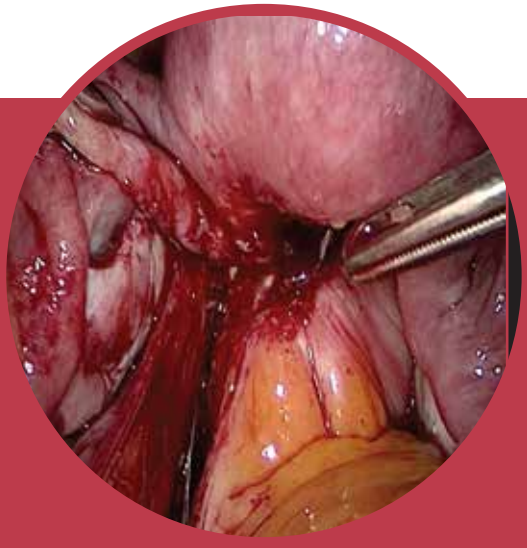
ENDOMETRIOSIS





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Dear FOGSIans

Greeting for the new year, wishing you all a very prosperous, friendly and academic FOGSI year.

This year theme is HER (Health, Empowerment and Respect) with QED (Quality, Ethics and Dignity). I urge and request all of you to work for women health, empowerment and respect with quality ethics and dignity.

FOGSI FOCUS are a wonderful tool of FOGSI to bring to you all academic evidences about one topic.

We start the year with this FOGSI FOUCS on Endometriosis, the current burning number are problem of girls and women a debilitating disease in which diagnosis, investigations and treatment options are confusing in words of Sir William Osler.

"He who understands endometriosis
Understands gynaecology."

Happy reading.

Do give your feedback to improve in future.

Preface

The greatest evil of mankind is the physical pain.

–Saint Augustine

Endometriosis is a highly frustrating and enigmatic disease, which can be a cause of significant pain and morbidity amongst women. It is a progressive, chronic disease, with an estimated 176 million women worldwide suffering from the condition every year. In this book, we have tried to compile the most up-to-date knowledge regarding endometriosis. This is an exclusive book that reviews the whole topic of endometriosis starting from its introduction to the management, along with the discussion of new medical options and future trends in the disease area. Divided into 4 sections and 13 chapters, the book offers detailed discussion on topics like endometriosis in fertility, endometriosis and ART and implantation in endometriosis. Relationship between endometriosis and fertility has been covered in a separate section, this being a common cause of infertility amongst women. Moreover, there is a special chapter on drug therapy in relation to endometriosis versus that in cases of fibroids, imparting a unique touch to this book.

Altogether this book would provide the readers with a detailed and complete explanation of the disease, which would enable the doctors and specialists not only to understand the disease in a better way, but also to manage the condition efficiently in their patients.

Writing a book is a colossal task. It can never be completed without Divine intervention and approval. Therefore, we have decided to end this preface with a small prayer of thanks to the Almighty.

"Father, lead me day by day, ever in thy own sweet way. Teach me to be pure and good and tell me what I ought to do."

—Amen

Simultaneously, we would like to extend our thanks and appreciation to all the related authors and publishers whose references have been used in this book. Book creation is teamwork and we acknowledge the way the entire staff of M/s Jaypee Brothers Medical Publishers (P) Ltd., New Delhi, India, worked hard on this manuscript to give it a final shape. We would especially like to thank Shri Jitendar P Vij (Group Chairman) and Mr Ankit Vij (Group President). Simultaneously we would like to acknowledge the help of various doctors and content strategists (Dr Arun Bhatia, Kanav Midha, Mampi Debnath and Shallu Mann) who helped in the necessary research and development of the manuscript within a short span of time. We believe that writing a book involves a continuous learning process. Though extreme care has been taken to maintain the accuracy while writing this book, constructive criticism would be greatly appreciated.

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Contents

1

CHAPTER

Endometriosis

GENERAL CONSIDERATIONS

Endometriosis is defined as the presence of functioning uterine glands and stroma in any site outside the uterus. The condition is one of unusual interest and, although it gives rise to tumor formation (that is, a swelling), it is not a neoplasm. This does not mean that ectopic endometrium cannot occasionally be the site for the development of a malignant growth, although this is uncommon.

This disease occurs in two forms:

- Extrauterine organs and tissues
- Uterine wall.

Extrauterine Endometriosis

In extrauterine endometriosis, ectopic endometrium is found, usually in other pelvic organs but sometimes in more remote sites (see below). Although the true nature of the lesions was recognized towards the end of the 19th century, it is only during the last 50 years that proper attention has been paid to the condition. Previously, pelvic endometriosis was mistaken for an inflammatory reaction because of the commonly associated adhesions. Now that it is recognized by the surgeon, it is realized that it is so common that evidence of present or past external endometriosis is found in 10–20% of laparotomies carried out by a gynecologist on white patients. It was thought to be comparatively rare in African and Asiatic women. However, it is recognized with increasing frequency in these populations also with the increasing use of laparoscopy and other diagnostic modalities.

Adenomyosis (Uterine Wall)

In adenomyosis, the myometrium is invaded by endometrial glands from within. A minor degree of microscopic invasion of the muscle by the basal endometrium is normal, and this can be somewhat exaggerated when the endometrium is hyperplastic. These facts explain the misleading statements to the effect that adenomyosis is found in 50% of all uteri removed. The penetration has to be at least one high power field from the basal endometrium for it to justify the label of adenomyosis (Fig. 1.1). If this criterion is accepted, adenomyosis is not particularly common, not nearly as frequent as uterine leiomyomas, although all three conditions may coexist.

GENERAL PATHOLOGICAL CONSIDERATIONS

An endometriotic lesion has the typical histological appearance of endometrium (Figs. 1.2 to 1.5). Both glands and stroma must be present to justify the designation, although the relative amounts of each vary. It is said that the glands appear first and act as organizers for the stroma. The lesion promotes a fibrous or fibromuscular tissue reaction in the host. This reaction is a diffuse one and, except sometimes in the ovary, does not lead to encapsulation of the endometrioma.

Ectopic endometrium also resembles the uterine mucosa, in that it is subservient to ovarian hormones. It therefore typically only proliferates when the ovaries are active and atrophies after the menopause. Ordinarily an islet of endometriosis shows the cyclical changes characteristic of menstruation and, during pregnancy, its stromal cells exhibit decidual reaction. However, there is no outlet for its menstrual discharge so blood and debris collect within the tissues to form a cyst. With each menstrual

Figure 1.1: A uterus bisected to show adenomyosis infiltrating its walls. In this case there are some small menstrual blood cysts although this condition is not very hormone-responsive. This specimen came from a woman aged 32 years complaining of infertility and menorrhagia.

episode the collection increases in size, but continual absorption of some of the fluid elements causes the blood to become inspissated and dark colored to produce a "tarry" or "chocolate" cyst (Figs. 1.6 and 1.7). As the cyst grows, its endometrial lining is thinned and ultimately destroyed. So larger tarry cysts, as are seen in the ovary, are lined by granulation tissue or by pseudoxanthoma cells rich in hemosiderin and their real nature may not be recognized. For this reason the operative diagnosis of extrauterine endometriosis is not confirmed histologically in more than 50% of cases. This figure rises if the pathologist consults with the surgeon when selecting tissues for section, and is prepared to examine many blocks. On the other hand, any ovarian cyst into which there has been hemorrhage may be diagnosed incorrectly as endometriosis if the presence of a tarry content and pigment-laden lining cells are accepted as the only criteria.

Rupture of endometriotic cysts, even small ones, is common; scatter of their contents, which include endometrial cells, can lead to the development of further areas of endometriosis. The peritoneum reacts sharply to the cyst material and this causes dense adhesions to seal the hole. Adhesion and fixation are also encouraged by the fact that endometriosis infiltrates adjacent tissues (Fig. 1.8). No matter how extensive the adhesions, however, it is characteristic of endometriosis that the fallopian tubes are almost invariably patent. This observation is of great importance from the standpoint of the retrograde menstruation theory of origin of the disease.

Although, it is generally recognized that the condition almost always becomes quiescent with the cessation of ovarian function, it is not always realized that it often does so before the climacteric. Indeed the lesion appears sometimes to have a very limited phase of activity, after which it becomes burnt out to leave merely adhesions and a few old blood cysts. This situation is not infrequently encountered unexpectedly at laparotomy.

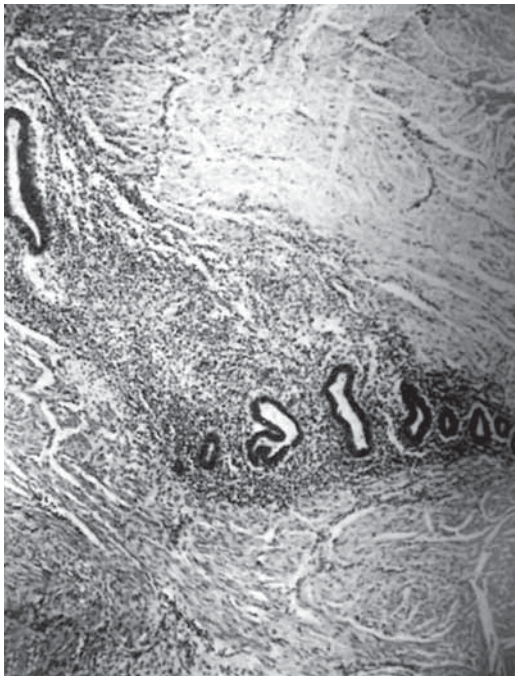


Figure 1.2: Adenomyosis uteri.

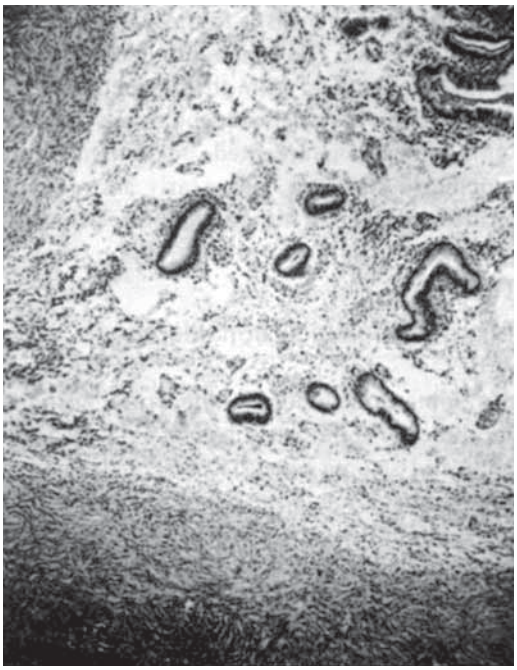


Figure 1.3: Endometriosis of the ovary.

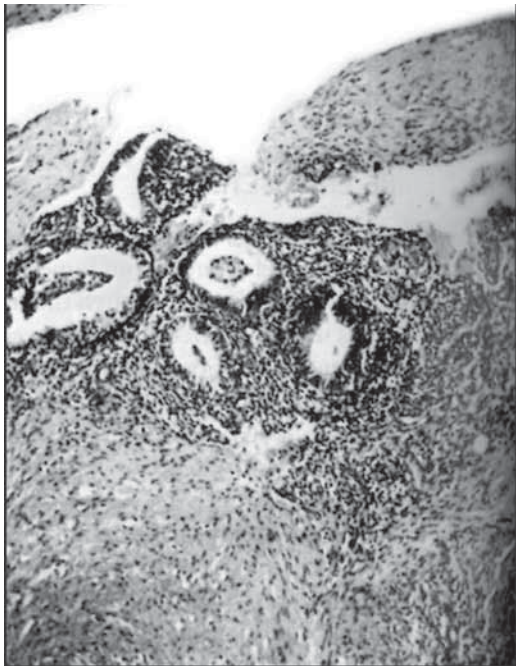


Figure 1.4: Endometriosis of the surface of the ovary.

One of the conditions which favor retrogression is pregnancy. Generally speaking, however, the disease continues to progress and is known to progress and to recur after therapy, recurrence rates reaching 40% in 5 years.

The possibility of adenocarcinoma or other malignant disease arising in an island of endometriosis is no longer disputed. A woman who had endometriosis of the abdominal wall for at least

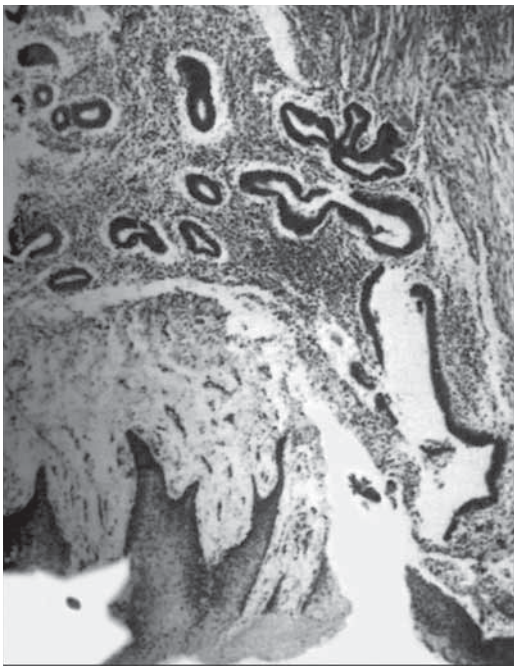


Figure 1.5: Endometriosis of the vulva. The squamous epithelium of the skin lies immediately below the lesion.

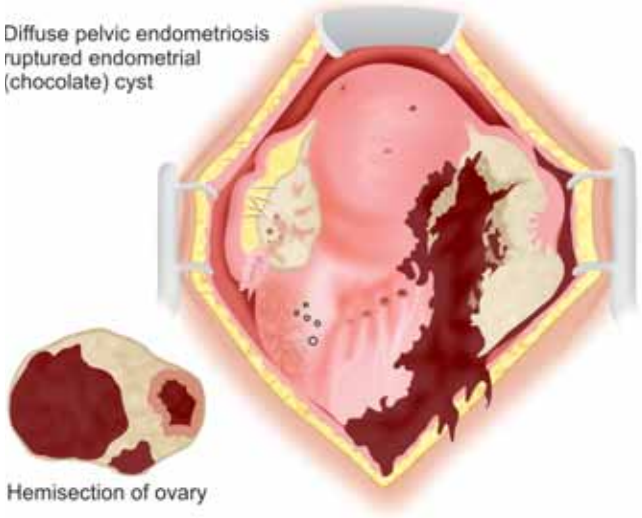


Figure 1.6: Pathological lesions in endometriosis.

10 years, during which time the lesion was proved to be benign by repeated biopsy, ultimately died from adenocarcinoma at this site. Similar developments are reported in endometriosis of the rectovaginal septum, ovaries, bowel and cervix, and in uterine adenomyosis.

ETIOLOGY

Endometriosis has a family history in many. The risk of endometriosis is seven times greater if a first-degree relative has been affected by endometriosis. Because no specific Mendelian

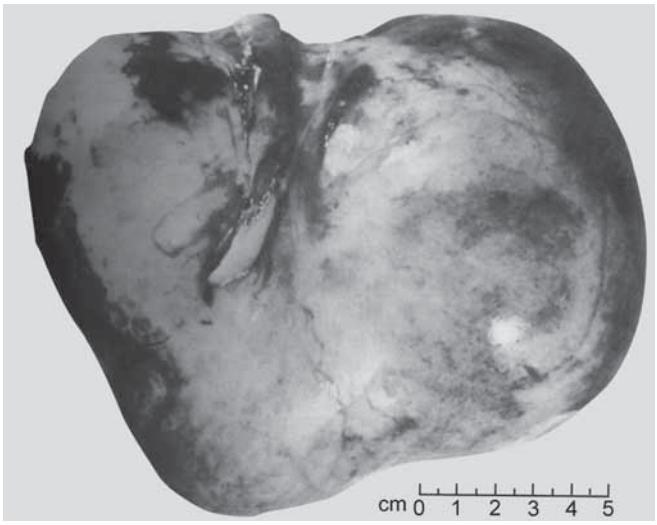


Figure 1.7: An unusually large endometriotic cyst of the ovary, with tarry fluid leaking on to its surface.

inheritance pattern has been identified, multifactorial inheritance has been postulated.

The known and supposed etiological factors are very similar to those of uterine leiomyoma; indeed, endometriosis and leiomyomas often occurs together (Fig. 1.9).

Age

Active endometriosis is seen most commonly between the ages of 30 and 40 years. It can, however, occur at any time between the menarche and the menopause, even before the age of 20 years.

Race and Family

The striking racial differences in incidence may be explained by economic and social factors, age of marriage and of childbearing as well as by genetic considerations. That genetic factors can operate, however, is suggested by the not uncommon finding of endometriosis, and of adenomyosis, affecting more than one member of a family. The risk of endometriosis is seven times higher if a first-degree relative has the disease, which is further increased in the case of homozygotic twins. The pattern of inheritance is probably multifactorial. Endometriosis has been linked with human leukocyte antigens.

Social and Economic Factors

Endometriosis is more common among highly civilized communities and among their well-to-do members. It is four times as frequent in private as in hospital practice and is therefore described as "a disease of the rich". This might be accounted for in part by late marriage and late childbearing in the higher income groups.

Parity

About 50–60% of affected women are childless; many of the others have had only one or two pregnancies and those a long time previously. The association of infertility and endometriosis

is established but it is difficult to say which is the cause and which the effect. It is alleged that the deliberate deferment of childbearing until a late age is a causal factor in that it exposes the susceptible tissues to an uninterrupted ovarian stimulus; pregnancy, it is said, protects by periodically suppressing ovarian activity (Box 1.1).

Estrogens and Prostaglandins

Although retrograde menstruation is common it is not always followed by endometriosis. It has been suggested that endometrial cells translocated from their normal site implant only in women with specific alterations in cell-mediated immunity. It is also possible that endometrial tissue arising as a consequence of serosal cell metaplasia might, by some unknown mechanism, become hormone-dependent. Beyond doubt is the fact that an estrogen influence is essential to the development and continued activity of ectopic endometrium in women. In the active stage of the disease the ectopic endometrial glands are out of phase with the uterine endometrial cycle and show signs of endometrial hyperplasia or atypical changes, without a secretory pattern. The altered response of the ectopic tissue to the ovarian cyclical activity may be attributed to the altered blood supply or the effect of the surrounding reactive changes.

It has been noted that endometriotic tissue, as well as normal endometrium, produces prostaglandins, and this may adversely affect ovum pick-up or tubal motility in the absence of any obvious impairment by adhesions. Increased levels of prostaglandins have also been noted in the peritoneal fluid of patients with endometriosis.

The association of endometriosis with the luteinization of an unruptured follicle has been noted and it has been suggested that, as a consequence of the reduced output of hormones, endometrial fragments might be able to take root and develop on the ovarian surface or pelvic peritoneum. Although, the evidence is limited, it does appear that some women suffer from recurrent luteinization of unruptured follicles, which might account for some women having both endometriosis and infertility problems.

Retroversion

Extrauterine endometriosis is often found with retroversion and it may be that the displacement is an etiological factor in that it favors retrograde menstruation.

Substantial evidence suggests that endometriosis is associated with a state of subclinical peritoneal inflammation, marked by an increased peritoneal fluid volume, increased peritoneal fluid white blood cell concentration (especially macrophages with increased activation status), and increased inflammatory cytokines, growth factors, and angiogenesis-promoting substances.

Box 1.1: Risk factors.

- Late marriages
- Late child bearing
- Genital tract obstruction
- Frequent and prolonged menstrual cycles
- Nulliparity
- Early menarche

SITES

Endometriosis can occur anywhere in the body and is described even in the tissues of the arm, leg, pleura, lungs, diaphragm and kidney. Usually, however, it is confined to the organs and tissues of the abdomen and pelvis, at or below the level of the umbilicus. These include the omentum. Visceral lesions are often multiple.

Ovary

The ovary is the most common site and is involved in 30–40% of cases. The lesion is nearly always bilateral. It sometimes takes the form of multiple "burnt match head" spots on the surface of the ovary (Figs. 1.9 and 1.10), sometimes as the typical tarry cysts in a disorganized organ surrounded by dense adhesions (Fig. 1.11). It should be noted, however, that not all "tarry cysts" in the ovaries are endometriotic. Any cyst containing old blood can present a similar naked-eye appearance.

An endometriotic cyst can reach the size of a fetal head but is rarely larger. It is usually impossible to remove it intact from its adhesions because the presence of these is a sign that the cyst wall has already been breached.

Pelvic Peritoneum Including the Uterovesical Pouch and the Pouch of Douglas

The peritoneum of the pouch of Douglas is the second most common site and a lesion there is often associated with one in the ovaries. It may represent secondary seeding from the ovarian condition. The tarry cysts seen on the pelvic peritoneum are rarely bigger than a pea; the lesions are manifested more by puckering and thickening of peritoneum and by adhesions. The last often occlude the uterorectal space, fixing the uterus in retroversion (Fig. 1. 8).

Outer Coat of Uterus

Endometriosis of the ovary, pelvic peritoneum and associated ligaments, when adherent to the uterus, often invades its outer

Figure 1.8: Endometriosis of the uterosacral ligaments and the rectovaginal septum. The dark areas are tiny chocolate cysts. The uterus is retroverted, and the ovary is adherent to the back of it and to the mass of endometriosis.

coat. The penetration is superficial and of little significance: it does not constitute adenomyosis.

Round Ligament, Uterosacral Ligament and Rectovaginal Septum

Endometriosis can involve the round ligament in either its pelvic or inguinal canal portion. In the latter case it forms an abdominal wall tumor. The uterosacral ligaments are much more commonly affected and a lesion there tends to spread into the rectovaginal connective tissue. Endometriosis of the uterosacral ligaments can occur with or without involvement of the peritoneum of the pouch of Douglas.

Fallopian Tube

Endometriosis of the outer surface of the fallopian tube occurs as part of peritoneal endometriosis.

Intestine

The rectum and pelvic colon can be implicated by invasion from peritoneal and ovarian deposits or by seeding. The ileum, cecum and appendix are also possible sites. No matter how extensive it may appear, the lesion rarely penetrates the mucosa, so rectal hemorrhage and the visualization of blood cysts on sigmoidoscopy are unlikely. The main pathological change is fibrotic thickening and puckering of the outer coats of the bowel, often with stricture formation and adhesions which can cause intestinal obstruction. The condition is easily mistaken for carcinoma of the rectum or pelvic colon, and many unexpected surgical cures of apparent malignant disease in these sites can be accounted for on this basis.

Bladder and Ureter

Endometriosis of these organs is usually explained by invasion from an adjacent site.

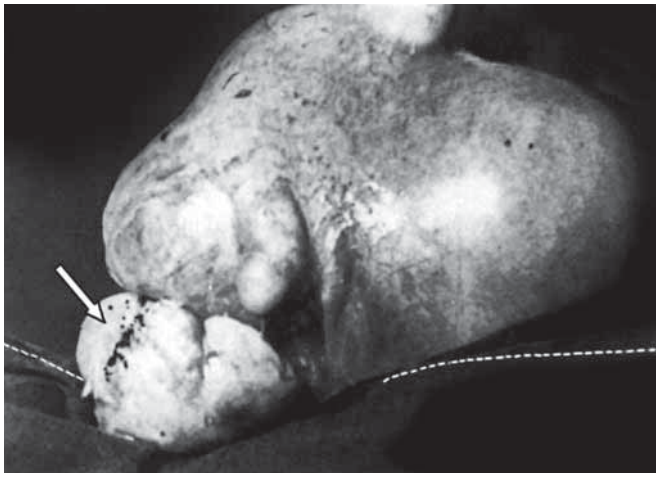
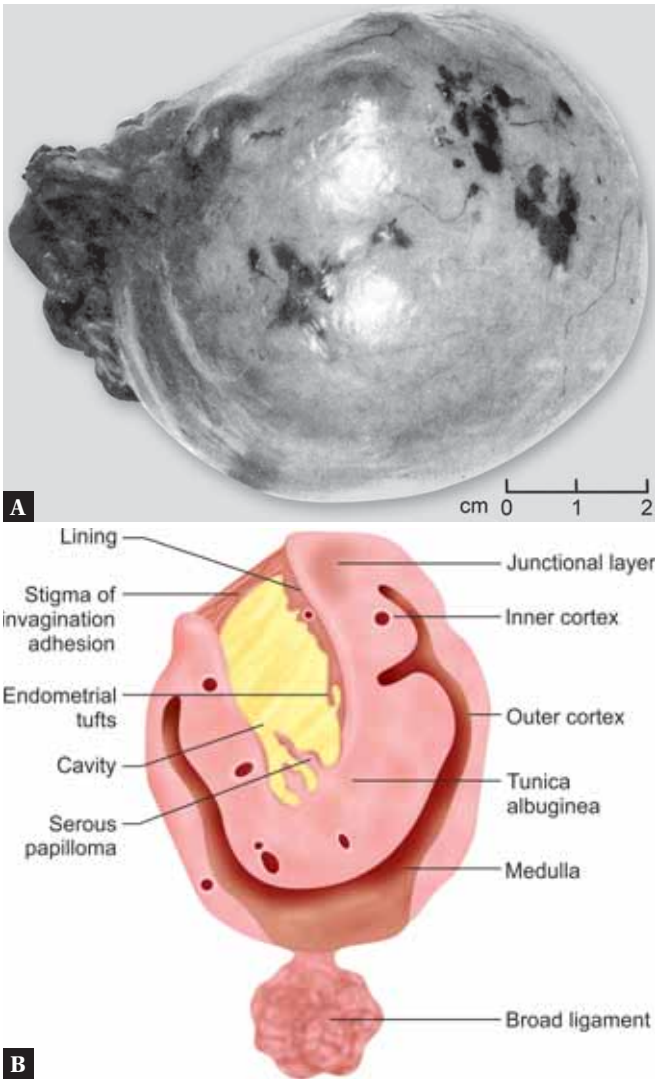


Figure 1.9: Surface endometriosis of the ovary (arrow) shown by the dark puckered areas and the ends of broken adhesions. As is so often the case, the lesion is associated with multiple leiomyomas in the uterus.



Figures 1.10A and B: (A) A serous cystadenoma of the ovary with multiple areas of menstruating endometriosis on its surface. This is a fortuitous combination but the appearance of the lesions is typical of pelvic endometriosis; (B) Endometriotic burrowing through ovarian tissue.

Vagina and Vulva

Islets of endometriosis are sometimes found in surgical or obstetrical scars in the vagina and perineum but the most common site for vaginal endometriosis is the posterior fornix which becomes infiltrated from the pouch of Douglas or from the rectovaginal septum. The lesion appears as multiple small blue-domed cysts in an indurated area of the vaginal vault (Figs. 1.12 and 1.13) and, when it becomes ulcerated, can be mistaken for carcinoma.

Abdominal Wall

Endometriosis occurs spontaneously in the umbilicus and in the inguinal canal, usually without any associated intrapelvic endometriotic lesion. It causes a swelling which becomes bigger and more painful about the time of menstruation. It may

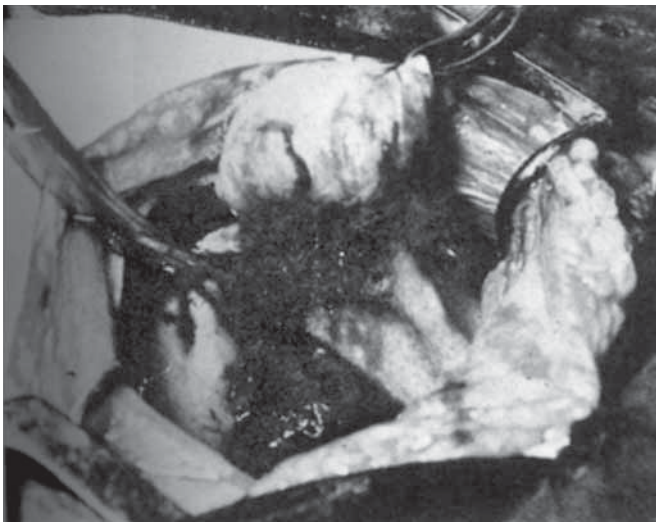


Figure 1.11: Pelvic endometriosis. The right ovary, the seat of an endometriotic cyst, has been lifted from a mass of adhesions in the pelvis. Tarry fluid is seen escaping from the cyst and lying in the pelvis. The patient in this case was young and the ovary was conserved after resection of the affected areas. A similar procedure can be carried out laparoscopically.

appear blue from an underlying blood cyst and sometimes it discharges menstrual blood. The tumor is not encapsulated and the surrounding tissue is indurated. A lesion with similar characteristics sometimes occurs in abdominal wall scars following operations on the uterus or tubes (scar endometriosis). The operations most likely to be followed by this complication are hysterotomy, classical cesarean section, myomectomy, ventrofixation, removal of pelvic endometriosis and operations involving section of the fallopian tube. It is also seen in episiotomy scars. All offer the possibility of spill of Müllerian epithelium into the incision (Fig. 1.14).

Lungs and Pleura

The pleura are more often affected than the lungs and, even-there, endometriosis is extremely rare. The characteristic effect is the cyclical development of pleuritic pain, and hemothorax (right-sided) or hemoptysis, with each menstrual period.

The cyclical occurrence of hemoptysis or hemothorax is suggestive but not conclusive evidence of an endometriotic lesion in the lungs or pleura.

MECHANISM OF ORIGIN

Many theories have been put forward to account for the development of external endometriosis but none explains all aspects of this disease (Table 1.1).

Endometrial Spill

Sampson's theory is that the growth arises as a result of spill of endometrial epithelium from the uterus when there is a backward flow of menstrual discharge through the tubes into the peritoneum. This falls first on the ovary and next into the pouch of Douglas to explain the most common sites for endometriosis. From these primary lesions there may be secondary scatter. Retrograde menstruation is a common phenomenon as can be seen during laparoscopy or laparotomy. It is said to be more likely when the uterus is the seat of leiomyomas, when it is retroverted and in cases of endometriosis as compared with normal women. It is now established that the menstrual discharge does contain viable endometrial fragments; these have been recovered from the dialysate in women undergoing peritoneal dialysis during the menstrual period. Endometriosis has been produced experimentally in monkeys by implants of their menstrual efflux or surgical transposition of the cervix to

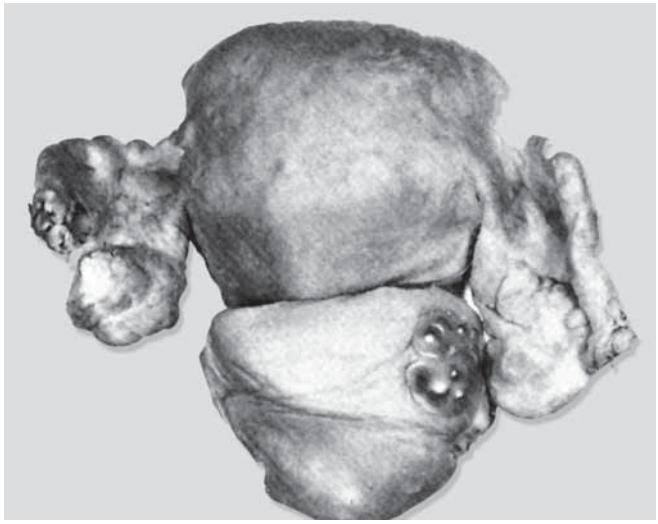


Figure 1.12: Endometriotic cysts in the vaginal vault. The cuff of the vagina, removed at the time of total hysterectomy, has been turned back to show the posterior fornix with the "blue-domed" cysts of menstrual blood lying subepithelially.

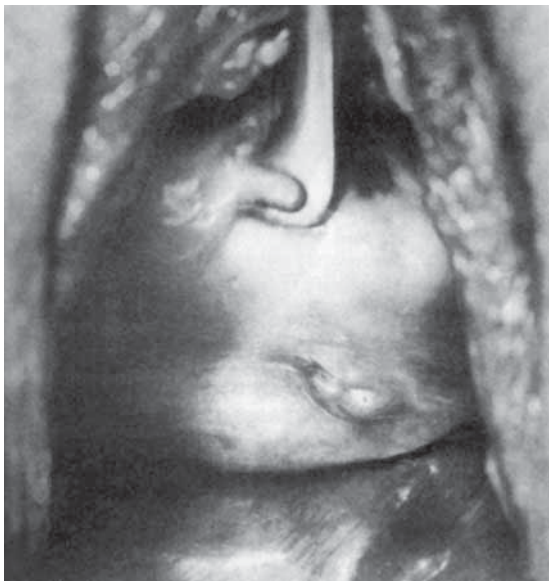


Figure 1.13: Endometriotic cysts in the posterior vaginal fornix, the cervix being pulled forward by a volsellum on its posterior lip.

TABLE 1.1: Theories of sites of endometriosis.

Site	*Theory*
Pelvic endometriosis	Retrograde menstruation
Pelvic peritoneum	Celomic metaplasia
Abdominal viscera Rectovaginal septum umbilicus	Celomic metaplasia
Abdominal scar Episiotomy scar Vagina and cervix	Direct implantation
Lymph nodes	Lymphatic spread
Others (lungs, pleura, skin)	Vascular Genetic Immunologic

produce intra-abdominal menstruation. Moreover, it has been shown that artificially produced retroversion in these animals favors the development of the condition.

The endometrial spill theory adequately explains endometriosis in scars in the abdominal wall, vagina and perineum following pelvic operations or childbirth; and accounts for the common finding of multiple pinhead-sized areas of endometriosis on the ovarian surface and pelvic peritoneum in adolescent girls suffering from cryptomenorrhea. In these, however, the disease does not persist or cause trouble once the obstruction to the outflow of menstrual blood is removed.

The spill theory fails to account for a primary lesion in the umbilicus and for endometriosis in remote areas such as the kidney and limbs.

Serosal Cell Metaplasia

This theory is associated with the names of Ivanoff and Meyer, and is based on the fact that the uterus develops from celomic cells which form the Müllerian ducts. It postulates that embryonic cells capable of differentiating into Müllerian tissue remain in and around the peritoneum of the pelvis and the surface epithelium of the ovary, or adult cells in these sites retain the potential to differentiate into endometrium and myometrium.

This concept offers an explanation for the common finding of fibromuscular tissue alongside ectopic endometrium. It can also account for lesions in all sites except those outside the abdomen and pelvis, and possibly those in the perineum. But even the last might have this basis because, during development, a tongue of celom accompanies the downgrowth of the mesodermal urorectal septum which goes to form the rectovaginal septum and perineum. It is said that even limb buds receive a contribution from coelom. However, this theory is not well-supported by clinical data.

The induction theory is an extension of the theory of celomic metaplasia and proposes that some biochemical factor may be responsible for the transformation of undifferentiated peritoneal cells to endometrial glands and stroma.

Lymphatic and Vascular Embolism

There is a body of evidence to show that tiny fragments of uterine endometrium frequently, and presumably normally, break off and enter the lymph or bloodstreams. They can be found in routine sections of lungs taken at autopsies, for example, moreover, microscopic islands of endometrium are demonstrable in the pelvic lymph nodes in a high proportion of cases of endometriosis. Cell embolism which, incidentally, was also postulated by Sampson, is becoming more and more acceptable in explanation of certain endometriotic lesions, especially those remote from the pelvis.

It may be concluded that, although endometriosis probably is usually a result of cellular spill, the present evidence suggests that it can arise by any of the above mechanisms. They are all, however, only potential causes of the disease for they are operating in all women. Once endometrial cells are shifted from their normal site it still requires other factors to make them survive and proliferate: one of the most important of these is a good supply of estrogen from the ovary.

Immunological

It has been proposed that certain immunologic factors may explain why all women who have retrograde menstruation do not develop endometriosis. However, there are no consistent reports regarding decreased natural killer cell activity or decreased autologous cell-mediated cytotoxicity in endometriosis. Increased secretion of tumor necrosis factor, of epidermal growth factor, of macrophage-derived growth factor from macrophages and of adhesion molecules like integrins may promote pelvic implantation of endometrial tissue. T- and B-lymphocytes can be recruited by activated macrophages. These lymphocytes may then synthesize antibodies which may play a role in the propagation of endometriosis.

Immune Factors

- Impaired cellular immune response to autologous endometrial antigen allows translocated endometrial cells to implant at ectopic sites
- Cytokines serve as immunomodulators, angiogenic factors or agents promoting endometrial cell growth
- 1L-6 is a T-cell derived cytokine. Its secretion is increased by peritoneal macrophages in endometriosis and by stromal cells of ectopic endometrium
- 1L-8 facilitates attachment of endometrial cells to peritoneal surfaces, invasion of extracellular matrix, local angiogenesis and endometrial proliferation
- TNF-α is secreted by activated macrophages and has potent inflammatory properties.

SYMPTOMS

Surprisingly, there may be no symptoms, even when the endometriosis is widespread and advanced. The five "Ds": Dysmenorrhea, Disorders of menstruation, Dysparunia, Dyschezia and Dull ache of abdomen. Infertility is a major problem with endometriosis.

Dysmenorrhea is progressive which is characteristic of endometriosis. Postmenstrual dysmenorrhea is the maximum compared to the premenstrual and menstrual as the ectopic endometrium bleeds a little later than the endometrium. The symptoms signs do not correlate with the findings as with small

lesion there may be maximum symptoms; maximum symptoms with minimal lesions.

Dysmenorrhea

The classical symptom of extrauterine endometriosis is secondary dysmenorrhea, commencing after the age of 30 years and gradually getting worse. In fact, it is present in only approximately 50% of cases. The explanations for this are: by the time the lesion is found it may have been inactive for several years; and not all endometriomas menstruate. The pain comes on gradually for a few days before the period, when the endometriosis is becoming congested, but is more severe during menstruation when there is bleeding into a closed space. It can reach a maximum at the end of menstruation. Thereafter, the pain subsides slowly, but may not disappear completely between periods.

The site of the pain depends on the site of the lesion. With multiple pelvic deposits it is deep seated in the lower abdomen, pelvis, rectum and lower back. The pain of endometriosis on the body surface is localized to the tumor itself.

Abnormal Menstruation

Excessive bleeding is present in approximately 60% of cases of pelvic endometriosis. Menorrhagia, polymenorrhea and polymenorrhagia are all seen. A change in cycle usually means ovarian involvement. Because of residual adhesions and vascular upset, abnormal bleeding can continue even when the disease is quiescent.

Infertility

The investigation of infertility, especially since the introduction of the laparoscope, has led to an increase in the diagnosis of endometriosis. Several possible mechanisms have been suggested for this association. The tubes are invariably open, but there may be pelvic adhesions, distorted anatomy and altered tubal motility which result in impaired ovum pick-up; the alterations in prostaglandins, macrophages and cytokines mentioned above may lead to enhanced phagocytosis of sperm; hormonal dysfunction may lead to anovulation, the luteinized unruptured follicle and luteal phase deficiency; and there may be early pregnancy losses. We still do not fully understand how endometriosis causes infertility or how infertility causes endometriosis (Flowchart 1.1).

Dyspareunia

Deep-seated pain on coitus is particularly likely when the pouch of Douglas and rectovaginal septum are affected, and when there is an associated fixed retroversion.

Pain on Defecation

This symptom is often only elicited by a leading question. It occurs when the endometriosis involves or is close to the rectum, and is more noticeable at the time of menstruation when the tumor is larger and more tender.

Tumor Formation

The patient may herself notice a swelling, especially in the case of a lesion of the abdominal wall or perineum. This exhibits cyclical enlargement and tenderness with menstruation and, if superficial, may discharge blood.

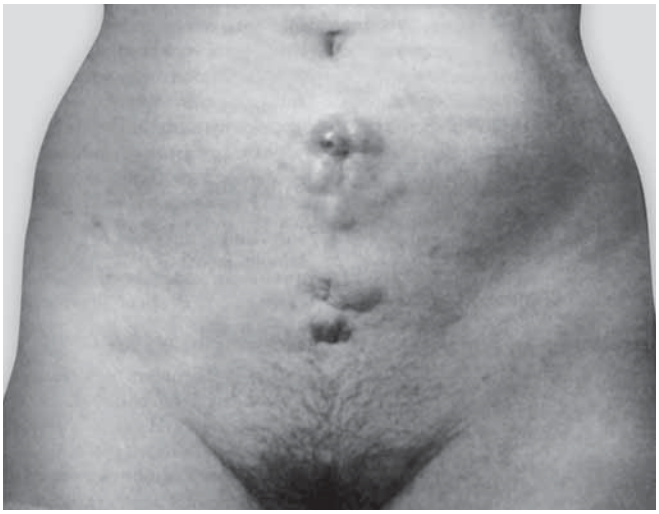


Figure 1.14: Endometriosis of an abdominal scar showing multiple small tumors with blood cysts. The woman affected was aged 49 years and had endometriotic cysts of the ovaries removed 5 years previously and, subsequently, local removal of cysts from the abdominal wall on two occasions. She complained of swelling of, and bleeding from, the abdominal wall lesions with each menstrual period. The endometriosis extended deeply and widely in the muscle of the abdominal wall and it did not respond to continuous high-dose treatment with an estrogen-progestogen preparation. So it, and any remaining ovarian tissue in the pelvis, was exposed to X-irradiation. This reduced the size of the mass and permitted its wide, although still incomplete, surgical excision. Four years later, the disease was as troublesome as ever and the masses were large. They again failed to respond to progestogen therapy and, when the woman was 55 years of age it was clear, clinically and histologically, that the lesion was malignant. During the previous 7–8 years, biopsy had been carried out on at least five occasions and always the microscopic appearances were those of endometriosis with no evidence of malignancy. There is no doubt that, in this case, a benign endometriotic condition ultimately changed to an adenocarcinoma and killed the patient.

Abdominal Pain

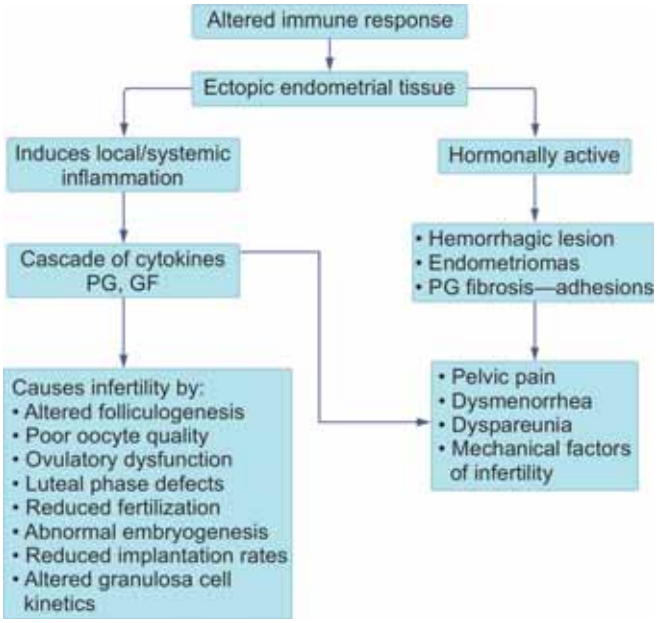
Mechanisms for pain in endometriosis:

- Production of substances such as cytokines and growth factors by activated macrophages associated with endometric implants
- Effect of bleeding from ectopic implants causing peritoneal irritation and fibrosis
- Invasion of pelvic nerves by endometriosis implants
- Enhanced aromatase expression detected in ectopic lesions which causes local accumulation of estradiol and stimulates growth of the tissue.

Dyspareunia is attributed to presence of endometriotic lesions over the uterosacrals and also due to presence of dense adhesions in cul-de-sac making uterus, retroverted with restricted mobility.

Chronic: Endometriosis forming cysts and adhesions among the pelvic organs causes a chronic aching discomfort in the lower

Flowchart 1.1: Altered immune response.



abdomen and pelvis sometimes referred to the groins, hips and thighs. This undergoes menstrual exacerbations.

Acute: A sudden and severe pain, with all the accompanying symptoms and signs of an acute abdomen, is experienced when a blood cyst ruptures. Such an accident is most likely about the time of menstruation and this coincidence, together with careful analysis of other symptoms and signs, helps to avoid the common error of diagnosing acute appendicitis. I have even seen such a case opened as a case of ectopic pregnancy.

OTHER SYMPTOMS

General ill-health and malaise are not uncommon with pelvic endometriosis. Intermittent pyrexia, especially at the time of menstruation, is present in at least 10% of cases and is caused by absorption of the degenerated products of the retained blood. Frequency, strangury and sometimes hematuria at the time of menstruation are features of urinary tract endometriosis. Other possibilities include symptoms of intestinal and ureteric obstruction.

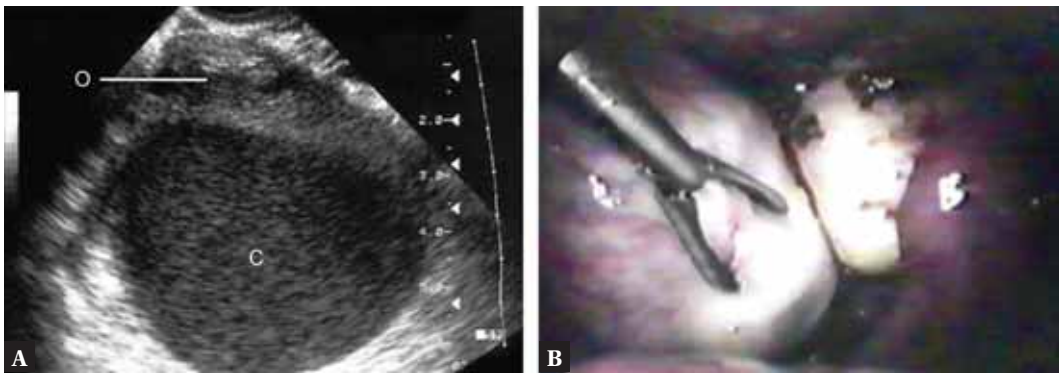
PHYSICAL SIGNS

Small multiple lesions may not give any sign of their presence during physical examination. The vulva, vagina and cervix should be inspected first with a speculum to rule out any deposits, though these are rare. Larger or easily accessible deposits are palpable as fixed, tender and nodular swellings with surrounding induration. Even if a definite tumor is not palpable, some or all of the pelvic organs are fixed and any attempt to move them reproduces the patient's pain. A fixed retroversion is a common finding. Involvement of the uterosacral ligaments and rectovaginal septum gives rise to a characteristic tender shotty thickening (*cobblestones*) above and behind the posterior fornix, which may be better appreciated during the menses.

INVESTIGATIONS

Investigations which may facilitate diagnosis are:

- *Urine β-hCG levels*: This helps in ruling out pregnancy-related complications.
- *Complete blood count*: Elevated leukocyte count points towards infection, whereas reduced hemoglobin level suggests anemia, which could be the result of chronic or acute blood loss.
- *Urine analysis/urine culture*: This helps in excluding out the presence of possible urolithiasis, cystitis and UTI.
- *Cervical cultures*: This may help in detecting infection such as gonorrhea and chlamydia.
- *Serum cancer antigen 125 (CA-125) test*: Serum CA-125 has been proposed as a biomarker for endometriosis. Presently, serum CA-125 measurement has limited potential for the diagnosis of endometriosis. CA-125 levels may be increased to values greater than 35 IU/mL in nearly 80% cases of endometriosis.
- *Imaging studies*: Ultrasound examination (both transabdominal and transvaginal) is the most commonly used investigation which may help in revealing the pelvic pathology responsible for producing pain. Imaging investigations such as CT and MRI may be helpful in some cases.
- *Transvaginal sonography*: Transvaginal sonography serves as a useful method for both identifying and ruling out deep rectal endometriosis and or an ovarian endometrioma. The following ultrasound characteristics are helpful in diagnosing an ovarian endometrioma in premenopausal women: Unilocular mass with ground glass echogenicity, one to four compartments (locules) and no papillary structures with detectable blood flow. Clinicians in many institutions across Europe are not experienced in performing TVS for the diagnosis of rectal endometriosis. Therefore, TVS cannot be recommended for the diagnosis of rectal endometriosis unless it is performed by clinicians who are highly experienced in TVS.
- *Magnetic resonance imaging*: Presently, the usefulness of MRI for diagnosing peritoneal endometriosis is not well-established. It may be, however, useful in the assessment of deep lesions.
- *Diagnostic laparoscopy*: Laparoscopy, backed by biopsy, remains the gold standard for the diagnosis of endometriosis (Fig. 1.15). However, the patient must be appropriately counseled prior to surgery. Laparoscopy can help in identifying the following lesions: endometriotic nodules or lesions having blue-black or a powder-burned appearance (Figs. 1.16 and 1.17). However, the lesions can be red, white or non-pigmented. Laparoscopy can also detect presence of blood (Fig. 1.18) or endometriotic deposits in cul-de-sac and its obliteration. Where appropriate, therapeutic treatment such as adhesiolysis or ablative surgical therapy of endometriotic lesions (Fig. 1.19) should be carried out in the same sitting. The operator must stage the disease on the basis of revised American Fertility classification of endometriosis (Table 1.2). Though this classification system is often used for deciding the disease management, it shows poor correlation with the symptom of pain.



Figures 1.15A and B: (A) Ultrasound pictures of endometriotic cyst which shows fine stippling inside ovary (ground glass appearance); (B) Laparoscopy findings of endometrioma.

- *Disease staging*: Stage I (minimal): 1–5; stage II (mild): 6–15; stage III (moderate): 16–40; stage IV (severe): >40.

A good quality laparoscopic procedure must involve a two-port approach and must include systematic inspection of the uterus and adnexa, peritoneum of ovarian fossae, vesicouterine fold, pouch of Douglas, pararectal spaces, the rectum and sigmoid, uterosacral ligaments, pelvic sidewalls, the appendix and cecum, and the diaphragm. Speculum examination and palpation of the vagina and cervix under laparoscopic control must also be done to look for any 'buried' nodules. At the time of laparoscopic examination, the ovaries must be carefully mobilized in order to inspect their anterior surface for the presence of adhesions, which is strongly suggestive of endometriosis. Biopsy may be performed to confirm the nature of the lesions in case of doubt. However, this is associated with a risk and therefore, there is no need for routine biopsy in all cases. Biopsy is typically recommended if the size of the lesions is greater than 3 cm. The ureters, bladder and bowel involvement must also be evaluated by additional imaging techniques if there is clinical suspicion of deep endometriosis.

A negative diagnostic laparoscopy (i.e. a laparoscopy during which no lesions of endometriosis are identified) appears to be highly accurate for exclusion of endometriosis. A woman with a negative laparoscopy can be adequately reassured that she does not require further testing or treatment. However, a positive laparoscopy (presence of visual changes suggestive of endometriosis) lacks specificity and is less informative. A positive laparoscopy is of limited value when used in isolation without histology. It presently remains controversial, whether medical treatment should be started first before embarking on an invasive procedure like a laparoscopy in women with symptoms and signs of endometriosis.

MANAGEMENT

Management of patients with endometriosis may be expectant, medical or surgical and is usually based on the presenting complaints and the disease staging (Table 1.2). One of the main criteria, which help the gynecologist decide whether to consider medical or surgical management, is whether the patient's main complaint is infertility or pelvic pain. The algorithm for treatment of endometriosis is described in Flowchart 1.2. While medical therapy has a role in the symptomatic management of endometriosis, it has no role in the management of

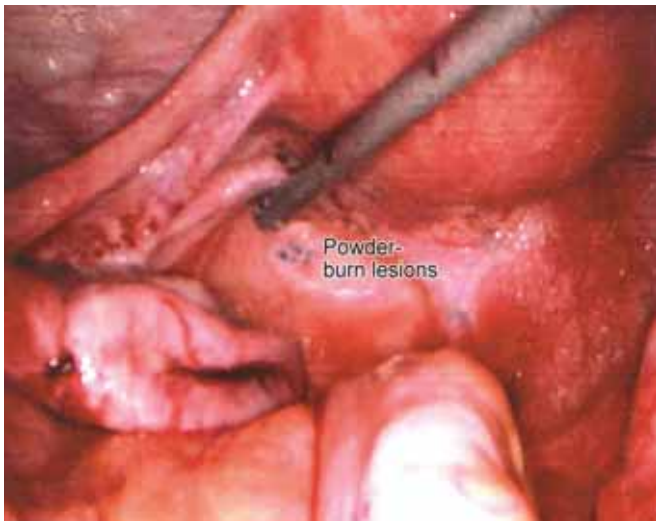


Figure 1.16: Powder-burn lesions over endometrial surface.

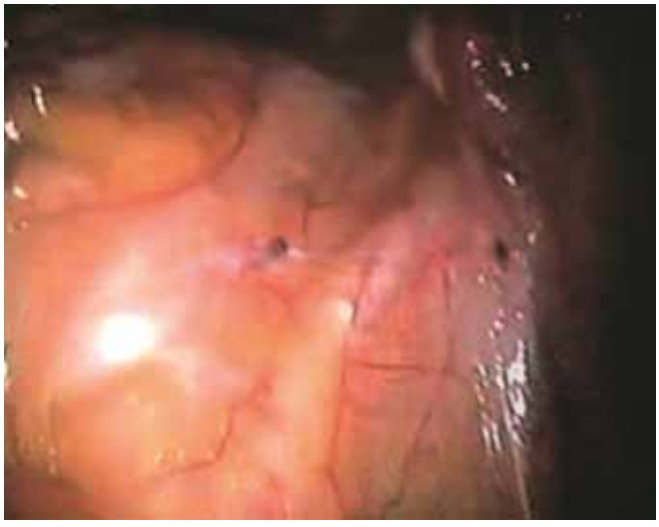


Figure 1.17: Nodular endometrial lesions.

endometriosis-associated infertility. In fact, hormonal therapy may rather enhance infertility.

MANAGEMENT WHEN PAIN IS THE MAIN PRESENTING COMPLAINT

Before starting empirical treatment, other causes of pelvic pain should be ruled out, as far as possible. Initial treatment comprises of using analgesic drugs, especially NSAIDs or combined oral contraceptives pills (COCPs). Use of levonorgestrel-releasing intrauterine system (LNG-IUS) or continuous progestogens can be considered if estrogenic preparations are contraindicated or give rise to side effects. These therapies can be used for long- term if effective and well-tolerated. Patients in whom the initial therapies (NSAIDs, OCPs, progestins) do not prove to be successful can be considered for GnRH agonists. The use of GnRH agonists is preferred over androgenic agents such as danazol and gestrinone because the latter drugs can cause unacceptable androgenic side-effects. Initially, a trial of GnRH agonists is tried for 2–3 months. This can be further continued for 6 months if the patient experiences relief from pain. This is likely to be more cost-effective than initial laparoscopy with local ablation in case of clinically suspected endometriosis given that the incidence of long-term symptom recurrence is similar for both the strategies.

Majority of medical therapies act by suppression of the ovaries and induction of amenorrhea. This merely inactivates and does not remove the local disease. Symptoms, therefore, may recur following the cessation of therapy in a high proportion of patients. Since both medical and surgical treatments are associated with a high risk of recurrence following the interruption of therapy, medical treatment may be required to be instituted on an intermittent basis in the long term. These treatment strategies are described next.

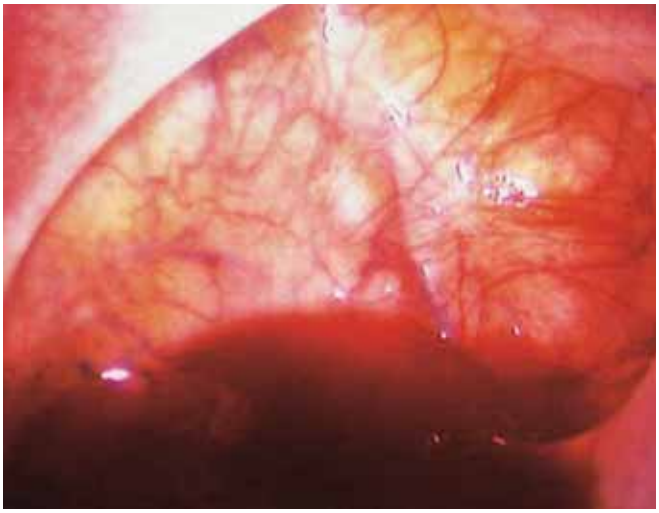


Figure 1.18: Presence of blood in cul-de-sac.

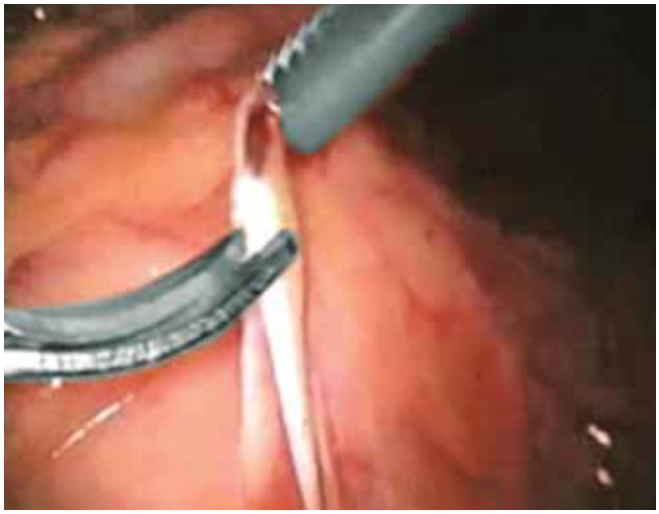


Figure 1.19: Laparoscopic excision of nodular endometrial lesions overlying the round ligament.

Analgesics for Treatment of Endometriosis-associated Pain

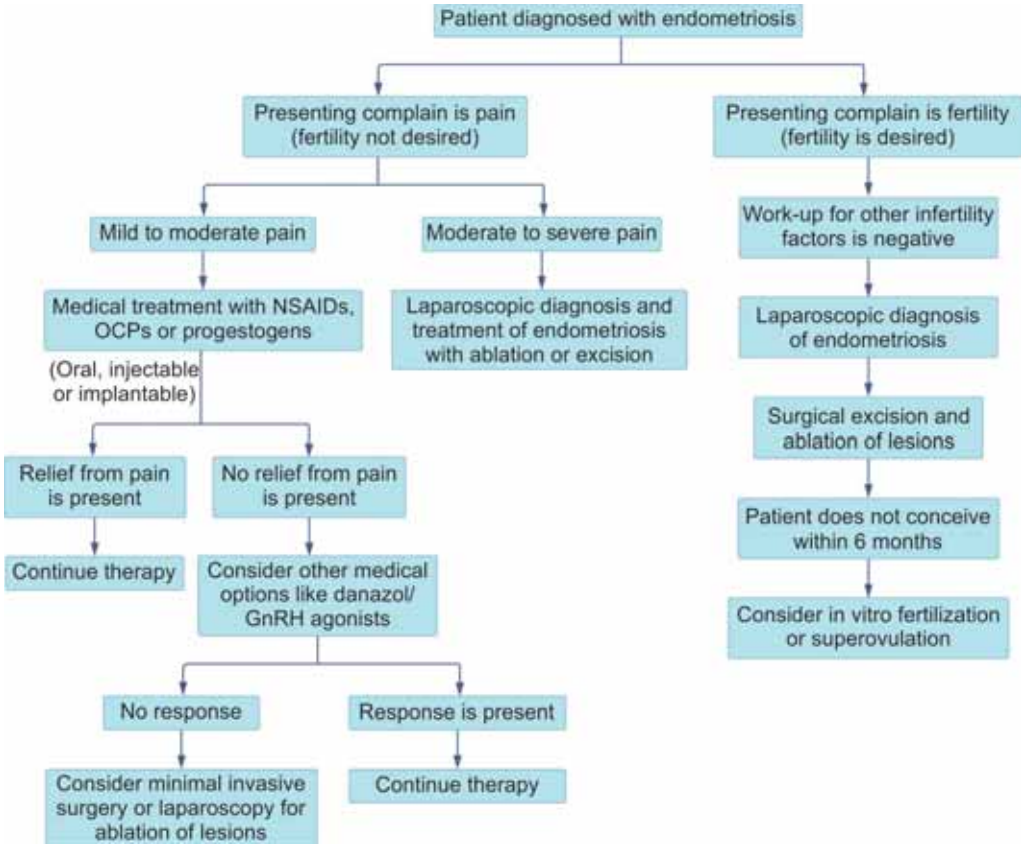
Pain is a cardinal symptom of endometriosis. Studies have demonstrated elevated prostaglandin levels in peritoneal fluid

TABLE 1.2: Revised American Fertility Society classification of endometriosis.

Peritoneum			
Endometriosis lesion	*Less than 1 cm*	*1–3 cm*	*More than 3 cm*
Superficial	1	2	4
Deep	***2***	***4***	***6***
Ovary			
Right superficial	1	2	4
Right deep	4	16	20
Left superficial	1	2	4
Left deep	4	16	20
Posterior cul-de-sac obliteration			
Partial		Complete	
4		40	
Ovary			
Adhesions	*Less than 1/3 enclosure*	*1/3–2/3 enclosure*	*More than 2/3 enclosure*
Right filmy	1	2	4
Right dense	4	8	16
Left filmy	1	2	4
Left dense	4	8	16
Tube			
Right filmy	1	2	4
Right dense	4*	8*	16
Left filmy	1	2	4
Left dense	4*	8*	16

* If the fimbriated end of the fallopian tube is completely enclosed, the point assignment is changed to 16.

Flowchart 1.2: Algorithm for treatment of patients with endometriosis



(OCPs: oral contraceptive pills; GnRH: gonadotropin releasing hormone; NSAIDs: non-steroidal anti-inflammatory drugs)

and endometriotic tissue in women with endometriosis. As a result, NSAIDs are widely used analgesics in clinical practice. Before prescribing NSAIDs to the patient, clinicians must discuss the role of NSAIDs in provision of pain relief along with its side-effects profile, including risk of gastric ulceration and cardiovascular disease. In conclusion, the effectiveness of NSAIDs (naproxen) in treating endometriosis-associated dysmenorrhea is not well established owing to a lack of studies.

Use of Hormonal Therapies

Endometriosis is considered a predominantly estrogen-dependent disease. Thus, hormonal suppression might be an attractive medical approach to treat the disease and its symptoms. Currently, hormonal contraceptives, progestogens, antiprogestogens, GnRH agonists and aromatase inhibitors are in clinical use. The guideline development group (GDG) recommends that clinicians must take patient preferences, side-effects, efficacy, costs and availability into consideration when choosing hormonal treatment for endometriosis-associated pain. Presently, there is no significant evidence supporting the efficacy of a particular treatment strategy over the others. Management plans must be individualized, taking into consideration various parameters, described previously. Woman should be able to make an informed choice based on a good understanding of the disease process and its effect on her body.

Hormonal Contraceptives

A systematic review by Vercellini et al., 2003 has shown that use of low-dose cyclic OCPs is effective in reducing pain symptoms in patients with endometriosis. Continuous rather than the cyclic use of OCPs is likely to be more effective for pain control. Clinicians may consider the use of a vaginal contraceptive ring or a transdermal (estrogen/progestin) patch to reduce endometriosis-associated dysmenorrhea, dyspareunia and chronic pelvic pain (CPP). Due to their good safety profile, combined OCPs are useful for long-term use.

Progestogens and Antiprogestogens

Continuous administration of progestogens is likely to cause inhibition of ovulation. They also exert an anti-proliferative effect on the endometriotic implants, causing their decidualization and eventual atrophy. A recent systematic Cochrane review by Brown et al., (2012) determined that there was no evidence to suggest a benefit of progestogens over other treatments. However, continuous progestogens serve as an effective therapy for the alleviation of painful symptoms associated with endometriosis. Nevertheless, progestogens must be used with caution due to the scarcity of data and absence of placebo-controlled studies. Also, progestogens may be associated with certain side effects, which can limit its use. The most common side effect of progestogens is breakthrough bleeding. Other side effects reported with the use

of progestogens include weight gain, breast tenderness, bloating, headache, nausea, etc.

Levonorgestrel-releasing Intrauterine System

Levonorgestrel-releasing intrauterine system (LNG-IUS) does not suppress ovulation but acts locally on the endometrium. Due to its locally mediated action, LNG-IUS is likely to serve useful for the management of endometriosis-associated pain. Three studies (Petta et al., 2005; Gomes et al., 2007 and Ferreira et al., 2010) have investigated the potential of a LNG-IUS for management of endometriosis-associated symptoms. These studies have concluded that LNG-IUS is effective for the management of endometriosis-associated pain as well for the maintenance of pain control following surgical treatment.

Gonadotropin-releasing Hormone Agonist

The results from the Cochrane review by Brown et al. (2010) suggest that GnRHa is more effective than placebo but inferior to the LNG-IUS or oral danazol in providing relief from the endometriosis-associated pain.[31] The most common side effects associated with the long-term use of GnRH agonists include the hypo-estrogenic side effects, especially reduction of the bone density. This can be prevented through addition of either oral or transdermal estrogens in combination with various progestogens, or tibolone (add-back therapy) to GnRHa therapy if it is used for more than 6 months. However, use of progestogens alone or calcium supplements is unlikely to be effective in preventing bone loss. Antiresorptive agents such agents such as bisphosphonates may help in providing bone protection in women in whom the add-back therapy is contraindicated or is not tolerated.

It can be concluded that GnRH agonists, with and without add-back therapy, are effective in the relief of endometriosis-associated pain, but there is limited evidence regarding its dosage or duration of treatment. No specific GnRHa can be recommended over another in relieving endometriosis-associated pain. There is evidence of severe side effects with GnRHa (e.g. reduced bone density, hot flushes, insomnia, vaginal dryness, reduced libido, headache, etc.) which should be discussed with the woman before prescribing GnRH agonists to her. Careful consideration must be given before prescribing GnRH agonists to the young women and adolescents, because these women may not have reached maximum bone density.

Androgenic Agents

Danazol: Danazol, a synthetic androgen, is the derivative of ethinyl testosterone, which has shown to be highly effective in relieving the symptoms of endometriosis by inhibiting pituitary gonadotropins (FSH and LH). This may result in the development of a relative hypo-estrogenic state. Danazol probably provides pain relief by producing endometrial atrophy. A Cochrane review by Farquhar et al., 2007 has shown that Danazol in the dosage of 400-600 mg daily is effective in treating the symptoms and signs of endometriosis. However, its use is limited by the occurrence of androgenic side effects. Recent studies indicate that vaginal danazol may be better tolerated. According to the ESHRE recommendations (2013), danazol should not be used if any other medical therapy is available, due to occurrence of severe side effects (acne, greasy skin, deepening of voice, hirsutism, vaginal spotting, weight gain, muscle cramps, etc.). Atherogenic effects on the lipid profile have also been reported. However, neither danazol nor gestrinone cause any adverse effect on the bone density. Therefore, these serve as beneficial alternatives to GnRH analogues in women who are susceptible to bone loss or those in whom estrogenic add-back preparations are contraindicated.

Gestrinone: Gestrinone is a 19-norsteroid derivative having antioestrogenic, antiprogestogenic, antigonadotropic and androgenic properties. It has a long half-life and is therefore administered twice weekly orally in a dose of 1.25–2.5 mg. The consumption of this drug induces amenorrhea in 50–100% of women with endometriosis. Resumption of menses occurs after cessation of treatment. Though the use of gestrinone can cause androgenic side effects, these are less intense in comparison to danazol. Gestrinone has been found to be as effective as GnRH agonists for providing relief from pelvic pain associated with endometriosis for up to 6 months after cessation of therapy.

Aromatase Inhibitors

The most common third-generation aromatase inhibitors letrozole and anastrozole are reversible inhibitors of the enzyme aromatase, which compete with androgens for aromatase-binding sites. Even though the evidence for increased expression of aromatase P450 in endometriotic tissue still remains controversial; aromatase inhibitors have been studied for treatment of pain in women with endometriosis. Two systematic reviews evaluating the potential of aromatase inhibitors for the treatment of endometriosis-associated pain (Ferrero et al., 2011; Nawathe et al., 2008) have concluded that future studies are required to assess if aromatase inhibitors would be useful in long-term for improvement of pain symptoms in comparison to the conventional therapy.

Use of these agents is likely to result in hypoestrogenic side effects, such as vaginal dryness, hot flushes and reduced bone mineral density.

Adjuvant Therapy

This includes the use of tricyclic antidepressants such as amitriptyline and antiepileptics such as gabapentin for the management of chronic pain of endometriosis in patients who are resistant to the conventional therapies.

Surgery for Treatment of Endometriosis-Associated Pain

Surgical treatment involving elimination of endometriotic lesions (through excision, diathermy or ablation/evaporation), division of adhesions (for restoring pelvic anatomy) and interruption of nerve pathways for alleviation of pain has long been used for the management of endometriosis. Surgical treatment of endometriomas must preferably be via laparoscopic cystectomy.

Laparotomy and laparoscopy are equally effective in the treatment of endometriosis-associated pain. Operative laparoscopy (excision/ablation) is more effective for the treatment of pelvic pain associated with all stages of endometriosis, compared to diagnostic laparoscopy only. Laparoscopic surgery is usually associated with less pain, shorter duration of hospital stay, quicker recovery and better cosmesis, in comparison to laparotomy. Therefore, laparoscopic surgery is usually preferred

to open surgery. If the clinician having relevant experience with laparoscopy is not available, the patient should be referred to a center of expertise because operative laparoscopy for advanced disease may be associated with a significant risk. When the lesions of endometriosis are identified at the time of diagnostic laparoscopy, clinicians are recommended to surgically treat these for reducing endometriosis-associated pain. While laparoscopic surgery is effective for the treatment of pain secondary to endometriosis, long-term recurrence of pain can occur in nearly 50% individuals.

Ablation versus Excision of Endometriosis

Clinicians may consider using either ablation or excision of peritoneal endometriosis for reducing endometriosis-associated pain because both the procedures have been found to be equally effective.

Laparoscopic Uterosacral Nerve Ablation versus Presacral Neurectomy

The minimally invasive procedure, laparoscopic utero-sacral nerve ablation (LUNA), has not been found to be useful for alleviation of pain related to endometriosis. Presacral neurectomy (PSN), on the other hand, has been found to be beneficial for treatment of endometriosis-associated midline pain as an adjunct to conservative laparoscopic surgery. However, PSN is a procedure requiring high degree of skill. Moreover, it may be associated with an increased risk of adverse effects such as bleeding, constipation, urinary urgency, etc.

Hysterectomy for Endometriosis-Associated Pain

Hysterectomy with removal of the ovaries and all visible endometriosis lesions can be considered as a treatment option in women who are not desirous of future childbearing and have failed to respond to more conser-vative treatments. Prior to the surgery, women should be informed that hysterectomy might not necessarily cure the symptoms or the disease because disease excision may be incomplete.

Prevention of Adhesions following Endometriosis Surgery

Clinical evidence: There are a number of barrier, fluid and pharmacological agents, which have been used for prevention of adhesions at the time of gynecological surgery. Some such agents include oxidized regenerated cellulose (Interceed®), polytetrafluoroethylene surgical membrane (Gore-Tex®), fibrin sheet, sodium hyaluronate and carboxymethylcellulose combination (Seprafilm®), polyethylene oxide and carboxymethylcellulose gel (Oxiplex/AP®), icodextrin 4% (Adept®), hyaluronic acid products and polyethylene glycol hydrogel (SprayGel®), etc. that the use of oxidized regenerated cellulose helps in preventing adhesion formation during operative laparoscopy for endometriosis. On the other hand, use of icodextrin after operative laparoscopy for endometriosis is not likely to prevent adhesion formation. Therefore, its use is not recommended. Clinicians should also be aware that other antiadhesion agents such as polytetrafluoroethylene surgical membrane, hyaluronic acid products, etc. have been studied and found to be effective for adhesion prevention in the perspective of pelvic surgery and not specifically in women with endometriosis.

TREATMENT OF ENDOMETRIOSIS-ASSOCIATED INFERTILITY

Various treatment options (medical, surgical, medical adjunct to surgery and alternative treatments) are used for improving fertility in women with endometriosis.

Hormonal Therapies for Treatment of Endometriosis-Associated Infertility

Use of hormonal treatment (e.g. danazol, GnRH analogues, OCPs, etc.) for suppression of ovarian function is unlikely to improve fertility in cases of minimal to mild endometriosis. The medical treatment of endometriosis associated pain are described in Table 1.3.

Surgery for Treatment of Endometriosis-Associated Infertility

Jacobson et al. (2010) have shown that operative laparoscopy including adhesiolysis is effective in increasing the pregnancy or live birth rate in comparison to diagnostic laparoscopy alone in women with minimal to mild endometriosis. If the patient does not conceive after 6 months of operative laparoscopy or in cases of severe endometriosis lesions, assisted reproductive techniques (in vitro fertilization and superovulation) can be considered.

In most women with endometriosis, preservation of reproductive function is desirable. Therefore, the least invasive and least expensive approach that is effective should be used. The goal of surgery is to excise or coagulate all visible endometriotic lesions and associated adhesions—peritoneal lesions, ovarian cysts, deep rectovaginal endometriosis—and to restore normal anatomy.

TABLE 1.3: Medical treatment of endometriosis-associated pain: effective regimens (Usual duration: 6 months).

Administration	*Dose*		*Frequency*
Progestogens			
Medroxyprogesterone acetate	PO	30 mg	Daily
Megestrol acetate	PO	40 mg	Daily
Lynoestrenol	PO	10 mg	Daily
Dydrogesterone	PO	20–30 mg	Daily
Antiprogestins			
Gestrinone	PO	1.25 or 2.5 mg	Twice weekly
Danazol	PO	400 mg	Daily
Gonadotropin-releasing hormone			
Leuprolide	SC IM	500 mg 3.75 mg	Daily Monthly
Goserelin	SC	3.6 mg	Monthly
Buserelin	IN SC	300 µg 200 µg	Daily Daily
Nafarelin	IN	200 µg	Daily
Triptorelin	IM	3.75 mg	Monthly

(PO: oral; SC: subcutaneous; IM: intramuscular; IN: intranasal)

Surgical management of minimal endometriosis: The association between infertility and minimal to mild endome-triosis is controversial and poorly understood. The clinical pregnancy rate (PR) per cycle after controlled ovarian hypersti-mulation (COH) with or without intrauterine insemination (IUI) is reportedly lower in women with surgically untreated minimal to mild endometriosis than in women with unexplained infertility. It is possible that prior laparoscopic removal of endometriosis has a positive effect on the clinical PR after COH and IUI. However, many studies have not proved this on a large study.

Tumors on the body surface are best excised. Deep-seated lesions call for surgery when symptoms are acute, when the diagnosis is in doubt, when tumor masses are large and when hormone therapy fails or is ruled out.

In general, it can be said that laparoscopic surgery is now the method of choice in most women who require conservative surgery. It is less invasive, less expensive, has less morbidity and better postoperative results than laparotomy. Endometriotic lesions and adhesions are excised or coagulated using bipolar coagulation or CO2 laser. The cyst wall of an endometrioma is removed and the remnants, if any, are fulgurated by bipolar electrocoagulation or laser. If the cyst is very small, it should be vaporized. It is important to remove the cyst wall if recurrence is to be prevented. At the same time, adhesiolysis and preservation of normal ovarian tissue is essential in the woman who desires fertility. In general, bipolar electrocoagulation results in less adhesion formation than the laser, but recurrence rates are the same with both procedures.

Where laparoscopic facilities are not available, the same conservative surgery can be performed at laparotomy too. Limited and incomplete excision of endometriosis is followed by surprisingly good results, even when ovarian function is not sacrificed. In young women the subsequent pregnancy rate is at least 30%, even when hormones are not administered postoperatively.

Ovarian endometriosis superficial ovarian lesions can be vaporized. Small ovarian endometrioma (<3 cm in diameter) can be aspirated, irrigated, and inspected with ovarian cystoscopy for intracystic lesions; their interior wall can be vaporized to destroy the mucosal lining of the cyst. Large (>3 cm in diameter) ovarian endometrioma should be aspirated, followed by incision and removal of the cyst wall from the ovarian cortex. To prevent recurrence, the cyst wall of the endometrioma must be removed, and normal ovarian tissue must be preserved.

There is increasing concern that ovarian cystectomy with concomitant removal or destruction of primordial follicles may reduce ovarian volume and reserve and diminish fertility. However, it was found that a higher incidence of recurrences of cyst when the cyst was not excised. Therefore, based on the current evidence, ovarian cystectomy appears to be the method of choice.

Laparotomy is usually considered for patients with advanced stage disease, over the age of 40, where fertility is no longer required. In such cases it is often best to remove the uterus and both ovaries. While it is important to remove as much endometriotic tissue as possible, small fragments can be left behind if there is a risk of injury to the bowel because of dense adhesions, and will usually retrogress of their own accord. If there are dense adhesions with the bowel and bladder, a subtotal hysterectomy may be a safer option.

Deep rectovaginal and rectosigmoidal endometriosis: The surgical excision of deeply infiltrating endometriosis (Table 1.4) both rectovaginal and rectosigmoidal endometriosis is difficult and can be associated with major complications. Postoperative bowel perforations with peritonitis have been reported in 2–3% of cases.

Oophorectomy and hysterectomy: Radical procedures such as oophorectomy or total hysterectomy are indicated only in severe situations and can be performed either laparoscopically or, by laparotomy. The exact procedure must vary from case to case. Rarely, in the case of obstruction, it is necessary to even resect the intestine.

ENDOSALPINGIOSIS

Tubal epithelium has the same origin as endometrium and has similar potentialities. Certain cases of ovarian endometriosis are thought by some authorities to be endosalpingiosis. This is because the lesions do not menstruate and because, on section, they show a tubal type of epithelium without typical endometrial stroma.

Endosalpingiosis of the tube causes no symptoms other than infertility and, as a rule, is only diagnosed by microscopic examination of the excised tissue. In the ovary, too, it is only a histological diagnosis.

CERVICAL ENDOMETRIOSIS

In cervical endometriosis, the ectopic glands are truly endometrial and menstruate to some extent (Fig. 1.20). Their presence is explained by direct implantation, by embolism, or by metaplasia of the Müllerian duct tissue. The condition is not uncommonly seen after operations which involve simultaneous injury to the cervix and spill of endometrium, for example, curettage with amputation of the cervix. Endometriosis of the posterior cervix may represent a spread from a lesion in the rectovaginal septum. Sometimes, however, the disease begins spontaneously in the substance of the cervix, and then extends in the same manner as cervical cancer—to the endocervix to

TABLE 1.4: Suggested surgical procedure according to classification of deeply infiltrating endometriosis (DIE).

Die classification	*Operative procedure*
A: Anterior DIE AI: Bladder	Laparoscopic partial cystectomy
P: Posterior DIE P1: Uterosacral ligament P2: Vagina	Laparoscopic resection of USL Laparoscopically-assisted vaginal resection of DIE infiltrating the posterior fornix
P3: Intestine Solely intestinal location Without vaginal infiltration (V–) With vaginal infiltration (V+)	Intestinal resection by laparoscopy or by laparotomy Laparoscopically-assisted vaginal intestinal resection or exeresis by laparotomy
Multiple intestinal location	Intestinal resection by laparotomy

(USL, uterosacral ligament)

Source: Chapron, C, Fauconnier A, Vieira M, et al. Anatomical distribution of deeply infiltrating endometriosis: surgical implications and proposition for a classification. Hum Reprod. 2003;18:157.

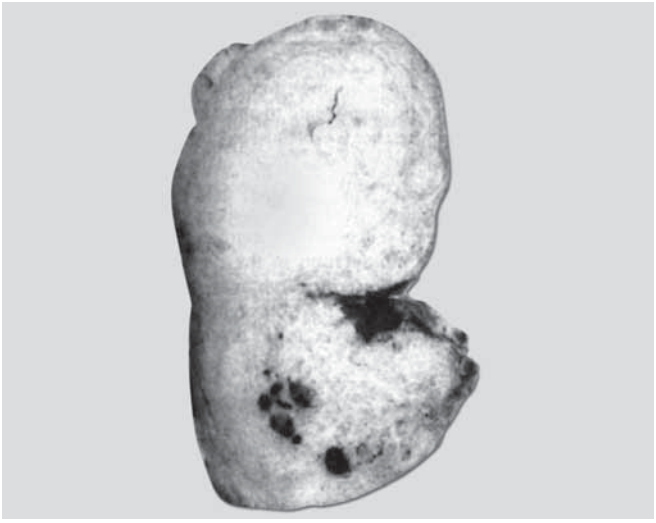
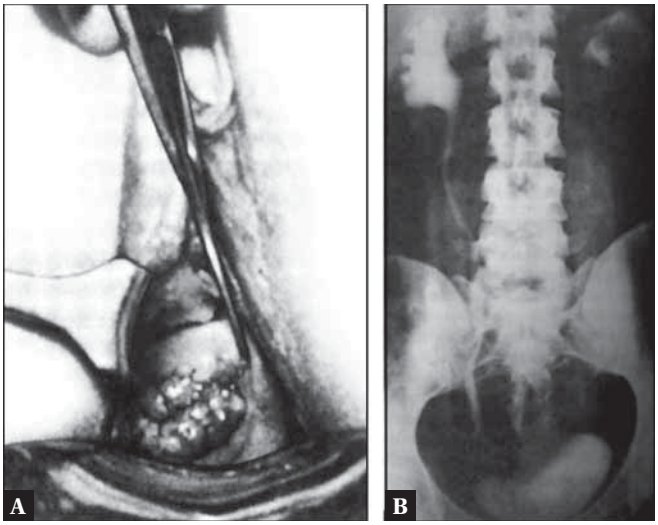


Figure 1.20: Endometriosis of the cervix with multiple small tarry cysts.



Figures 1.21A and B: Endometriosis of the cervix in a woman aged 30 years and complaining of a bloodstained vaginal discharge for 18 months in addition to infertility. (A) A polypoid mass of endometriotic tissue protruding through the external os. The lesion was primarily in the posterior wall of the cervix but fungated into the cervical canal and also caused an opening into the posterior fornix. Extension into the right broad ligament produced physical signs similar to those of a Stage II or Stage III cancer of the cervix, (B) Pyelography reveals obstruction of the lower end of the right ureter by the extension of the endometriosis into the broad ligament on that side. The patient was ultimately treated by total hysterectomy and bilateral salpingo-oophorectomy because of the threat to renal function.

produce polypoid masses, to the posterior fornix to produce cysts and sinuses, to the bases of the broad ligaments to surround and obstruct the ureters (Figs. 1.21A and B).

The lesions vary. They may be merely superficial tiny blood cysts on the portio; they may be deep seated to cause distortion and fibrosis of the cervix with adhesions to the bladder base. Sometimes the cervix is grossly enlarged, completely fixed and ulcerated, the physical signs being similar to those of cancer except for the absence of friability. Cervical endometriosis may cause no symptoms. Otherwise the complaints are irregular bleeding and discharge, contact bleeding, dyspareunia and bladder irritability.

If surgical treatment becomes necessary because of failure to respond to drug therapy, extracervical adhesions and spread can create great technical difficulties. It is usually impossible to dissect broad ligament endometriosis from around the ureters, and renal function is sometimes only saved by resecting the ureter or by sacrificing both ovaries. In one case it proved necessary to form an ileal conduit because of ureteric obstruction.

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2

CHAPTER

Adenomyosis

INTRODUCTION

Adenomyosis is a condition in which there is a growth of endometrial cells inside the uterine myometrium (usually >2.5 mm beneath the basal endometrium). It is associated with myometrial hypertrophy and may be either diffuse or focal (adenomyoma). Microscopically, there are ectopic, non-neoplastic endometrial glands and stroma, surrounded by hypertrophic and hyperplastic myometrium (Fig. 2.1).

The majority of cases of adenomyosis are diagnosed following histological examination of hysterectomy specimens showing a prevalence varying between 5% and 70%. The prevalence in general population, however, remains unclear. The majority of cases are reported amongst women in the age groups of 40–50 years and there is a positive association with parity. Multiparas between the ages of 30 years and 50 years are most commonly affected with this disease. No association has been observed with age at menarche, menopausal status, or age at hysterectomy or its indication.

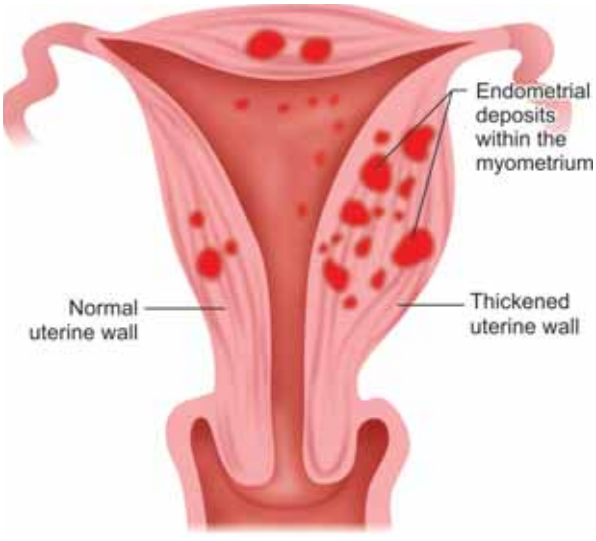

Figure 2.1: Adenomyosis.

Associated Pathology

Nearly 80% of women with adenomyomas may also have other lesions, most common being the leiomyomas. Other lesions which may frequently occur in these cases include endometrial polyps, endometrial hyperplasia (with or without atypia), adenocarcinoma and pelvic endometriosis. Presence of adenomyosis, however, has no adverse effect on cancer survival.

ETIOLOGY

Abnormal ingrowth and invagination of the basal endometrium into the subendometrial myometrium at the endometrial-myometrial interface is likely to result in development of adenomyosis. In case of adenomyosis, the margins are poorly defined because the endometrial glands and stroma are in direct contact with the myometrium. Hence, these lesions cannot be enucleated. Though the exact cause of adenomyosis remains unknown, various factors, such as hormonal, genetic and immunological, are likely to play a role in the pathogenesis of adenomyosis. Some likely causes are as follows:

Uterine trauma: Various causes of uterine trauma that may break the barrier between the endometrium and myometrium include surgical procedures such as cesarean section, tubal ligation, and pregnancy termination. Pregnancy is another factor which can break this barrier.

Oestrogen dominance: Conditions associated with the localized production of excessive estrogens may predispose the woman to develop adenomyosis.

Abnormal level of various cytokines: Increased levels of interleukin 18 (IL-18) receptor messenger RNA (mRNA) and the ratio of IL-18 binding protein to IL-18, and dysregulation of leukemia inhibitory factor.

DIAGNOSIS

The diagnosis of adenomyosis can only be confirmed by a pathologist.

Clinical Presentation

Nearly 35% of women with adenomyosis uteri are asymptomatic. Commonly occurring symptoms include menorrhagia (unres-

ponsive to hormonal therapy or uterine curettage) and progressively increasing dysmenorrhea. Menorrhagia can occur in nearly 40–50% cases, dysmenorrhea in 10–30% cases and metrorrhagia in 10–12% cases. Menorrhagia may be due to dysfunctional contractility of the myometrium, endometrial hyperplasia and anovulation. Other symptoms may include pelvic pain, backache, dyspareunia, dyschezia and subfertility. Older women tend to be more symptomatic in comparison to younger women.

Pelvic Examination

- Uterus may become diffuse and enlarged in cases of diffuse adenomyosis. Uterus may be enlarged to about 12–14 weeks in size and may be tender to touch, soft and boggy
- Adenomyosis is associated with uterine fibroids in about 6–20% cases.

Investigations

Presently, there is lack of a reliable, noninvasive diagnostic test for diagnosing adenomyosis. No serum markers for the diagnosis of adenomyosis are currently available. Some investigations, which are commonly performed, include the following:

- *Ultrasound examination*: Transvaginal sonography (TVS) is better than transabdominal sonography (TAS) in demonstrating the subtle features suggestive of adenomyosis uteri. Some features suggestive of adenomyosis on TVS are enlisted in Box 2.1. Presently, there is no consensus regarding whether one or some of these criteria should be used for making the diagnosis of adenomyosis. Most authorities presently use three or more of these criteria for making the diagnosis of adenomyosis. A recent meta-analysis has indicated that ultrasound features such as presence of myometrial cysts, linear myometrial striations, poor delineation of the endomyometrial junction and a heterogeneous myometrium are associated with an increased probability of the presence of disease (Fig. 2.2).

  In the normal woman, the myometrium has three distinct sonographic layers of which the middle layer is the most echogenic and the inner layer is hypoechoic relative to the middle and outer layers. This hypoechogenicity is responsible for producing the subendometrial or myometrial halo. The presence of adenomyosis uteri can cause alterations in the sonographic appearance of these zones. Studies regarding the accuracy of TVS for detection of adenomyosis have reported the rates of sensitivity varying between 53% and 89% and specificity varying between 50% and 99%. Three-dimensional ultrasonography is likely to offer higher accuracy in determining uterine volume and pathology.
- *Magnetic resonance imaging*: This is superior to ultrasound for the diagnosis of adenomyosis. There has been growing evidence to support the use of magnetic resonance imaging (MRI) in the diagnosis of adenomyosis uteri. MRI may be considered when findings on TVS appear to be inconclusive. However, its high cost and limited availability may impede its routine use. The presence of heterotopic endometrial glands and stroma in the myometrium appear as bright foci within the myometrium on T2-weighted MR images (Fig. 2.3). Adjacent smooth muscle hyperplasia may present as areas of reduced signal intensity on MRI. On MRI examination, there is considerable variation in the thickness of junctional zone, ranging from 2 mm to 8 mm. The appearance of diffuse or focal widening of the junctional zone on MRI is suggestive of adenomyosis uteri. Several studies which have compared the accuracy of TVS and MRI have found both these techniques to have comparable sensitivities and specificities. Nevertheless, MRI is less observer-dependent. MRI has proved to be superior to TVS in the presence of associated leiomyomas or additional pathologies. MRI is more useful in distinguishing adenomyosis from fibroids in an enlarged uterus.
- *CA-125*: Level of CA-125 in the peripheral blood may be raised.
- *Histopathological examination*: The final diagnosis is established by histopathological examination of the hysterectomy specimen.

DIFFERENTIAL DIAGNOSIS

Leiomyomas: Adenomyosis is most commonly confused with leiomyomas. TVS is an effective, noninvasive and relatively inexpensive procedure for establishing the diagnosis of adenomyoma preoperatively.

MANAGEMENT

Different surgical and medical modalities of treatment have been used for the management of cases of adenomyosis uteri. Management is often directed at the treatment of symptoms. Presently, there is limited evidence regarding the use of medical, nonhormonal therapy for the treatment of cases of adenomyosis. These treatment strategies are likely to result in a variable and unpredictable degree of symptomatic relief, which is usually limited to the duration of treatment.

MEDICAL THERAPY

Medical treatment for cases of adenomyosis comprises of nonsteroidal anti-inflammatory drugs (NSAIDs), hormone

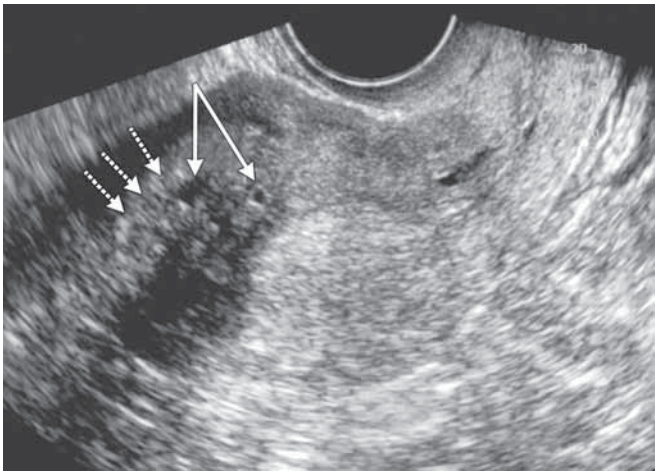

Figure 2.2: Ultrasound showing mottled texture of the myometrium and presence of hypoechoic areas within the hyperechoic area in the fundal region which is suggestive of adenomyosis.

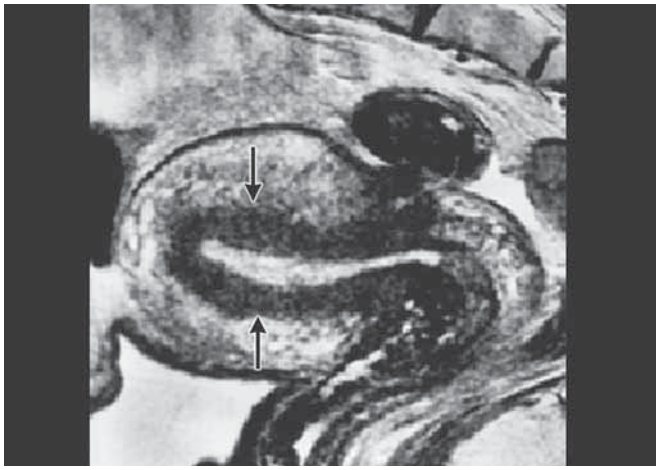

Figure 2.3: Sagittal T2-weighted MR image showing diffuse, even thickening of the junctional zone (as depicted by arrows) which is consistent with the diagnosis of diffuse adenomyosis.

Box 2.1: Criteria used to diagnose adenomyosis using TVS.

- Globular uterine enlargement in the absence of leiomyomas
- Asymmetric enlargement of the anterior or posterior myometrial wall
- Heterogeneous, poorly circumscribed anechoic areas within the myometrium
- Hyperechoic islands or nodules, finger-like projections or linear striations, indistinct endometrial stripe
- Anechoic lacunae or cystic spaces of varying size, which may be blood-filled
- Focal or diffuse thickening of the junctional zone
- Low-signal intensity uterine mass with ill-defined border
- Junctional zone thickness: 12 mm
- Indistinct endometrial-myometrial border
- Localized high signal foci within an area of low signal intensity
- Myometrial linear striations
- Parallel shadowing
- Bright foci in endometrium of similar intensity to the myometrium (T_1-weighted)
- Ratio of maximal junctional zone thickness to myometrium thickness: 40%
- Subendometrial halo thickening.

therapy, danazol, gonadotropin-releasing hormone (GnRH) agonists and Mirena® intrauterine contraceptive device (IUCD). Medical nonhormonal therapy, including mefenamic and tranexamic acid, may be effective for the symptomatic relief of menorrhagia in patients with uterine adenomyosis. Symptomatic relief is also obtained using hormonal treatment including progestogens, the combined oral contraceptive pills (OCPs) and GnRH analogues.

Combined oral contraceptive pills: Use of low-dose, continuous combined oral contraceptives with withdrawal bleeding after every 4–6 months may be effective in relieving menorrhagia and dysmenorrhea associated with adenomyosis. However, there is no specific study related to this therapy in cases with adenomyosis.

Gonadotropin-releasing hormone analogues: Use of GnRH analogues is also likely to be useful for the treatment of adenomyosis uteri by reducing uterine volume and providing symptomatic relief. However, these benefits are rapidly reversed following the cessation of treatment. Moreover, they are also likely to cause skeletal and general side effects. There could be a role for long-term use of GnRH therapy in association with add-back therapy as described with uterine fibroids and endometriosis.

Danazol: The use of danazol has largely become out-dated due to its androgenic side effects. Danazol-loaded intrauterine device has been used as a non-invasive method for the treatment of infertile women with adenomyosis uteri. This method is likely to result in pregnancy following the discontinuation of treatment. Moreover, it is associated with preservation of both menstrual and ovulatory functions and a significant decrease in dysmenorrhea.

Levonorgestrel intrauterine system: Levonorgestrel intrauterine system (LNG-IUS) has been tried as the treatment option of moderate or severe dysmenorrhoea and/or menorrhagia associated with adenomyosis. There is some evidence that the presence of deep lesions of adenomyosis is associated with the failure of endometrial ablation. In these situations, LNG-IUS has also been successfully used for the treatment of adenomyosis-associated menorrhagia, especially when inserted immediately after endometrial ablation. In these situations, LNG-IUS has also been successfully used for the treatment of adenomyosis-associated menorrhagia, especially when inserted immediately after endometrial ablation.

SURGICAL MANAGEMENT

Hysterectomy

Total hysterectomy with or without bilateral salpingo-oophorectomy is the treatment of choice in elderly patients who are past their childbearing age or those who have completed their childbearing. Decision to perform a hysterectomy is usually based on the presence of other pathologies such as leiomyomas or failure of medical or conservative management in cases of menorrhagia. Conservative surgery may be performed in the younger patients.

Conservative Surgery

Uterine Artery Embolization

Uterine artery embolization (UAE) is presently developing as an effective and safe method for the treatment of adenomyosis. UAE, by causing reduction of the uterine blood flow by blocking the uterine artery, has been shown to reduce the symptoms associated with adenomyosis uteri and to improve the quality of life. However, the recurrence rate of adenomyosis following the procedure has yet not been evaluated. UAE can be considered as a recognised and effective treatment option for women with adenomyosis having concurrent fibroids. However, there is limited evidence regarding the efficacy of UAE in cases where the predominant lesion is adenomyosis and all patients undergoing UAE should be counselled regarding the chances of treatment failure, recurrence rates and the requirement for hysterectomy in future. The chances of a subsequent successful pregnancy following the procedure are unclear.

Endomyometrial Ablation

Endometrial ablation or resection can be considered as an option for women with superficial adenomyosis, presenting with the complaints of menorrhagia. However, the option of endometrial ablation cannot be used in women desiring future pregnancy. Moreover, this procedure is likely to be associated with an increased failure rate in patients with heavy menstrual bleeding in case of deep adenomyosis.

Magnetic Resonance-guided Focussed Ultrasound

Magnetic resonance-guided focussed ultrasound (MRg-FUS) has also been tried as a noninvasive option for the treatment of adenomyosis. However, further studies are required in future for assessment of the overall safety and long-term effectiveness of MRgFUS for the treatment of adenomyosis.

Laparoscopic/Hysteroscopic Biopsy

The role of invasive hysteroscopic or laparoscopic biopsy for diagnosing adenomyosis remains limited.

COMPLICATIONS

- Adenomyosis can be associated with considerable morbidity due to the presence of debilitating symptoms such as menorrhagia, dysmenorrhea, chronic pelvic pain, etc.
- Reduced fertility
- Coexistence of pelvic abnormalities such as uterine fibroids, endometrial hyperplasia and endometrial adenocarcinoma.

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3

CHAPTER

Surgery for Endometriosis

INTRODUCTION

Endometriosis, which is an important cause of infertility, is a clinical entity characterized by the presence of ectopic endometrial glands and stroma outside the uterine cavity. The common sites of endometrial implants include the pelvic cavity, ovaries, uterine ligaments, rectovaginal septum, parietal peritoneum, intestinal serosa, etc. (Fig. 3.1). This disease can be associated with a varied clinical presentation. There can be pelvic symptoms (e.g. dysmenorrhea, dyspareunia, chronic pelvic pain, sciatica, premenstrual spotting, etc.); gastrointestinal symptoms (e.g. constipation, diarrhea, dyschezia, tenes-mus, hematochezia, etc.); urinary symptoms (e.g. flank, abdominal and back pain, urinary urgency, frequency and hematuria); infertility and pulmonary symptoms (e.g. hemoptysis, chest pain, pneumothorax, etc.). Endometriosis may be responsible for nearly 20% cases of infertility. Approximately 20–40% of women with endometriosis are infertile.

The mechanisms by which endometriosis can cause infertility are still not clear.[1] The disease can produce an inflammatory response, which can have a harmful effect on the tubal function. It can cause mechanical interference for the migration of sperm and ova by producing pelvic adhesions, chronic salpingitis, altered tubal motility, distortion of tubo-ovarian relationship and impaired oocyte pickup. There can be impaired peristaltic activity of the fallopian tube. The presence of endometrial implants is often associated with the markers of inflammation, such as impaired concentration of prostaglandins, increased number of activated macrophages, and impaired production of cytokines. All these may result in an increased phagocytosis of sperms. Endometriosis can also produce hormonal or ovulatory dysfunction, which can result in defective folliculogenesis, hyperprolactinemia, luteal phase deficiency and luteinized unruptured follicle syndrome. It can cause a failure of fertilization or implantation. Abnormalities in immune response can also

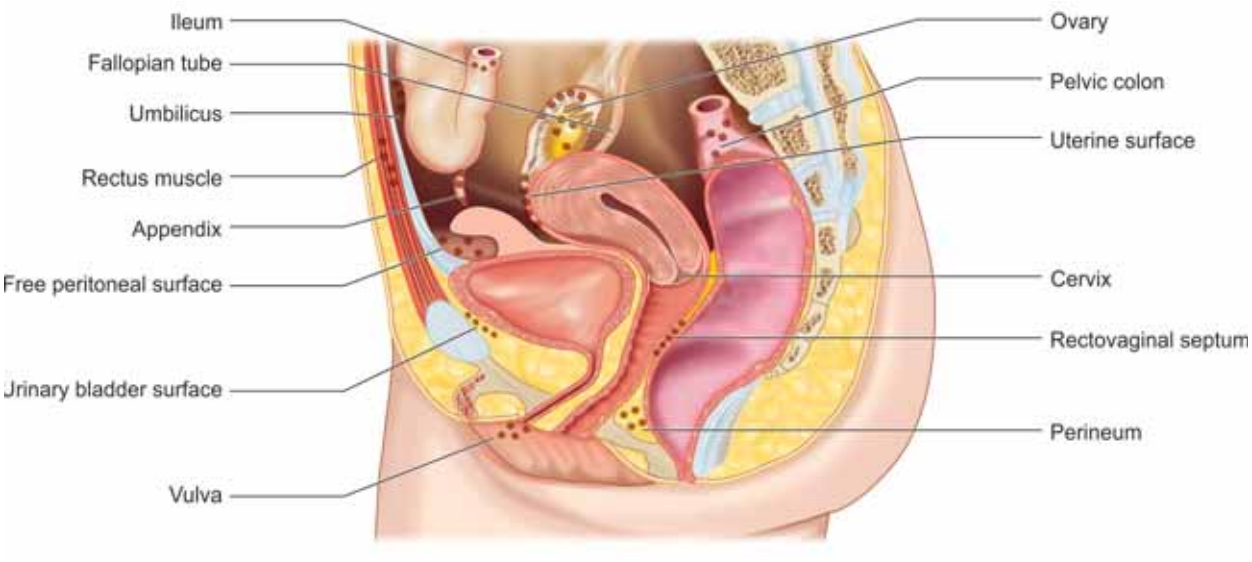


Figure 3.1: Common sites of endometrial implants.

cause injury to the gametes and production of autoantibodies against the endometrium.

Endometriosis can be categorized into four stages: stage 1 to stage 4 (Figs. 3.2A to D). Before initiating treatment for endometriosis, it is important to classify the disease as minimal, mild, moderate or severe. The American Fertility Society's revised staging for endometriosis is currently the most widely used staging system.[2] In this scoring system, point scores are assigned based on the number of lesions, their bilaterality, size of the lesions, depth of endometrial implants, presence and extent of adnexal adhesions, and degree of obliteration of the pouch of Douglas. It, however, does not take into account the complaints like infertility or pelvic pain. This classification is a fairly accurate method of recording laparoscopic findings and can help standardize the patient's findings and documenting the patient's baseline condition and subsequent progress.

OVERVIEW OF SURGERY

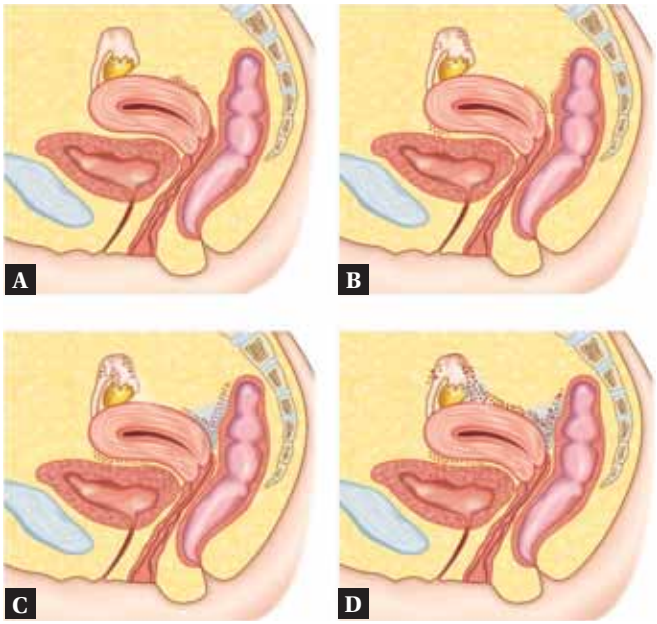
A laparoscopic examination is required if the hormonal treatment used for treatment of mild or moderate cases of endometriosis fails, or if endometriosis is severe or debilitating. Patients presenting with symptoms indicative of endometriosis require visual inspection of the pelvis at the time of laparoscopy, and histologic confirmation of at least one lesion.

Presently laparoscopy has become the gold standard test for diagnosing endometriosis in clinical practice.[3-7] Endometriotic implants may show varied appearance. The lesions may appear as black, dark-brown or bluish implants or deposits, although red, serous and even clear vesicles have been reported (Fig. 3.3). Endometriotic nodules or lesions having blue-black or a powder burned appearance (Figs. 3.4A and B and 3.5) are a late consequence related to cyclic growth and regression of the lesions resulting in bleeding and hemosiderin staining of the tissues. Endometriosis can also be detected by the presence of either blood (Fig. 3.6) or endometriotic deposits in cul-de-sac, and its obliteration due to adhesions. Various morphological lesions indicative of endometriosis include vesicles, flat plaques, raised lesions, polypoid structures, peritoneal defects and adhesions (Figs. 3.7 to 3.9). Yellow, brown, blue or black discoloration of endometriotic lesions is proportional to the amount of hemosiderin deposition. Endometriotic lesions of the ovary can result in the formation of ovarian cysts, which are often referred to as "endometriomas" and/or "chocolate cysts" (Fig. 3.10).

Diagnosing endometriosis exclusively on visual identification, however, can result in both misdiagnosis as well as overdiagnosis. Biopsy helps in confirming the diagnosis and reveals endometrial glands and fibrous stroma. Near-contact laparoscopy, which results in up to an eightfold magnification of lesions can help to identify atypical implants as small as 400 μm.

Aims Of Surgery

Surgery for endometriosis aims at destroying all visible endometriotic lesions and any associated adhesions. However, there may be no correlation between the amount of visible endometriosis seen at the time of surgery and the extent of symptoms. Surgery in case of patients presenting with infertility may involve the following:[3]



Figures 3.2 A to D: Stages of endometriosis. (A) Stage 1 (minimal); (B) Stage 2 (mild); (C) Stage 3 (moderate); (D) Stage 4 (severe).

- Removal or destruction of endometrial implants
- Removal or destruction of ovarian endometriomas
- Removal, lysis or destruction of adhesions
- Removal of deep rectovaginal and rectosigmoid endometriosis
- Dissection of ovaries from cul-de-sac or pelvic sidewall, freeing tubal adhesions
- Uterosacral nerve ablation or presacral nerve resection for chronic pelvic pain.

Parietal and visceral peritoneal adhesions to pelvic organs, bowel and omentum can be carefully dissected using atraumatic forceps and aquadissection or blunt dissection. Thick or fibrous bands may require cauterization and sharp dissection.

Mild to moderate endometriosis is treated by ablation or cauterization of the endometriotic deposits. Diathermy, yttrium-aluminium-garnet (YAG) or carbon dioxide laser and helium thermal coagulator (Helica) are the three electrosurgical devices available. Coagulation can be achieved with help of monopolar or bipolar cautery (bipolar cautery is associated with lesser tissue damage in comparison to monopolar cautery), thermocoagulation or laser therapy (CO_2 laser is more accurate than fiber laser). In Stage III or IV endometriosis, conservative surgery to excise or ablate all endometriotic lesions is recommended.

Genitourinary and gastrointestinal lesions are best operated by advanced laparoscopic surgeons as involve-ment of the bladder, ureter, intestine and rectum is common.

Indications

Indications for surgery include the following:

- *Patients desiring fertility*: In patients with endometriosis desiring fertility, surgical treatment is usually preferred over the medical treatment. The likelihood of subsequent conception can significantly be increased by undertaking surgery in

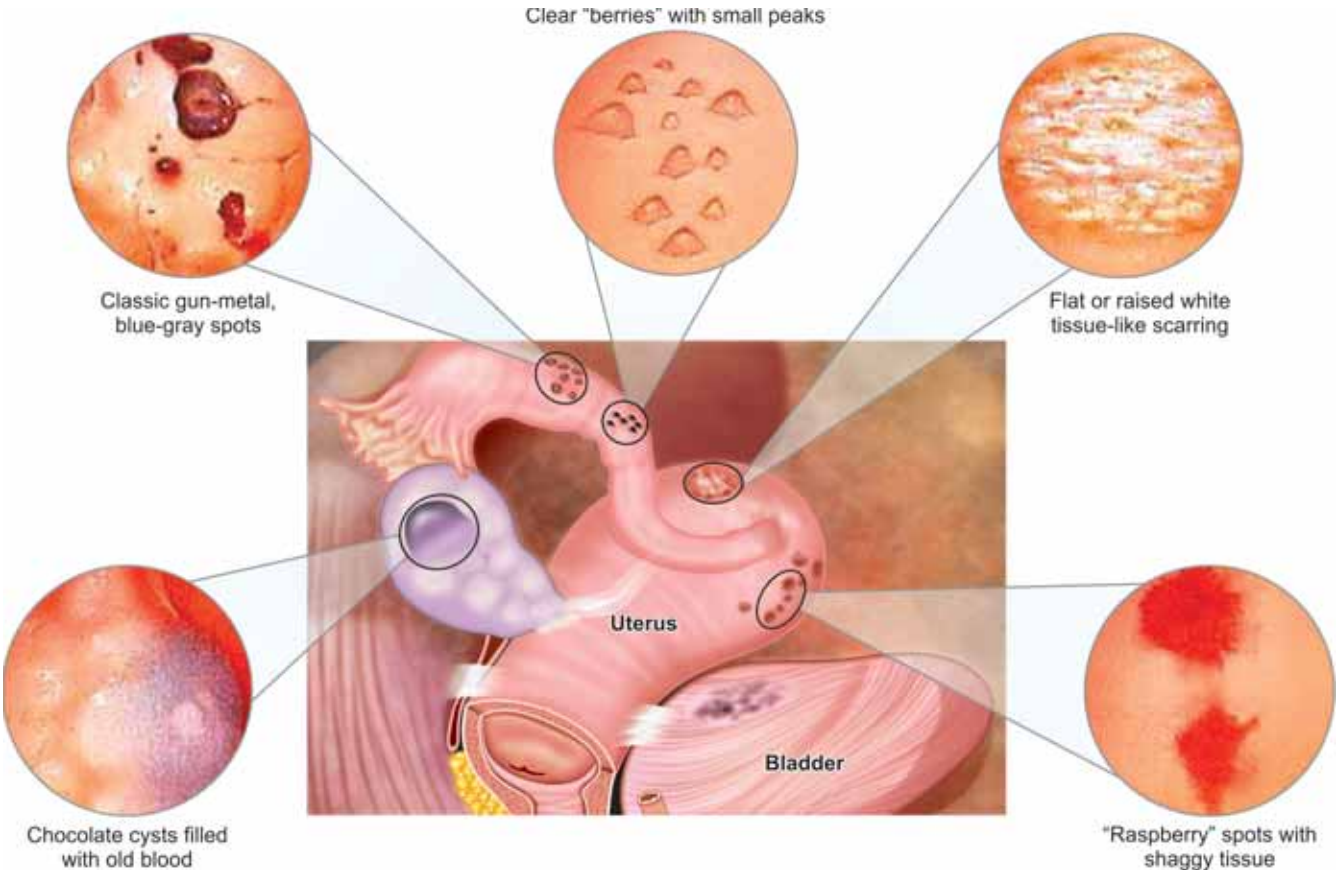
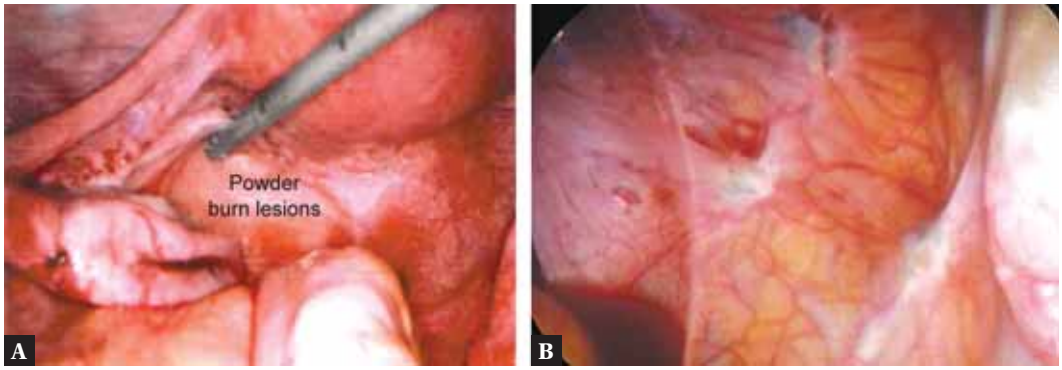


Figure 3.3: Diagrammatic representation of various endometriotic lesions.



Figures 3.4A and B: Powder burn lesions.

patients with endometriosis presenting with infertility. Moreover, medical treatment has not been shown to help the patients with endometriosis conceive. Furthermore, pregnancy is contraindicated in patients receiving medical treatment and is in fact unlikely, because the drugs that are used may interfere with ovulation and endometrial implantation. However, some authorities do believe that endometriosis should be suppressed prophylactically by using continuous medical therapy such as combined oral contraceptives, gonadotropin-releasing hormone analogs, medroxyprogesterone or danazol in order to cause regression of asymptomatic disease and enhance subsequent fertility. Surgical treatment remains the preferred approach for treatment of infertile patients with advanced endometriosis. The benefit of surgery in these patients may be entirely due to the mechanical clearance of adhesions and obstructive lesions.

Surgical care can be broadly classified as conservative when reproductive potential is retained, semiconservative when reproductive ability is eliminated but ovarian function is retained and radical when both the uterus and ovaries are removed. Age, desire for future childbearing and deterioration of quality of

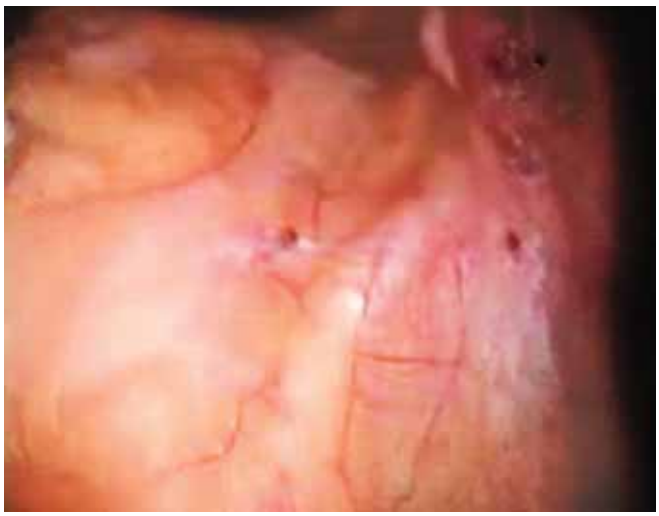


Figure 3.5: Nodular endometrial lesions.

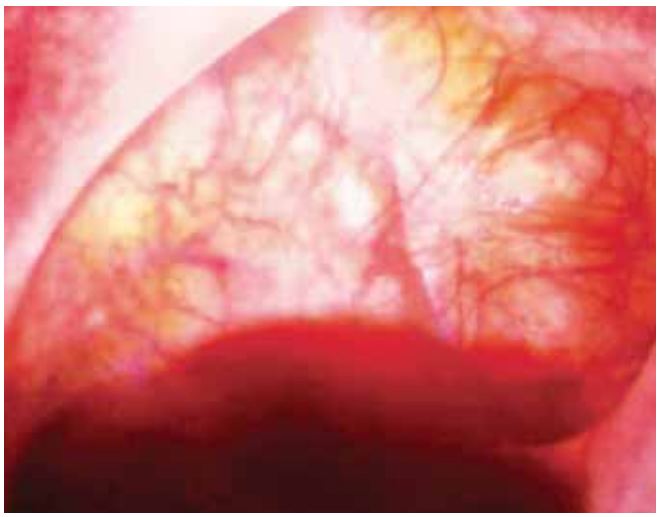
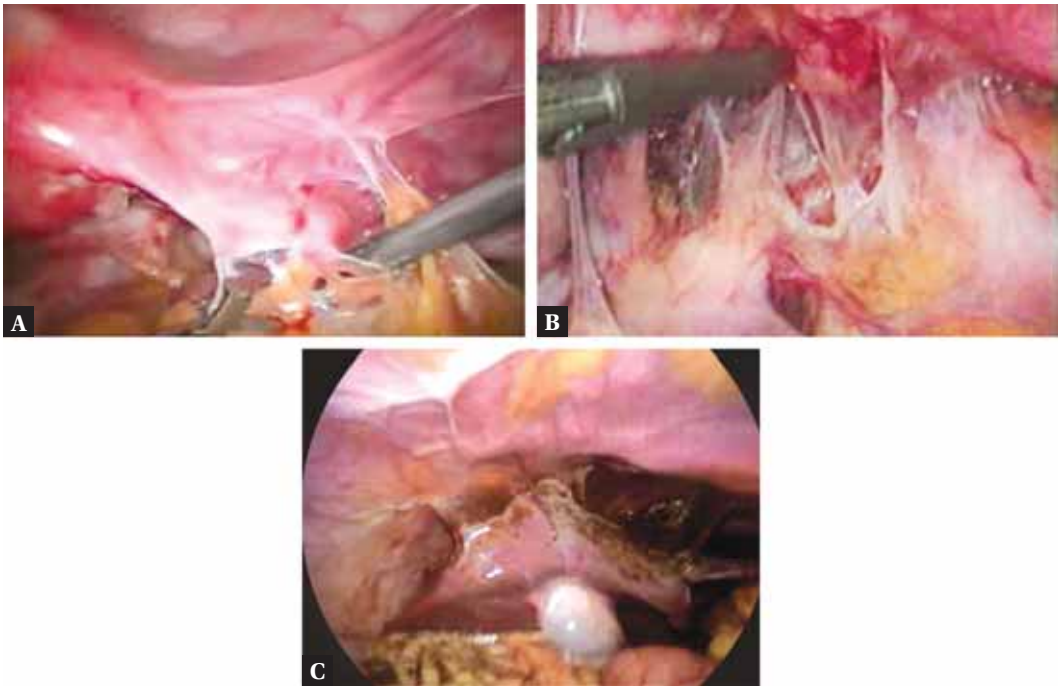


Figure 3.6: Presence of blood in cul-de-sac.



Figures 3.7A to C: Presence of adhesions: (A) Presence of flimsy adhesions over the pelvic peritoneum; (B) Dense adhesions between the intestines and pelvic organs; (C) Adhesions between the liver and the undersurface of diaphragm.

life are the main considerations when deciding on the extent of surgery.

- *Extensive pelvic endometriosis:* Correction of pain, infertility or other symptoms in patients with extensive pelvic endometriosis.
- *Failure of hormonal therapy:* Surgery may also be required in lesser stages of the disease when the hormonal manipulation fails to adequately reduce the symptoms of pain. There is sufficient evidence indicating that surgical procedure is effective in relieving pain in majority of the women with endometriosis, where there is a failure of hormonal method.[8]

PREOPERATIVE PREPARATION

The preoperative care is similar to any other laparoscopic or laparotomy procedure. In cases of endometriosis, the following investigations may be required:

- *Diagnostic laparoscopy:* Diagnostic laparoscopy is the gold standard investigation for establishing the diagnosis of endometriosis. Findings of laparoscopy must be validated by peritoneal and tissue biopsy.
- *Imaging studies:* These may include transvaginal sonography, Magnetic resonance imaging (MRI) and Computed Tomo-

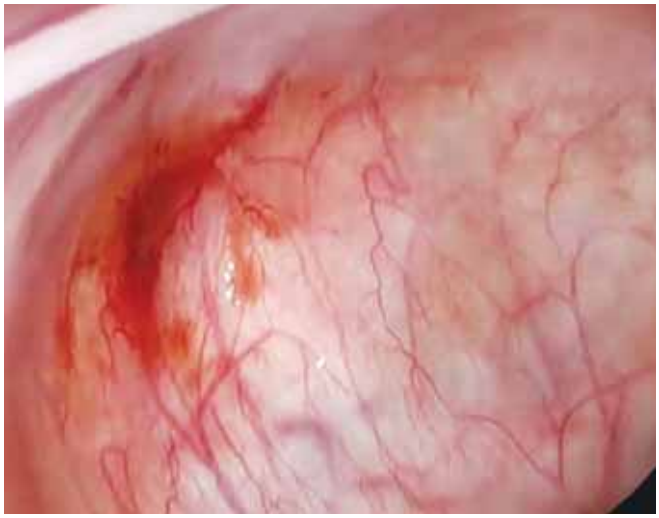


Figure 3.8: Reddish-brown plaque-like lesion of endometriosis.

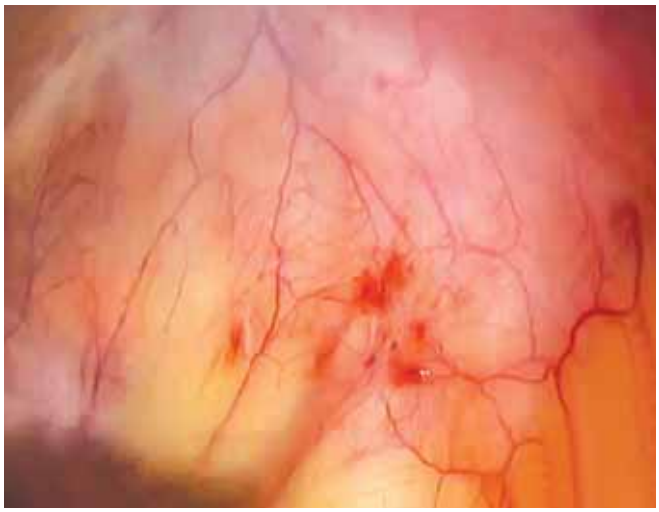


Figure 3.9: Red raspberry spots of endometriosis.

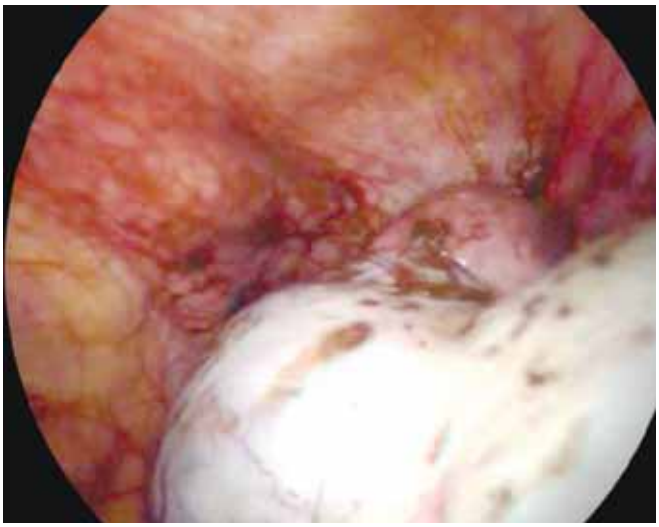


Figure 3.10: Portion of a large endometrial cyst of the left ovary.

graphy (CT) scan. Transvaginal sonography has a sensitivity of 83% and a specificity of 98% in establishing the diagnosis of endometriosis. MRI examination may be helpful in predicting the disease extension.

- *CA 125 levels:* CA 125 levels are raised to more than 35 U/mL in more than 80% cases of endometriosis. However, this is not a specific test because its levels may also be raised in presence of other pathologies such as pelvic inflammatory disease, malignant ovarian tumors, abdominal tuberculosis, etc.
- *Cystoscopy:* A cystoscopic examination may be required to identify extension to the bladder.
- *Sigmoidoscopy:* Preoperative sigmoidoscopy with intravenous pyelography is recommended in patients having symptoms suggestive of deep invasive endometriosis of the posterior cul-de-sac and rectovaginal septum.

SURGICAL STEPS

Surgical Equipment Used

Microsurgery can be used both at the time of endometriotic surgery as well as tubal reconstruction surgery.

Surgery For Endometriosis

Laparoscopic surgery is nowadays considered for most of the cases of endometriosis (Figs. 3.11 to 3.13) unless there is difficulty in establishing the appropriate tissue planes or dissection, or unless improved access is required for the atraumatic manipulation of the involved organs.[9] The decision regarding whether surgical resection of the endometriotic lesions should be performed via laparoscopic route or laparotomy is usually not dependent on the disease stage. Specific endoscopic procedures, which can be performed, include ablation of endometriotic implants, adhesiolysis, ovarian cystectomy, oophorectomy and salpingectomy. Laparoscopy is associated with reduced duration of hospital stay as well as health care expenses.[10]

Laparoscopy also helps in providing better visualization of the cul-de-sac by enabling higher degree of magnification of the peritoneal surfaces, which helps in the identification of the subtle disease as well. Moreover, laparoscopic approach is associated with minimal bleeding and minimal risk of adhesion formation and reduced duration of hospital stay. Several endoscopic techniques, which can be used for ablation of endometriotic lesions, include excision, coagulation and vaporization. Coagulation can be attained by monopolar or bipolar cautery, thermocoagulation or laser.

Small peritoneal endometriotic lesions, which are less than 5 mm in diameter can be treated with laser or bipolar coagulation while application of constant irrigation. Deep lesions or more extensive peritoneal disease must be excised with a tissue margin of 2–4 mm because microscopic lesions may be present along with the macroscopic lesions. The identification and isolation of the ureter must be performed just before the dissection of pelvic sidewall.

Laparoscopic Management of Endometriosis

Mild to moderate endometriosis: The endometriosis spots are destroyed by diathermy, where an electric current is passed

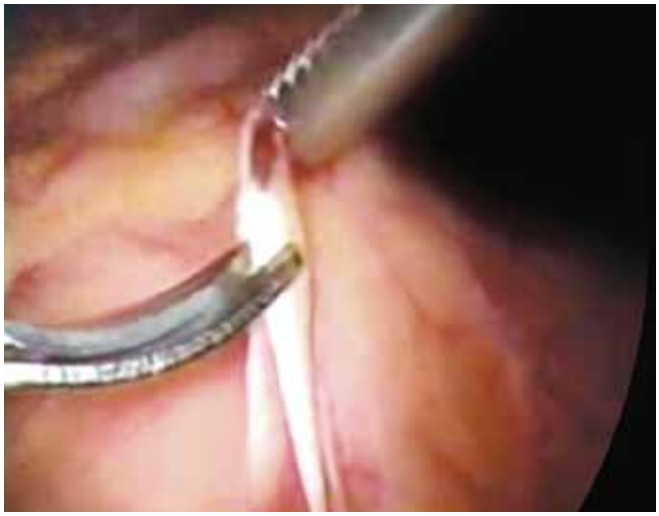


Figure 3.11: Laparoscopic excision of nodular endometrial lesions overlying the round ligament.

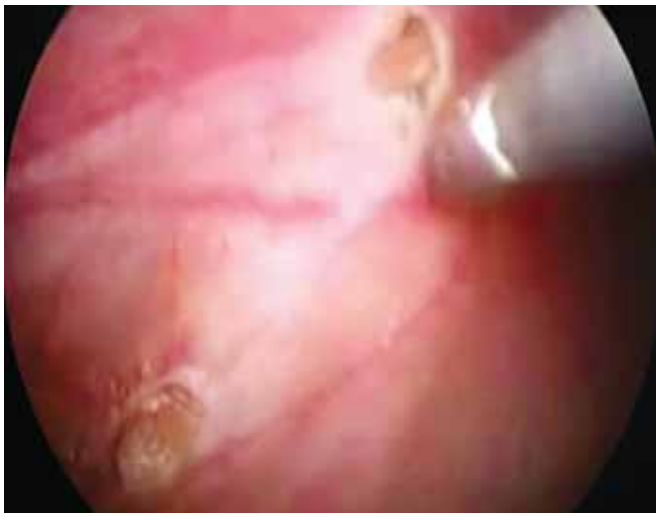


Figure 3.12: Laser ablation of endometriotic lesions.

down a fine probe. Some surgeons use laser to evaporate the endometriosis. Fine adhesions can be cut using small scissors. It has been found that laparoscopic destruction of lesions results in a 13% increase in pregnancy rate.[11]

Moderate to severe endometriosis: Laparoscopic option can also be used in cases of moderate to severe endometriosis, where there is severe scarring or adhesion formation or presence of an ovarian endometrioma.[12] In women with moderate endometriosis, one can expect pregnancy success rates of around 60%, whereas with more severe disease the pregnancy rate is around 35%.[13] If a pregnancy does not occur within 2 years of surgery for endometriosis, the chances of success are poor, and referral for in vitro fertilization should be made.

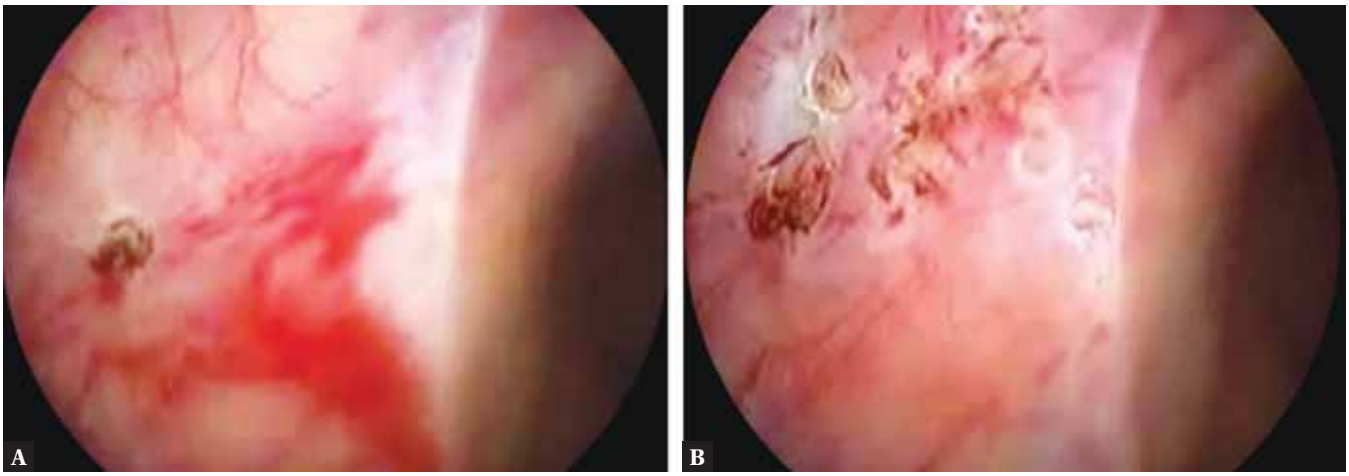
Laparotomy

This is the usual method of approaching the more severe degrees of endometriosis, particularly where endometriomas are large, and there is more extensive scarring involving the bowel and bladder. Conservative resection of the disease by laparotomy is most commonly performed in the following cases:

- Extensive, dense pelvic adhesions
- Endometriomas greater than 5 cm in size
- Deep involvement of the rectovaginal septum
- Invasion of bowel/bladder musculature
- Endometriotic infiltration in the region of uterine vessels and ureter.

Hysterectomy or oophorectomy should be considered in patients with severe endometriosis not desiring fertility.[14] The rather extreme surgical treatment of hysterectomy with bilateral salpingo-oophorectomy serves an option in older women past their childbearing age, or for women who suffer from intractable pelvic pain. In this procedure, care should be taken to ensure that all visible endometriotic tissues are removed. Bilateral salpingo-oophorectomy also results in improved pain relief.

Uterine suspension techniques have been devised to reduce adhesion formation at the denuded peritoneal surfaces of the posterior cul-de-sac, uterine serosa and broad ligament. The most commonly used technique is the modified Gilliam's procedure. Elevation of the adnexa may prevent adhesion reformation of the fallopian tube or ovary at a site where the existing adhesions have been excised. This procedure is especially indicated in



Figures 3.13A and B: Appearance of the uterine surface after the ablation of endometriotic lesions.

cases of dyspareunia after the resection of posterior cul-de-sac endometriosis. The modified Gilliam's procedure offers advantages over other forms of uterine suspension procedures due to its ability to maintain the normal anatomical relationships. In this procedure, the uterus is elevated and a 2-0 absorbable suture is placed around each round ligament about 3–4 cm from its insertion into the uterus.

Management of Ovarian Endometriosis

The treatment of ovarian endometriosis depends on the type of lesion and its size. Superficial ovarian implants can be destroyed by coagulation or vaporization. Endometriomas less than 2 cm in diameter may be coagulated, laser ablated or excised using scissors or biopsy forceps. All visible lesions and scars must be coagulated or excised from the ovarian surface to prevent recurrence. Small ovarian endometrial cysts can also be punctured and drained. The inner lining of the cyst can be destroyed by coagulation or vaporization. Large ovarian cysts greater than 3 cm in diameter can be excised, or drained and coagulated. It is recommended that large ovarian cysts greater than 3 cm in diameter be excised rather than drained and coagulated.

In case of the excision of an ovarian endometrioma, an incision must be made on the ovarian cortex in such a way that the normal anatomical relationships of the ovary remain preserved. A shallow longitudinal incision is made over the endometrioma with a monopolar microneedle, scalpel or a laser.[15] Dissection can be performed with the help of a blunt curved scissors or a flat probe or a knife handle.[16] Care must be taken at the time of dissection of the hilar region in order to maintain hemostasis and preserve primordial follicles. As much of normal ovarian cortex as possible must be preserved. The reconstruction of ovaries can be performed by placing one to two purse-string sutures of polyglycolic acid or polygalctin in order to eliminate the dead space and to maximize hemostasis. Placing an adhesion barrier, such as interceed, between the raw peritoneal surfaces helps in improving the healing process and preventing the development of adhesions. Ovarian endometriomas less than 4–5 cm in diameter can be removed laparoscopically. However, in case of lesions greater than this, it may be difficult to remove them laparoscopically due to the presence of dense adhesions.

Cystectomy (Figs 3.14A to K) is recommended for endometriomas of or greater than 2 cm diameter. This is especially important in these cases because simply draining the endometrioma or even partial resection of the cyst wall can cause recurrence due to presence of functional residual tissue in the remaining tissue. The cyst is punctured and the contents aspirated with the suction probe (Figs 3.14B to E). The cyst wall should be separated and peeled off entirely from the ovarian stroma to prevent recurrence (Figs 3.14F and G). Any bleeding vessels from the stroma should be coagulated (Fig. 3.13H). The ovarian wall usually does not require closure, but if the defect is greater than 5 cm, laparoscopic suturing with 4-0 or 5-0 absorbable nonreactive material may be required to approximate the edges (Fig. 3.14I and J). The knots of these sutures must be placed internally to diminish the possibility of its becoming the nidus of adhesion formation. Smaller ovarian defects must be left to heal spontaneously because ischemia associated with suture placement can aggravate adhesion formation. Sometimes such large defects can be approximated with help of fibrin sealants in order to reduce the formation of adhesions.[17]

Laparoscopic Uterine Nerve Ablation and Laparoscopic Presacral Neurectomy

Laparoscopic uterine nerve ablation (LUNA) and laparoscopic presacral neurectomy (LPSN) are two procedures that involve cutting the nerves from the uterus to the brain in order to relieve chronic pain.[18] Presacral neurectomy, involves the interruption of sympathetic innervation of the uterus and central pelvis at the level of the superior hypogastric plexus. This may be performed either by laparoscopy or by laparotomy and serves as an adjunctive procedure to eliminate the uterine component of dysmenorrhea.

Second-Look Laparoscopy

This has been suggested as an appropriate option for lysis of pelvic adhesions in patients who have undergone a laparotomy or laparoscopy for the resection of endometriosis. It is usually scheduled 8 days to 6 weeks after the initial dissection. It allows separation of any remnant adhesions, which may still be filmy in consistency.

Laparoscopic Helium Plasma Coagulation

Laparoscopic helium plasma coagulation (Helica) is a more recent minimally invasive procedure in which the endometrial deposits are vaporized using an ionized beam of helium gas directed at the endometrial deposits.[19] However, presently there is lack of current evidence regarding the safety and efficacy of this procedure. Therefore, this procedure is used only under research settings. The presently available evidence does not suggest any major safety concerns associated with laparoscopic helium plasma coagulation for the treatment of endometriosis. (NICE, 2006). Until date, there has not been any comparative trial to measure the efficacy of ablation using Helica with that of other electrosurgical devices.

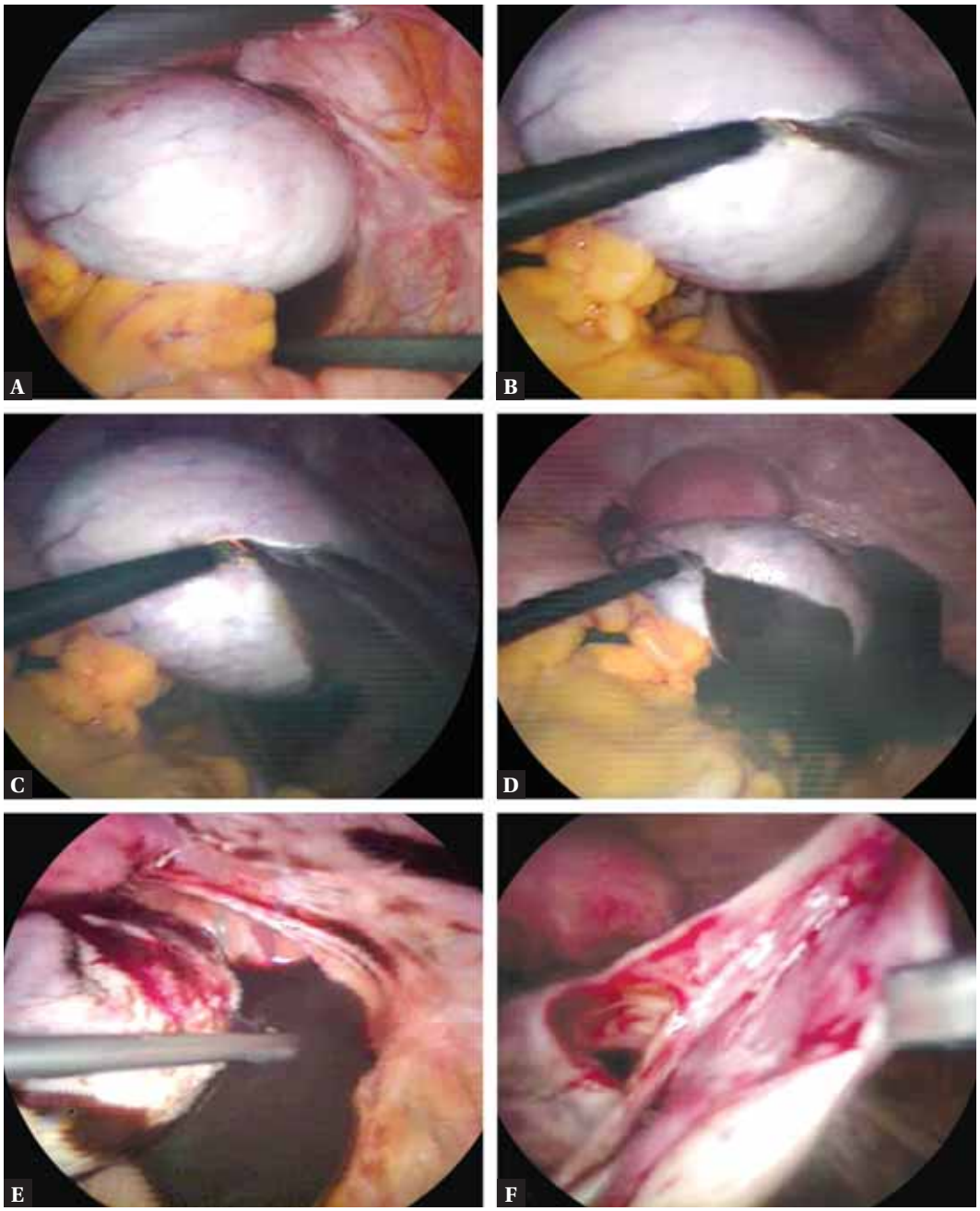
Postoperative Care

The postoperative care is similar to any other laparoscopic or laparotomy procedure. In case the patient is unable to conceive even after 1 year of active intercourse following surgery, IVF is the only option, which may help the patient conceive and this must be offered to her. Most clinicians do not recommend the use of postoperative hormonal therapy in patients suffering from pain, undergoing surgery for endometriosis. Presently, there is no evidence regarding the benefit of postoperative treatment with hormonal therapy in patients suffering from pain, undergoing surgery for endometriosis.[20-24]

ADVANTAGES

Besides the general advantages of laparoscopic surgery, in case of surgery for endometriotic lesions, use of laparoscope is associated with the following advantages:

- High degree of magnification provided by laparoscope allows for better visualization of cul-de-sac and peritoneal surfaces
- High degree of magnification also helps in identi-fication of subtle disease.



Figures 3.14A to F

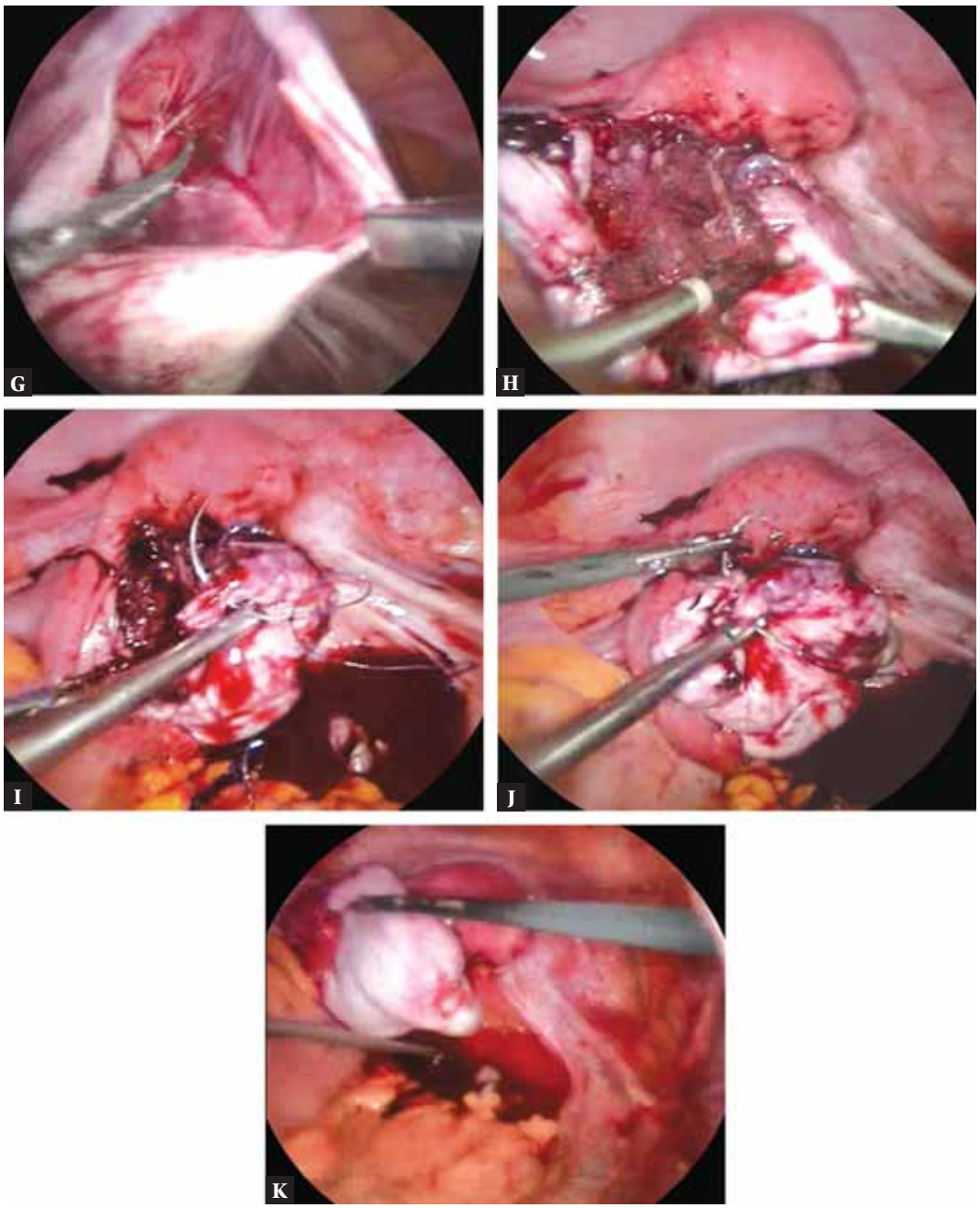
COMPLICATIONS

The following complications can occur in relation to the above-mentioned surgical procedures for infertility:[23,25]

- Complications related to laparoscopy
- Complications related to anesthesia
- *Complications related to laparotomy:* A surgical intervention may result in complications such as difficulty emptying the bladder, wound infection, urinary infection, infection of the uterus and vaginal discharge.

Other complications related to endometriotic surgery are as follows:

- *Constipation:* Constipation often occurs when surgery is performed on or around the bowel.
- *Diarrhea:* Diarrhea may also result from surgery around or on the bowel.
- *Shoulder pain:* This may be due to pneumoperitoneum related to laparoscopic surgery. The gas used during surgery often gets trapped under the diaphragm, causing pain that radiate up to the shoulder.
- *Urinary tract infection:* Urinary tract infection is a common occurrence in cases where the bladder is catheterized prior to the surgery.



Figures 3.14G to K

Figures 3.14A to K: Laparoscopic cystectomy of an endometrioma cyst: (A) Endometrial cyst of the right ovary; (B) The cyst wall is punctured; (C and D) Contents of the endometrioma spilling into the pelvic cavity; (E) The spilled contents aspirated with the suction probe; (F) The cyst wall is separated and peeled off from the ovarian stroma; (G) The cyst has been completely removed from the ovarian stroma; (H) Any bleeding vessels from the stroma should be coagulated; (I and J) Suturing of the defect in the ovarian wall with a single layer of sutures to approximate the edges; (K) The reconstruction of the ovary is complete.

- *Phlebitis or irritated veins:* Inflammation of a vein can occur due to intravenous injection of drugs. This can result in redness, tenderness and swelling of the affected arm. Treatment usually comprises of heat compresses, analgesics for pain, and elevation of the affected arm.
- *Nausea and vomiting:* Nausea and vomiting can commonly occur after surgery as a result of the adverse effect of anesthetic medications and/or painkillers.
- Pain.
- *Infection:* All surgery is associated with some risk of infection. Some signs of infection include fever [oral temperature above 100°F (37.8°C)] or development of any redness, discharge or swelling (hematomas, seromas, etc.) at the incision site or occurrence of discharge per vaginum, etc.

DISCUSSION

Until recently, surgery in infertile patients with limited endometrial disease was thought to be no better than expectant management. However, according to the recent evidence, surgery has been found to significantly improve the fertility rates among infertile women with minimal or mild endometriosis.[11] When the diagnosis of endometriosis is made at laparoscopy, surgical ablation of the lesions is frequently performed. Surgical treatment improves pregnancy rate and is the preferred initial treatment for infertility caused by endometriosis. Surgery also appears to provide better long-term pain relief in comparison to the medical treatment. Infertile patients with documented endometriosis can also benefit from the reproductive techniques such as superovulation, in vitro fertilization, etc.[12] Bilateral oophorectomy and hysterectomy are treatment options for patients with intractable pain, if childbearing is no longer desired. Women who have undergone oophorectomy must be treated with estrogen replacement therapy in order to prevent the side effects related to premature menopause.

Two modalities found to be beneficial and supported by evidence-based medicine for the treatment of endometriosis-associated infertility are conservative surgical treatment by laparoscopy and assisted reproductive technology. Present evidence indicates that in cases of minimal and mild endometriosis, surgical ablation of endometriotic lesions along with adhesiolysis is very effective in improving fertility in about 40–70% cases, and improvement in fertility is inversely proportional to the severity of endometriosis. However, in moderate to severe cases, improvement of fertility rate after surgical treatment of endometriosis has not been established. Overall, pregnancy rate are highest 6–18 months after surgical treatment of endometriosis.

The treatment option of choice for an infertile couple must be made after taking into consideration various technical and nontechnical factors. Therefore, the treatment must be individualized for each patient. The information about success and complication rate of the various procedures must be explained to the patients before undertaking any kind of treatment intervention.

CONCLUSION

Diagnostic laparoscopy has now become the gold standard investigation of choice for the diagnosis of endometriosis. It is also useful for treatment of endometriosis. However, visual identification, although usually adequate, can lead to misdiagnosis, and histologic confirmation of at least one lesion is considered ideal. Besides removing the endometriotic lesions, the minimally invasive surgery is also useful in restoration of patient's fertility and in improving the woman's chances of conception. Complete ablation of endometriotic lesions help in reducing disease-related pain, enhancing fertility and reducing the chances of recurrence. Cyst-wall excision of endometrioma having a size greater than or equal to 2 cm is essential for reducing recurrence and providing better pain relief.

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4

CHAPTER

Laparoscopic Treatment of Endometriosis

INTRODUCTION

Endometriosis is one of the most common disorders encountered in surgical gynecology which arise from the ectopic deposits of the endometrium outside the uterine cavity (peritoneal cavity, abdominal and pelvic organs and pelvic ligaments).[1] Determining the prevalence of endometriosis is very difficult, but it been estimated that it affects around 5–15% of the women who are in their reproductive age, it has also been seen to have an increasing prevalence in the last 15–20 years.[2]

The patient of endometriosis mainly has characteristic pelvic pain that may be generally due to dyspareunia, dysme-norrhea, dysuria, or dyschezia. Other symptom includes infertility.[3] Being a chronic condition, it may often results in intermittent or chronic pelvic pain, and can also impact significantly on organ function and thus impairing women's quality of life. Endometriosis can occur in various locations within the pelvis. Based on the location, there are two main forms of endometriosis:

1. Endometriomas
2. Deep infiltrating endometriosis (DIE).

Endometrioma

It is a cystic ovarian mass which arises when the ectopic endometrium gets implanted on the surface of ovary. It commonly gets implanted at the level of the posterior leaf of the broad ligament. Now this cyst which develops contains a brown fluid that is typical to this disease, if it is not pathognomonic.

Deep Endometriosis

It develops when an endometrial lesion invades the peritoneal surface for more than 5 mm of depth. The most common location where endometrial lesion invades is at the rectovaginal septum, uterosacral ligaments, pararectal fossa, and vesicouterine pouch.

Gold standard for diagnosing the endometriosis has been laparoscopy as it can provide direct visualization of endometriotic implants. The laparoscopic technique, the planning of the surgical intervention, the extent of information provided to patients and the interdisciplinary coordination make it a challenging intervention. Complete resection of all visible foci of disease offers the best control of symptoms. Other than this advance diagnostic tools like transvaginal sonography (TVS) and magnetic resonance imaging (MRI) have made these tools increasingly useful to aid the diagnosis, and evaluate the specific location and it has also made possible to evaluate the extent of infiltration of the lesion.[4]

In the last decade, endoscopic surgery has been evolved a lot and has revolutionized the surgical approach to the treatment of endometriosis.[5] As it is a minimally invasive approach which has specific advantages that can assist the surgeon facing complex and multivariable disease.

Endoscope allows image magnification which enables the operator to recognize subtle lesions in DIE that may get overlooked otherwise. In addition, laparoscopy also improves precision and fine movement facilitating more complex dissection, making surgeries more easy.

STRATEGY IN ENDOMETRIOSIS TREATMENT

Endometriosis is disease which can lead to anatomical distortion making and hence making its surgical treatment technically challenging and may also lead to higher risk of complications as a result. Endometriosis is a multicentric complex disease and it can affect the entire pelvis including the organ systems like urinary tract, bowel, and rectovaginal septum, etc. Involvement of these additional organ systems requires a specific expertise and knowledge of what we call 'transversal competencies' to facilitate safe and effective treatment.

To make surgical treatment of endometriosis easier, reproducible, less time consuming, and to minimize the resultant complications a systemic approach is generally used. To avert the risk of excessive or incomplete surgical treatment systemic approach to the treatment of endometriosis is very important. This type of systematic approach can be further subdivided into general strategy and organ-specific strategy (Flowchart 4.1).

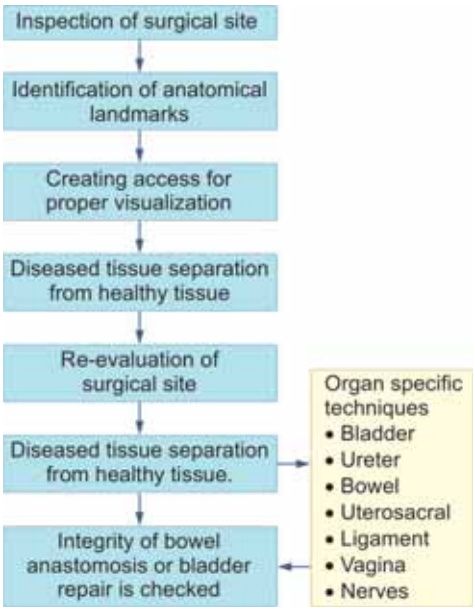
GENERAL STRATEGY

The aim of this strategy is three-folded, which include achieving exposure, identifying important landmarks which need to be preserved during dissection, and separating the diseased tissue.

Care Full Inspection

To help the surgeon, the procedure is started with a vaginal examination under general anesthesia. This is performed to

Flowchart 4.1: Strategic approach for surgical management of endometriosis.



localize any rectovaginal disease that serves as a benchmark in cases where sequential examination may be indicated to adequately identify the limits of the nodule.

Identification of landmarks

After insertion of trocars and positioning of the uterine manipulator patient is positioned in Trendelenburg position. Following this the surgery begins with a thorough inspection of the intra-abdominal cavity. In DIE, exposing the operative field is very essential.

Separating the Diseased Tissue

Adhesiolysis is performed to restore normal anatomy. Both ovaries are freed from their fossae and any endometriotic cysts are drained to facilitate access to the pouch of Douglas. If necessary, the ovaries are suspended from the anterior abdominal wall using either a T-lift device or suture on a straight needle, which improves exposure and frees the assistant.

The normal physiological attachments of the sigmoid colon are also detached from the left parietal wall by dividing the peritoneum while avoiding entering the retroperitoneal space.

Advantage of Adhesiolysis

There are four advantages to achieving this step:

1. It allows the colon to be mobilized, displaced cranially, and suspended, if needed, giving access to the left adnexa.
2. It allows access to the left infundibulopelvic ligament and identification and subsequent preservation of the adnexae is achieved.
3. The course of the left ureter can be visualized. The ureter is most easily identified at the left of the pelvic brim as it is the first structure medial to the infundibulopelvic ligament. This is a key step in deep endometriosis, as it is often medialized as a result of retraction and fibrosis of the disease process. Once identified, it can then be lateralized and preserved during central dissection.
4. It provides adequate exposure to access to the left pararectal fossa, an avascular space, which can be developed either at the level of the pelvic brim or caudally close to the rectovaginal space in the absence of any anatomical distortion. The sigmoid is pulled cranially and laterally to the right in order to identify the limits of the left pararectal fossa.

After the procedure has been performed the operative site should be re-evaluated to decide the further treatment plan. Thus, the surgery is tailored according to the location of the endometriotic lesions and severity of the disease, with emphasis on preserving organ function.

SPECIFIC STRATEGY

Endometrioma

Surgical management of endometriomas is not so difficult and technically challenging procedure; however, effect of cystectomy on the ovarian reserve and consequent fertility has always been a controversial topic.

Surgical management of endometrioma should be aimed not only to relieve the pain by treating the cyst but also to preserve the anatomy and functionality of ovaries by preserving the follicle count (ovarian reserve). Surgeon should also make sure of the completeness of the procedure so that recurrence and adhesions can be avoided so that repeated surgical intervention can be avoided.

The recurrence can be completely eliminated by executing the surgical technique that can completely remove the pathological tissue while preserving healthy ovarian tissue. The current available techniques are excision, ablation, or a combined approach. Out of which, excision of endometriomas has been considered to be the preferred method of treatment as it has less risk of recurrence.[6]

Preoperative Management

Endometriomas are easily diagnosed by TVS, and are typically described as having a 'ground glass echogenicity of the cyst fluid' (Fig. 4.1).[7] Endometriomas serve as a good indicator of deep endometriosis and are associated with more extensive disease in up to 98% of cases.[2] "Carpet-like" echoes or "grinded glass appearance" are found in 82% of endometriomas.[8] Sometimes it is difficult to differentiate an endometrioma from a hemorrhagic ovarian cyst, or corpus luteum cyst but the sonographer should always bear in mind the typical morphological features of endometrioma which are thick walls, homogenicity of the echogenic content, bilaterality and multiplicity of the lesions.[9]

Surgical Technique

The surgical technique consists of following approaches:

- Excision or endometrioma stripping
- Ablation
- Combined technique
- Three-step procedure

Excision or endometrioma stripping: In the beginning of the surgery ovaries are mobilized. This will make the endometriotic cyst to rupture and chocolate content of the cyst would spill (Fig. 4.2). After cleaning, the ruptured point is then found and

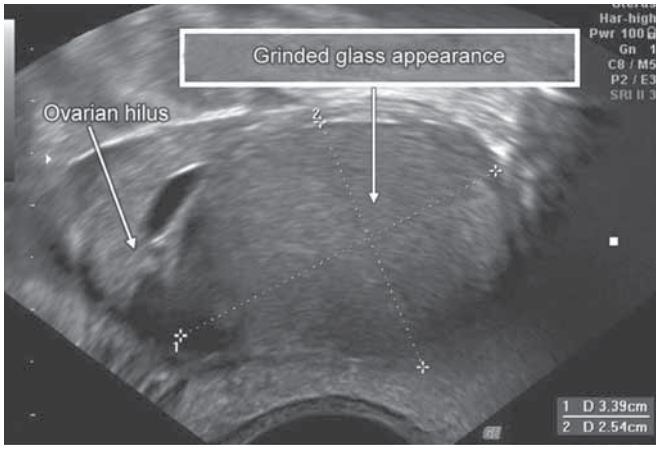


Figure 4.1: Transvaginal ultrasound scan of ovarian endometrioma. Grinded glass appearance of cystic content is typical for ovarian endometrioma.

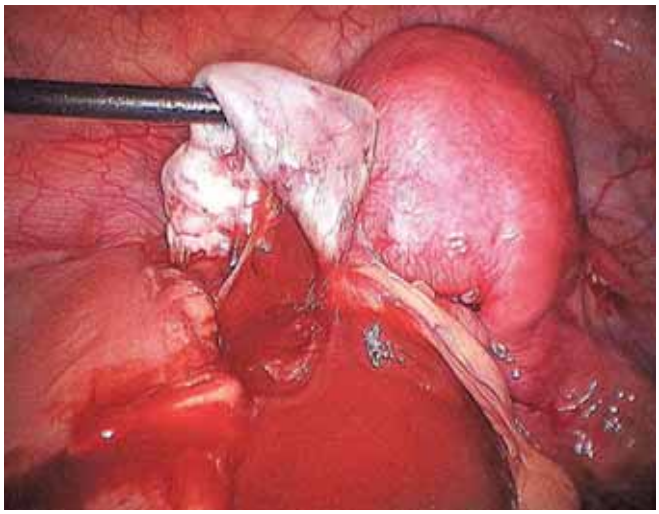


Figure 4.2: Drainage of thick chocolate material during adhesiolysis from the endometrioma.

the opening is enlarged to evert the cyst. The bed of the cyst is incised using scissors, preferably avoiding the use of energy. This is to prevent the cyst from fusing with the adjacent stroma, and consequently losing the cleavage plane. The cyst is stripped using two graspers with opposing divergent forces. Half of the cyst and half of the ovary are held to strip the cyst capsule free from the ovarian parenchyma. This is particularly important in the case of large endometriomas where during stripping of the cyst identification of normal ovarian tissue and endometrioma may be difficult for the surgeon to distinguish.

This stripping technique is mostly a bloodless procedure but hemostasis is usually required only close to the ovarian hilum. Hemostasis can be achieved using bipolar coagulation that should be used sparingly in short bursts to avoid devascularization. An alternative option is suturing the ovary, which closes the dead space thereby minimizing blood loss, in addition to restoring its normal anatomical shape.[10]

Ablation: Ablative treatment consists of aspiration, irrigation, and biopsy of the cyst to exclude malignancy. The thermal effect of either bipolar coagulation, CO_2 laser, or plasma energy is then utilized to destroy the cyst wall.

Combined technique: Sometimes a combined approach using both excisional and ablative techniques can also be used which will consist of performing a classical technique of excision of the endometrioma utilizing the stripping technique along the cleavage plane. This would treat 90% of the cyst. The remaining 10% of the cyst wall which is adjacent to the ovarian hilum is often more vascular due to fusion of the cleavage plane. In order to avoid the excessive bleeding, a partial cystectomy is performed along with subsequent ablation of the remaining endometrial foci using either CO_2 laser or bipolar diathermy.

The three-step procedure: Endometriomas larger than 5–6 cm, a procedure called three-step procedure may be considered where the cyst is opened, emptied, irrigated, and biopsied. In this procedure, following the initial drainage, a 12-week medical treatment with a gonadotropin releasing hormone (GnRH) agonist is prescribed which would help to reduce the size of the cyst. By literature reduction in size of the cyst up to 50% has been reported. After reduction in size, laparoscopy may then be performed to do ablation of the remaining cyst wall.

Postoperative Management and Prognosis

Medicines are helpful in reducing the size and growth speed of the endometrial lesion and hence are effective in the secondary prevention of endometriomas. This can be achieved by using medical regimens of medicines like progestrogens, oral contraceptive pills, and GnRH. Patients who have undergone surgical treatment of endometriomas who do not wish to conceive immediately but require long-term management may benefit most from oral contraceptives as they can be given indefinitely. Postoperative oral contraceptives have been shown to be effective in decreasing the rate of recurrence of endometriomas.[11]

The rationale for endometrioma ablation is that it avoids inadvertent excision of normal ovarian tissue and the thermal effect is limited and therefore considered harmless.

Regardless of what ever surgical technique is used, the surgery should be as atraumatic as possible to preserve the anatomy and functionality of the normal organs. One should keep in mind the potential deleterious effect on ovarian reserve. Thus patients should be carefully assessed (preoperative serum AMH levels may be of benefit) and counseled accordingly.

Future Fertility Management

Patients are immediately allowed active management of infertility in the postoperative phase. Only patients who seem to have an aggressive disease or very active endometriosis are given a shot of GnRH analog. They are not routinely administered in 3 or 6 doses as just after the surgery it is the best time to conceive and this time should not be wasted in iatrogenic amenorrhea caused by GnRH analogs. The onus is on a complete and confident surgery working in good surgical planes, avoiding bleeding and taking measures to prevent adhesion formation. All of these rather than GnRH analogs or other medical management are important for conception. Active management in form of COH and IUI would help. As this is a progressive disease so conception should be tried early.

DIE of the Posterior Compartment

Rectovaginal endometriosis typically refers to infiltrative disease or adenomyosis externa of more than 5 mm involving the cervix, vagina rectovaginal septum, and rectum (Fig. 4.3). Rectovaginal adenomyosis is the most severe form of disease. It is characterized by complete or partial obliteration of the cul-de-sac. The disease can occur in isolation or extend to cause distortion of pelvic anatomy and in some cases complete obliteration of the pouch of Douglas.

When there is an endometrioma, severe dysmenorrhea is not directly related with the characteristics specific to the ovarian cysts.[12] Moreover, extent of rectovaginal endometriosis also does not correlate with pain severity, and as a result may remain undiagnosed for many years.

Diagnosis: Imaging techniques are becoming more and more important to preoperatively determine the presence and extent of the surgical pathology. Correlation between symptoms and various locations of DIE do exist; however, physical examination has limited value for assessing the true extent of the disease.[12,13] Unfortunately, distinguishing between infiltrative and noninfiltrative rectovaginal disease is challenging and no single imaging modality can predict infiltrative disease with certainty.

Advance diagnostic technique such as MRI has been used successfully for diagnosing and locating DIE. Other than intestinal endometriosis, transrectal sonography is often poor at detecting DIE at the uterosacral ligaments.[13] TVS has been found to have a slightly lower sensitivity when compared to MRI (78.3% versus 84.4%); however, this may be operator-dependent.[13] Rectovaginal endometriosis is often associated with infiltrative disease at various locations and in cases where TVS is equivocal MRI may provide more reliable mapping as to the true extent of the disease.

Treatment: An effective method of treatment of isolated uterosacral endometriosis is laparoscopic surgical excision. Surgical dissection commences with identification of key anatomical landmarks, specifically the ureter, which may be medialized due to the fibrotic effect of the disease process. If the ureter is not clearly seen, ureterolysis may be indicated and the course of the ureter should be followed caudally until it enters the ureteric channel. Any endometriotic nodules involving the uterosacral ligaments can then be dissected and removed safely with minimal risk of ureteric injury.

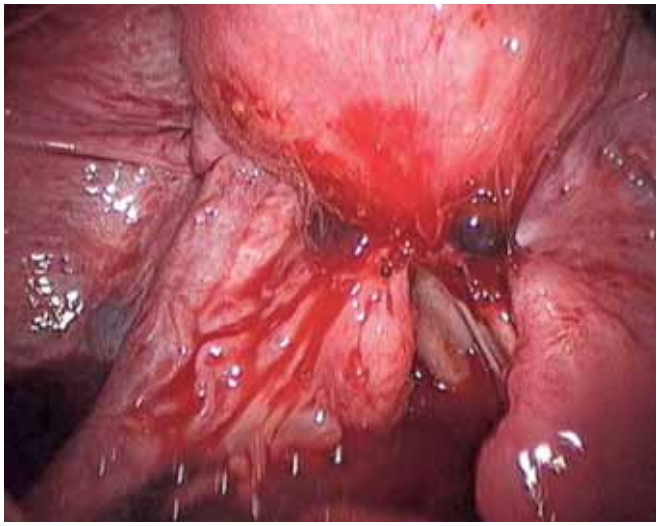


Figure 4.3: Laparoscopic appearance of deep infiltrating endometriosis.

The pararectal fossa can then be identified and dissected, moving cranially to caudally. Once the pararectal spaces are opened, the vaginal nodule can be approached laterally from both sides. Periodic vaginal examinations may be required to help delineate the limits of the nodule. In cases of bilateral involvement of the uterosacral ligaments or where a coexisting vaginal nodule is present, the ureter should be identified bilaterally and ureterolysis performed if necessary. If attached to the bowel wall, it should be freed by carefully shaving the nodule off. Following its removal from the bowel wall, it will then remain attached to the posterior uterine wall/cervix and vagina. The nodule is then re-evaluated and the disease excised using, e.g. a monopolar hook. All glands and endometriotic disease should be removed even if this results in entering the vagina, which can subsequently be sutured using a 2/0 monofilament.

In cases of bilateral uterosacral disease, care should be taken to preserve nerve supply and function as much as possible. Dissection beyond the level of the uterine vein can result in inadvertent damage to the autonomic splanchnic nerves, which serve an important role in maintaining urinary and bowel function. When dissecting the uterosacral ligaments, the hypogastric inferior plexus may be compromised, putting women at risk of sexual dysfunction and urinary retention requiring intermittent self-catheterization. In patients who underwent radical surgery for DIE of the uterosacral ligaments, postoperative urinary retention was reported in up to 29% of patients.[14] As endometriosis is a benign disease affecting young women, care should be taken to dissect and preserve the pelvic autonomic nerves and patients should be informed of these potential adverse effects.[15]

Bowel Endometriosis

Bowel endometriosis occurs in 3–37% of cases and in 90% of cases the rectum, sigmoid colon, or both are most commonly involved.[16] Out of different laparoscopic techniques, which type should be used for the diagnosis of bowel endometriosis is still controversial today. Earlier the removal of deep endometriotic lesions of the bowel was generally escaped due to the significant associated morbidity for what is essentially a benign disease affecting women wishing to safeguard their fertility. With improved understanding of the disease process and development of innovative techniques, in the hands of an experienced surgeon, the morbidity associated with bowel resection is more acceptable.

Preoperative Management

Several techniques such as transrectal/TVS, MRI, computed tomography, colonoscopy, and barium enema have been proposed. However, the practicality of their use is dependent on availability and also expertise in interpreting radiological findings. Preoperative diagnosis of bowel endometriosis is difficult and no consensus exists on the most appropriate tool for diagnosing intestinal involvement. MRI has demonstrated

a sensitivity of 83% and specificity of 98%.[17,18] Endorectal ultrasonography has been demonstrated as having a high sensitivity for detecting and assessing degree of infiltration of the rectal wall. However, endorectal ultrasound may be limited in detecting multifocal lesions or nodules located further away from the probe. Regarding TVS, a sensitivity and specificity of 98% and 100% has been reported. Similarly Double contrast barium enema has also been shown to be effective, specifically in detecting stenotic bowel lesions with a sensitivity of 93.7% and specificity of 94.2%.[19]

Surgical Management

Several laparoscopic surgical options exist for the management of bowel endometriosis, which include:

- Shaving
- Discoid excision
- Segmental resections

Out of these, there is no clear evidence that which surgical technique is the most effective form of treatment with regard to outcomes and complications. Selection of a specific surgical strategy is often dependent on the surgeon's expertise and experience following careful evaluation of the lesion.

Surgical techniques: Various surgical techniques for the management of bowel endometriosis are:

Shaving: Laparoscopic "shaving" or "skinning" involves dissecting largely superficial disease from the bowel wall without entering the bowel lumen. Exposed areas of bowel mucosa are identified and sutured using interrupted 3/0 Monocryl to reinforce any areas of weakness and to maintain the integrity of the bowel wall.

Discoid resection: In cases of more extensive disease where full-thickness invasion of the bowel wall is suspected, discoid excision may be considered. This involves anterior resection of a small segment of the bowel wall using a transanal circular stapler device. Depending on the size of the nodule, initial debulking using the 'shaving' technique may be necessary. A guide suture is then placed at the level of the nodule and a 33 mm circular stapler is inserted transanally. The device is fully opened and the area of bowel to be excised is placed in the groove between the anvil and the stapler. The stapler is angled upward to ensure only the anterior portion of the rectal wall is included in the stapler. The device is then closed and fired and removed from the anus, completing the anterior discoid resection. This procedure can be used for the excision of infiltrative bowel lesions up to 2–3 cm in size.

In this technique, lesions, more than 15 cm from the anal verge, are inaccessible due to the fixed length of the stapler. Thus with concurrent stenotic lesions, it is nearly impossible to pass the stapling device beyond the lesion. Nodules more than 3 cm are not suitable for resection using this technique due to the confined distance between the anvil and base of the circular stapler.

Segmental bowel resection: Segmental resection is a technique which becomes mandatory to be performed when the nodule found is more than 3 cm and involves the sigmoid region of bowel and where there is more than 50% circumferential disease or bowel stenosis, and in cases of multicentric disease.

Segmental resection often involves resecting all visible and detectable endometriosis; however, following histological analysis, positive disease margins have been recorded in up to 20% of cases.[20] Before concluding that safety margins are not obligatory, and radical surgery should be avoided in favor of a more economic approach more information from randomized control trials (RCTs) is required.

To preserve vasculature, lymphatics, and nerve supply, and thus minimizing associated functional complications, the bowel is dissected at the edge of the mesentery. For the NOSE technique, once the diseased segment has been adequately dissected, the bowel is divided caudal to the lesion using a linear stapler device. The bowel segment containing the disease is extracted through the vagina or anus. A colotomy is made at the distal part of the extracted bowel or in cases of stenosis, above the lesion. The anvil attached to a long suture is introduced using a retrograde technique and is deposited above the pathological segment of the proximal colon. The diseased segment is then resected using the endoscopic linear stapler and removed transvaginally or transanally. The anvil is partially extracted using the fishing technique and a 2-0 purse string suture used to secure the anvil head in position. A circular stapler is introduced through the anus and used to perforate the rectal stump. The head of the anvil is then attached and an intracorporeal mechanical anastomosis performed completing the side to end anastomosis.

A conservative approach can be adopted with limited dissection of the bowel mesentery so as to preserve as much of the vasculature and nerve supply as possible. Indications for a routine protecting stoma even in cases of ultralow resections (7 cm from anal verge) should be questioned and reserved only for complex operations with suspected defective anastomosis.

Outcomes

Low complication rates have been reported using shaving technique with a 1.4% risk of rectal perforation in a series of 500 patients and a recurrence rate of 7%. Discoid resection has shown to be effective in the treatment of pelvic pain with associated complication rates ranging from 0–12.5%. Similar studies have observed no complication rates following discoid resection. Retrospective studies have also demonstrated high patient satisfaction with improvement in symptoms such as pelvic pain and dyspareunia.[21,22] *Segmental bowel resection* appears to be safe with a low rate of significant short-term complications. In 5–26% of cases complications have been reported. In one study, the complication rate after excluding women with uncomplicated pyrexia was only 3.2%.[23] Similarly in a large series of 750 cases of bowel resection, the overall surgical morbidity was 9%.[24] This included rates of anastomotic leak, rectovaginal fistula, and intra-abdominal bleeding, which were 3%, 2%, and 1%, respectively.[24]

Conservative surgery (i.e. shaving) may carry a lower risk of major complications, although in some studies additional surgery such as ureterolysis, uterosacral ligament resection, and hysterectomy may have had an impact.[25]

The most appropriate surgical strategy in cases of infertility related to severe endometriosis is unclear. No RCTs have assessed whether fertility improves following radical surgery for stage 3 and 4 disease, although observational studies have shown promising results. In one study, spontaneous pregnancy rate was lower in patients found to have bowel endometriosis, and in these women improved reproductive outcome was noted if bowel resection was performed.[26] The place for segmental bowel resection in cases of DIE in patients whose only symptom

is infertility in the absence of pain has not been determined. Bowel resection is not without its risk, and the extent to which rectovaginal endometriosis affects infertility is unclear. Patients should therefore be carefully selected and counseled regarding the specific risk of complications and uncertain benefits of surgery.

Urinary Endometriosis

Urinary endometriosis is a condition where endometriotic tissue infiltrates urinary tract which includes bladder, ureter, kidney, and urethra. This condition is rare with a reported prevalence of approximately 1%. Though this value is likely to be underestimated as in patient series with severe endometriosis the prevalence can rise up to 20%.[27,28] The proportion of urinary tract localization in patients with urinary endometriosis is bladder (84%), ureter (10%), kidney (4%), and urethra (2%).[29,30] Ureteric involvement occurs less frequently than bladder endometriosis (BE); however, the proportion can differ significantly between case series depending on whether extrinsic compression of the ureter is included.

Symptoms associated with urinary endometriosis are dysuria and hematuria, although it is more commonly associated with the nonspecific symptoms such as dysmenorrhea, dyspareunia, and chronic pelvic pain.

Bladder Endometriosis

In bladder endometriosis (BE), the deposits of endometrial glands and stroma are found infiltrated within the serosa muscularis, and/or mucosa of the bladder tissue. The occurrence of this endometriosis is close to 11% and can be associated with symptoms such as dysuria (42%), hematuria (9–15%), and recurrent urinary tract infections (18%).[28]

In almost 50% of cases of bladder endometriosis, the patient has found to have a history of previous pelvic surgery, suggesting an iatrogenic cause, typically occurring following cesarean section. This data should be considered in cases suggestive of BE.[31]

Preoperative Management

Preoperative management includes:

- Urine analysis
- Physical examination
- Transvaginal sonography (TVS)
- Magnetic resonance imaging (MRI)
- Cystoscopy.

Urine analysis: It is important for diagnosis as endometriosis can cause blood to be seen in blood. As this blood is not always visible with naked eyes, hence urine analysis can be a great tool for diagnosing bladder endometriosis.

Physical examination: It includes bimanual examination of vagina. But it has not been found very informative, except in few cases where there are large nodules of the vesicovaginal septum and it is possible to palpate a thickened area, or a cystic expansion that evokes pain on pressure.[32]

Transvaginal sonography: The low cost and readily available diagnostic test is TVS. It is usually considered as the first-line investigation in cases suggestive of BE. The nodule usually appears as a heterogeneous, hyperechoic, almost spherical lesion with a small number of vessels on Power-Doppler protruding into the bladder from the posterior wall of the bladder.[33]

MRI: It is considered the gold standard for diagnosis of BE with a sensitivity of up to 88% and specificity of up to 99%. It is useful in detecting associated lesions such as ureteric dilatation, providing a more detailed description of the pelvis[34] (Fig. 4.4).

Cystoscopy: It can also be used as a cost-effective method for diagnosis. Typically lesions appear as a nodular mass at the base or dome of the bladder with a distinctive shape and associated color change, from red-brown to blue-black. For smaller lesions, however, the findings may be equivocal due to the intraperitoneal origin of the disease. Cystoscopy can also be performed intraoperatively to further assess the mucosal involvement and distance from the ureteric orifices, in order to optimize perioperative planning (shaving vs. partial bladder resection) and consider placement of double-J stents if indicated.[35]

Surgical Technique

Surgeon should use a technique which is customized for different cases with different level of invasion and depth of the lesion of the bladder. Depending on the level of involvement of the bladder, the following procedures can be considered:

- Shaving
- Mucosal skinning
- Partial cystectomy (progressing from superficial to more invasive disease).

First thing to be followed in any surgical procedure is preserving the anatomy of bladder. The nodule present can lead to retraction of the bladder onto the anterior aspect of the uterus and anterior wall with subsequent involvement of both round ligaments (Fig. 4.5). After the restoration of normal anatomy of bladder, the BE nodule must be isolated by opening first both paravesical fossa, medial to the umbilical artery and then the vesicovaginal septum.

Shaving technique: This technique can be applied if the nodule involves only the serosa of the bladder and suturing may not be necessary if the muscularis is not compromised.

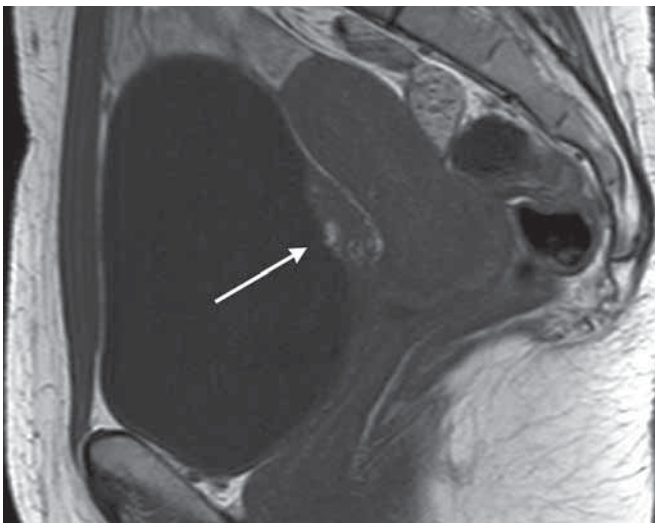


Figure 4.4: Magnetic resonance image (MRI) showing an infiltrative bladder endometriosis nodule. MRI is useful in determining presence and extent of deep infiltrating endometriosis.

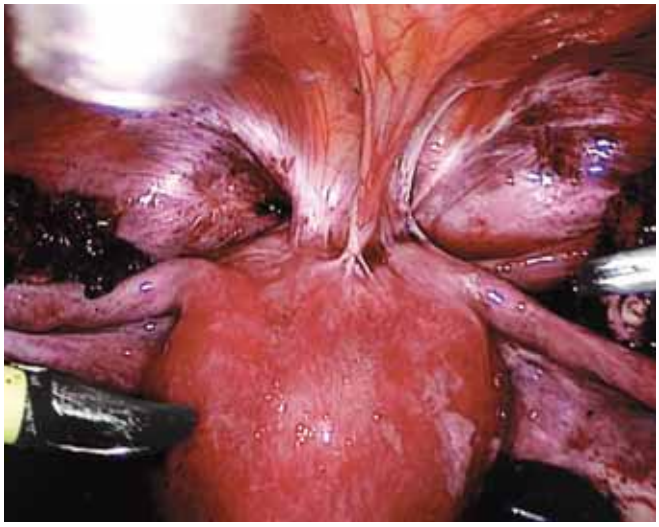


Figure 4.5: Typical laparoscopic appearance of a bladder nodule. The uterus is anteverted with bilateral retraction of both round ligaments toward the midline.

Mucosal skinning: It is performed in cases of more extensive disease, where the detrusor muscle is involved. The main difference between these two techniques is that in partial cystectomy the full thickness of the muscle is transected, whereas in mucosal skinning the urothelium is preserved.

Cystoscopy: It may help identify bladder lesions extending to the mucosa and can assist the surgeon in deciding between the two techniques; however, often the final decision is only made intraoperatively.

In both cases, the defect must be closed using absorbable monofilament 3/0 in a single-layer suture using either intracorporeal or extracorporeal knotting techniques.

At the end of the procedure, a blue dye test must be carried out to confirm bladder integrity by filing the bladder with 150–200 mL of solution. Cystoscopy is important to evaluate the distance between the sutures and the ureteric orifices and can help determine whether ureteric stenting is required.

At the end of the procedure, a Foley catheter should be left in place for minimum of 10–14 days depending on the width of the resection and the inflammatory response. Immediately prior to removal of the catheter, a low-pressure cystography can be performed to assess integrity of the repair. If a double-J stent has been cited, and if no ureteric procedures have been performed intraoperatively, it can also be removed at the same time.

Prognosis

After the resection surgery of bladder patients have reported urgency along with frequent urination. Though this sensation is temporary and normally completely resolves after a few months. Laparoscopic surgery leads to a low recurrence rates when compared with cystoscopic resection.[27]

Ureteral Endometriosis

Ureteral endometriosis is typically unilateral and is more frequently confined to the lower third of the ureter, with a higher predisposition for the left side. These lesion are often extensions of retrocervical endometriosis.[36]

Ureteric endometriosis can be divided into extrinsic and intrinsic disease, according to the depth of ureteral invasion occurring with a ratio of 4:1 respectively.[37] Extrinsic disease is caused by infiltration of the surrounding connective tissue and ureteral adventitia by the endometriotic nodule. Intrinsic disease, on the other hand, consists of disease infiltrating the muscularis and in some cases, the uroepithelium.

Symptoms associated with ureteral endometriosis are usually nonspecific, consisting of pelvic pain, flank pain, or renal colic and less commonly, hematuria. In up to 30% of patients, silent kidney loss can occur.[38]

Preoperative Management

Physical examination: Physical examination is not useful in predicting ureteric involvement, but it should be suspected in cases where a palpable retrocervical nodule more than 2 cm with uterosacral ligament involvement is present.

Ultrasound: It is routinely used for endometriosis screening and can be used to detect ureteral dilatation and secondary ureteral obstruction with resultant hydronephrosis.

MRI: It is an effective diagnostic tool as it provides additional information regarding the level, extension, and degree of obstruction, in addition to a comprehensive analysis of the pelvis.[39]

Surgical Technique

Like all the treatment procedures talked till now, the first step is always to restore the normal anatomy of the uterosacral ligament as the anatomy is often distorted as a result of peritoneal inflammation caused by the disease. First surgeon needs to identify the pelvic landmarks in particular the ureter in order to perform a safe ureterolysis. To identify the ureter on the left side, the physiological attachments of the sigmoid colon should be divided and the ureter identified at the pelvic brim where it crosses the iliac vessels.

After performing ureterolysis, the surgeon will be able to discriminate between intrinsic and extrinsic disease. In cases of extrinsic lesions, the surgeon should be aware that fibrosis of the surrounding diseased tissue can lead to medialization of the ureter especially in its lower third. It is therefore important that the course of the ureter is followed until the ureteric channel where it crosses the parametrium.

The ureteric adventitia consists of a dense vascular network, which supplies the ureter along its course. In order to adequately resect endometriotic nodules, some of these arteries may need to be sacrificed; however, careful dissection should be performed so as to avoid complete devascularization of the ureter. If the adventitia cannot be adequately preserved as a direct result of the disease, placement of a double-J stent should be considered, to decrease the risk of fistula formation. Stent placement is also recommended in cases of persistent stenosis following removal of extrinsic lesions.

Regarding the management of intrinsic lesions, a partial ureteric resection with end-to-end anastomosis can be performed. The anastomosis can be guided by placement of a double-J stent followed by insertion of 3/4 intracorporeal stitches using 4-0 absorbable monofilament. If the lesion is located close to the bladder junction (approximately <2 cm), ureteric reimplantation should be considered. In order to perform an adequate antireflux system, a 2 cm mucosal skinning of the bladder is performed

with ureteric implantation at one edge, which is then covered with the muscularis. It is important to avoid excessive tension on the anastomosis. If following resection there is inadequate ureteral length, a psoas hitch suspension of the bladder can be performed to ensure a tension-free repair.

If wide dissection of the adventitia is performed, it is recommended to leave in place a double-J stent for approximately 6–8 weeks, after which time it can be removed without the need for additional investigations. In contrast, if an end-to-end anastomosis or neoureterocystostomy is performed a urinary catheter should be left in place for a minimum of 10 days.

Prognosis

In our series of 91 women who underwent laparoscopic surgical treatment of ureteral endometriosis, we reported that in 85.7% of cases a simple ureterolysis was appropriate to treat the patients and in only 10% a resection was required.[28] These findings are comparable with similar studies. The presence of moderate-to-severe hydronephrosis, however, can increase the risk of ureteric resection by up to 30% respectively.[37]

Surgical outcomes after 3 years of follow-up showed significant improvement in both urinary and nonspecific symptoms.[40]

NEW CHALLENGES

The difficulty in surgical treatment of DIE is twofold as patient wants symptomatic relief as well as fertility who are wishing to conceive immediately or in the future. As the disease affects younger patients who later on wants fertility, thus, the challenge is not simply to treat infertility but to preserve future fertility.

Disease involving the ovaries should be carefully removed to maintain ovarian reserve and a meticulous surgical approach should be adopted to minimize adhesion formation.

New challenges exist in determining which surgical technique is most favorable. Unfortunately evidence is lacking and there are few long-term follow-up studies from which any clear conclusion can be made. Further research, specifically analyzing fertility outcomes following surgical treatment of DIE, is required in order to counsel patients appropriately and recommend the most appropriate treatment of women desiring a pregnancy.

CONCLUSION

Endometriosis is one of the most common disorders encountered in surgical gynecology which arise from the ectopic deposits of the endometrium outside the uterine cavity (peritoneal cavity, abdominal and pelvic organs and pelvic ligaments). Laparoscopy has become the gold standard for the treatment of endometriosis. Image magnification using the laparoscope has made more complex procedures possible, challenging gynecologists to both develop and advance their surgical techniques. A standardized surgical approach is recommended in order to improve reproducibility, reduce operating times, and minimize complications.

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5

CHAPTER

Suturing Applications in Endometriosis Surgery

INTRODUCTION

The adequate treatment of deep endometriosis (DE) with laparoscopic resection requires complete excision which would be again requiring the surgeon with who can perform the surgery with well-planned complete laparoscopic manage-ment. The complete and best knowledge of using laparoscopy would be required by the surgeon so that he can completely focus on surgery. The first step for treating every endometriotic lesion is to identify and preserve the anatomy of the affected organ. Hence in treatment of DE, where pelvic anatomy usually is distorted to a degree where pelvic organs can hardly be distinguished, surgeon need to identify the them well before starting any dissection **(**Fig. 5.1**)**. This distorted anatomy would have been impossible to understand and treat if laparoscopy would have been not invented.

The most important laparoscopic skills which helps surgeon for a successful surgery, is suturing technique. Here in this chapter, we will discuss about suturing techniques which surgeon should master and applications of suturing in endometriosis resection. Without mastering this required skill, it is considered impossible for a surgeon to perform resection of deep endometriosis. Suturing of the ovaries, bladder, vagina and bowel will be generally needed during surgery. Mastering these suturing techniques will help the surgeon to resolve vascular complication related to surgery and also help them preserving organ structure as much as possible.

Figure 5.1: Major anatomic distortion caused by severe deep endometriosis in 22-year-old patient. The uterus (*) is fixed, there is complete blockage of the cul-de-sac with endometriosis in the rectosigmoid, and the only adnexal structure is identifiable in the right tube with extensive hydrosalpinx (**).

SUTURING ARMAMENTARIUM

To perform laparoscopic suturing, one will need:

- One (or two) needle holder,
- One assistant needle holder, and
- One knot-pusher (Fig. 5.2).

Five-millimeter diameter and 33 cm long needle holders are more suitable for use in gynecologic procedures. The needle holder has two basic characteristics: type of handle and direction

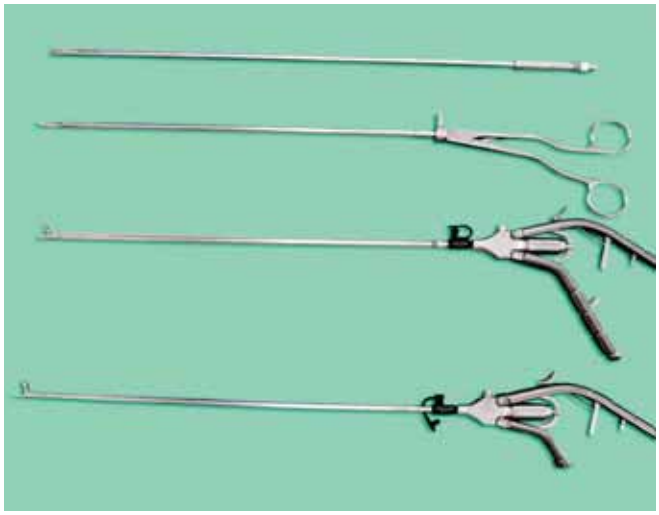


Figure 5.2: Basic set for laparoscopic suturing: From top to below, a knot-pusher, an assistant needle holder, and two needle holders (one with right-curved and another with left-curved jaws).

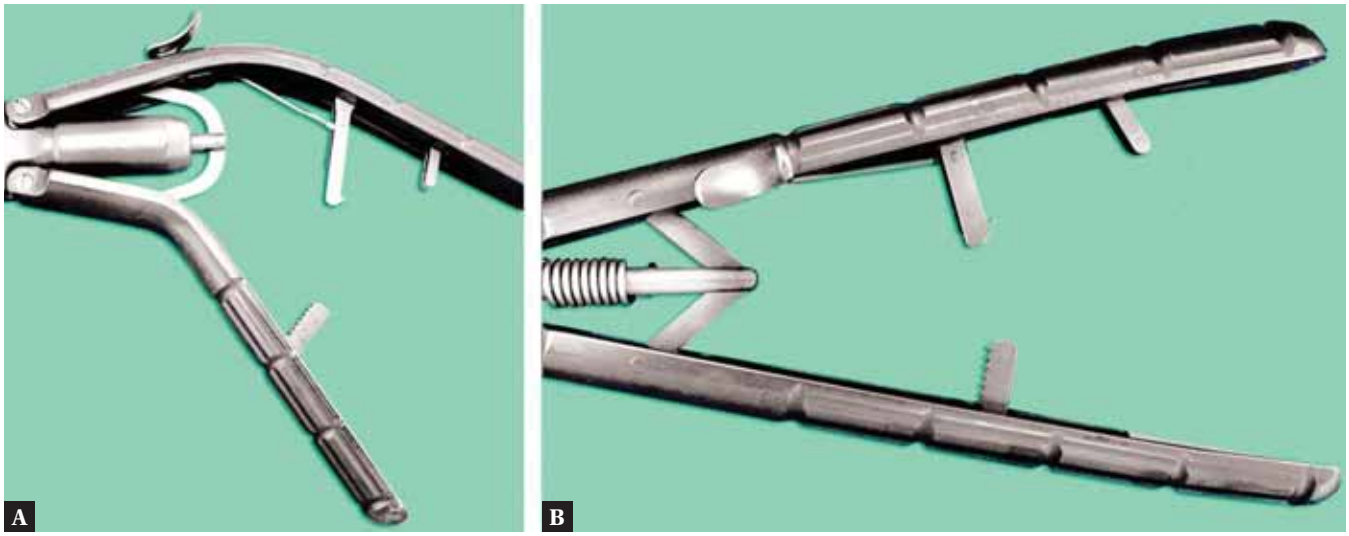
of the jaws. Ergonomic axial handles (Fig. 5.3A) allow a more comfortable handling, but its rotation is limited to the same 180 degrees rotation of the wrist. These needle holders can be used either in a lateral or central position, considering a typical 4-puncture laparoscopy. On the other side, ergonomic straight handles (Fig. 5.3B) may be rotated 360 degrees and should be used in the central puncture.

Needle Holder

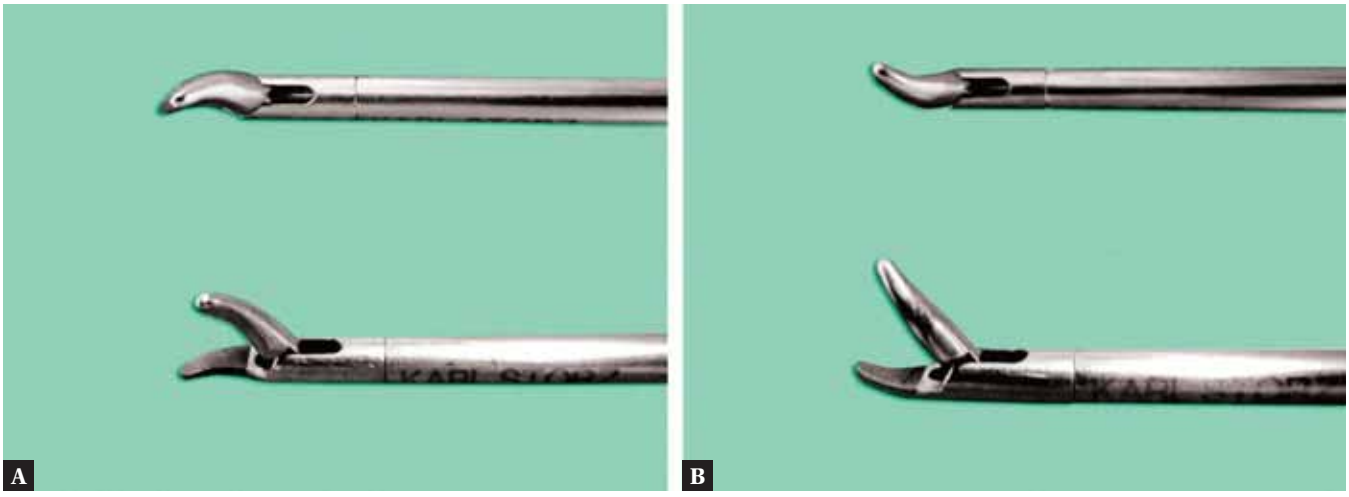
The usefulness of needle holder depends upon shape of jaw which can be straight, right or left-curved jaws. Laparoscopic needle holders with curved jaws should be used like the Heaney needle holders used in vaginal surgeries. Therefore as a rule it is always that needle tip should always face the opposite side of the jaws curve. For example, a needle holder with left-curved jaws should hold the needle with its tip turned to the right (Fig. 5.4A). Accordingly, needle holder with right-curved jaws should be used in the right hand holding the needle with its tip faced to the left (Fig. 5.4B). There should be a 90° angle between the needle holder jaw and the needle after positioning it (Figs. 5.5A and B). Conversely, needle holders with straight jaws might be used indistinguishably either in the right or left hands. Curved jaws allow for an increased angle of suturing while approaching the tissue, which makes the difference especially in a situation of diminished space for performing the suture.

Assistant Needle Holder

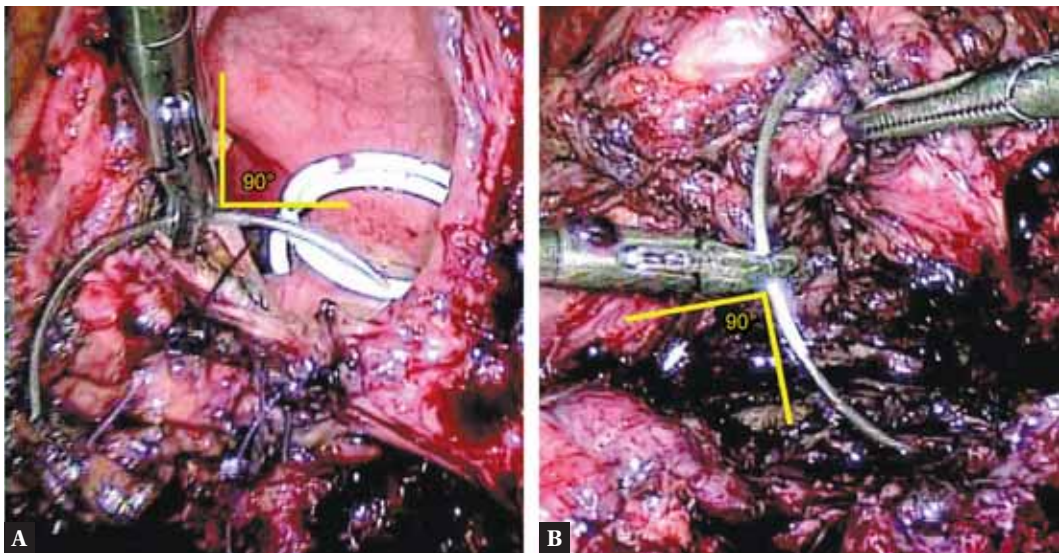
The assistant needle holder, also called grasper, should be strong enough to grasp and exert traction on tissues, but still gentle enough to hold the needle delicately and precisely. Assistant



Figures 5.3A and B: Laparoscopic needle holder handles. (A) Axial handles are more ergonomic, however, their rotation in limited to the 180° rotation of the wrist; (B) Straight handles allow for 360° rotation, and should be preferentially used in the central port.



Figures 5.4 A and B: Laparoscopic needle holders with curved jaws. Jaws may be either curved to the left (A) or to the right (B), and should be used in the left and right hands respectively. Curved jaws permit wider movements and angles for suturing.



Figures 5.5A and B: The tip of the needle should face opposite to the curve of the jaw, and there must be an angle of 90º between the needle and the jaw for better performance of laparoscopic suturing. (A) Position with needle holder in right hand in the central port; (B) Position with needle holder in left hand in the lateral port.

needle holders should not be used for direct suturing (or transfixing the tissue) itself, but instead they should be used to refine positioning of the needle in the needle holder.

Knot Pusher

One more special instrument which a surgeon would require for suturing is a knot pusher (Fig. 5.6) which is helpful for extracorporeal suturing.

SUTURING TECHNIQUE

Introducing the Needle

For suturing the tissue the step is to introduce the needle and the suture into the pelvic cavity. Small (<2.5 cm) curved needles can be passed through an 11 mm or 12 mm trocar, but these needles are usually suitable only for suturing small amounts of tissue. For larger tissue to be held in proper position, the lager needles are required. In the uterus, the larger needle is required. To introduce the needle of any size into the cavity, transparietal technique is the best recognized one. The trocar is first removed (even a trocar as small as 5 mm), and the needle holder is passed inside the trocar to grasp the suture about 2–3 cm away from the needle. They are introduced both through the puncture in the abdominal wall, even if the needle is bigger in length (Figs. 5.7A and B). For safe manipulation and introduction of needle into the cavity suture should be grasped instead of needle. This will also help to avoid any injury to the patient.

Transfixing the Tissue

The next step in performing the suture is to transfix the tissue. It can be performed either from a lateral or central port, either with the right or left hand. The surgeon should be able to perform with both the hands. Surgeon might opt to use one needle holder and one assistant needle holder, or use two needle holders, one in each hand. By using an assistant needle holder, the surgeon grasps the tissue easily; by using two needle holders, the surgeon has the option to use either his right or left hand to suture, which gives him or her all the options and different angles of approach in the pelvis. The concept of the angle of approach, which is the angle between the needle and the tissue, is exemplified elsewhere.[1]

Figure 5.6: Laparoscopic knot pusher for extracorporeal knots.

Suturing which is performed from lateral ports usually has more favorable angles, and it means that a surgeon who is standing on the left side of the patient may favorably perform suturing with the left hand in the left lateral port, or with the right hand in the right lateral port. It has also been seen that suturing performed with the right hand in the central port have more limited angles of approach.

Knotting

The tissue transfixed, the knot is to be done. There are two basic techniques for laparoscopic knotting:

1. Intracorporeal
2. Extracorporeal

Intracorporeal Knot

In intracorporeal knotting, the knot is made inside the cavity. To tie this knot, the needle holder drops the needle and grasps the thread close to the suture in order to close it well. This knotting requires great manual dexterity and it must absolutely be mastered by every surgeon. (Figs. 5.8A and B).

Extracorporeal Knot

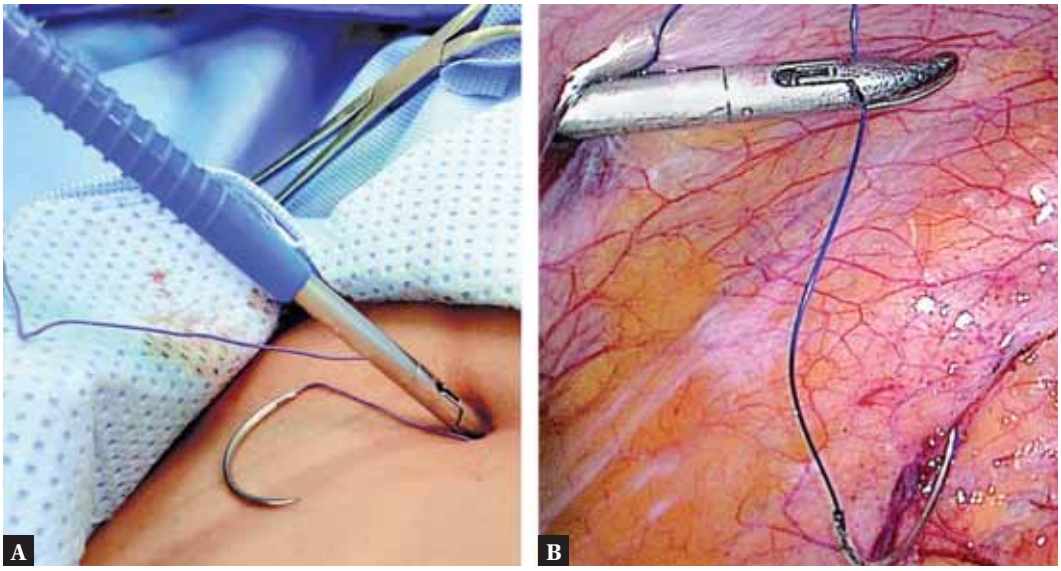
In extracorporeal suturing, we use a 90 cm suture and pass only one end of the suture inside the cavity. After transfixing the tissue, we pull the suture and needle outside the cavity. A sequence of semi-knots is made manually and each one of them is pushed separately toward the tissue using a knot pusher, to finally construct a complete knot.

SUTURING APPLICATIONS IN ENDOMETRIOSIS SURGERY

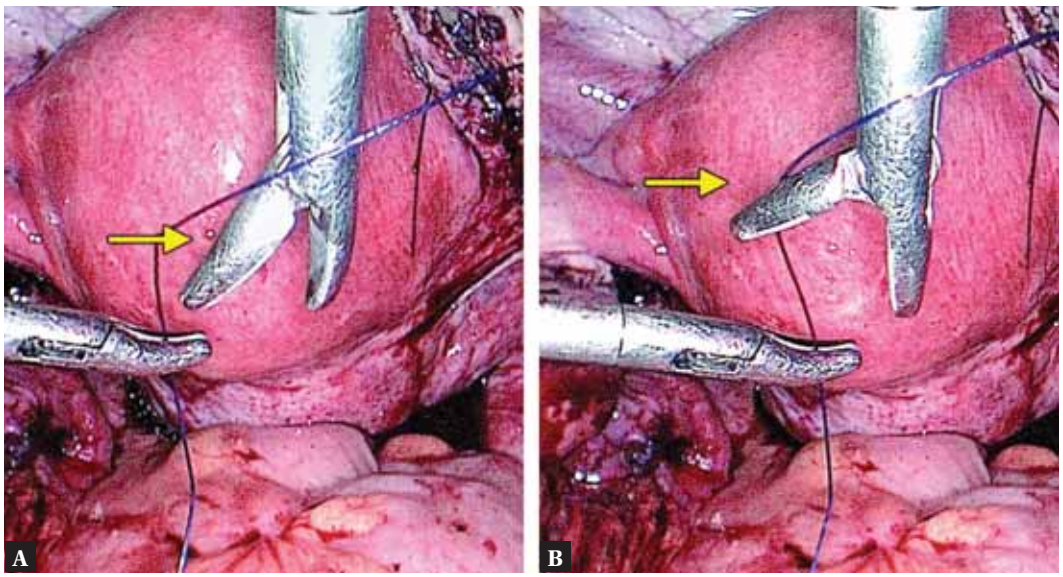
Exposure of the Surgical Field

In the laparoscopic treatment of DE which affects the posterior pelvic the most, the field exposure is the basic step. The exposure of field will help the surgeon in direct visualization of the lesion

In female pelvis both ovaries and rectosigmoid are present in the posterior pelvis. Except for the virgin patient, a uterine



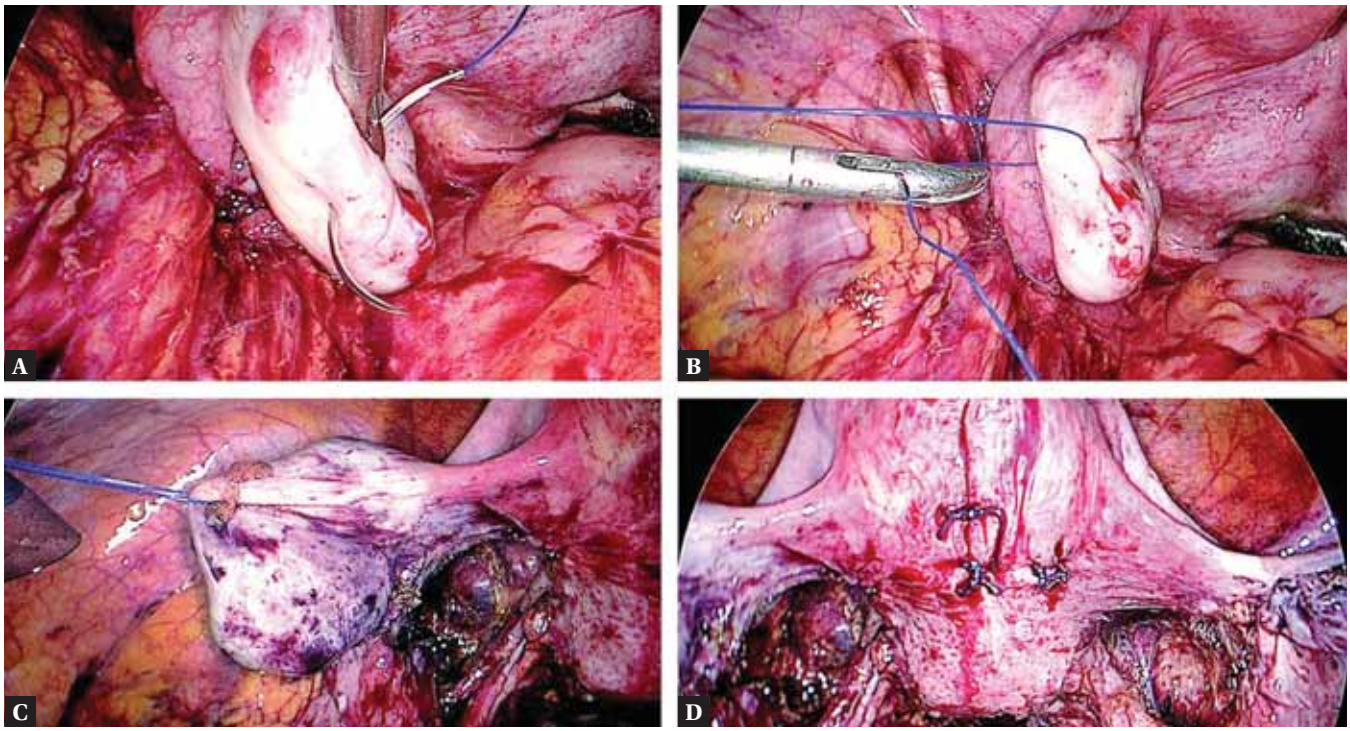
Figures 5.7A and B: Needle of any size can be introduced in the pelvic cavity by the transparietal technique.



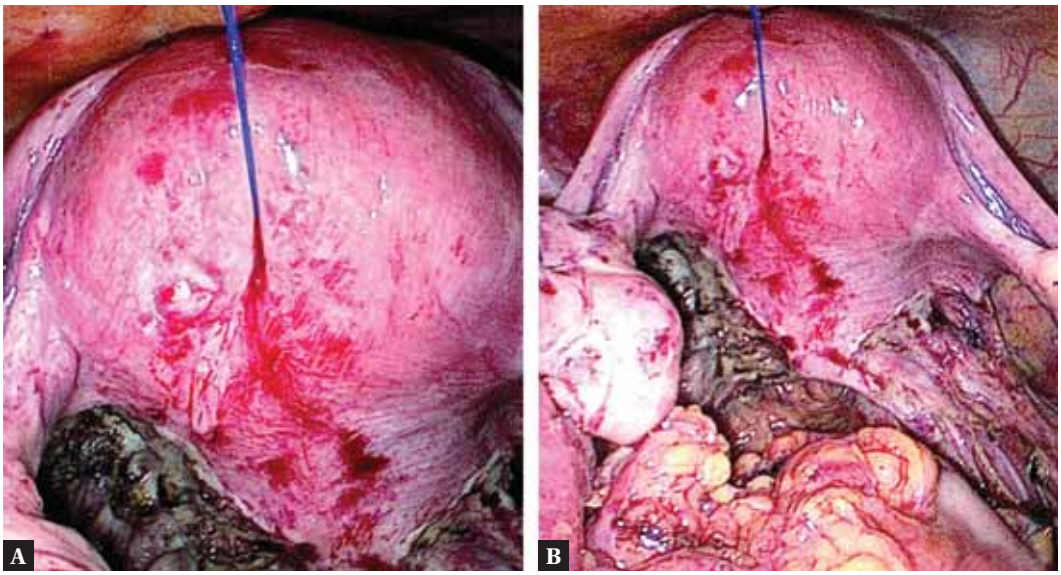
Figures 5.8A and B: The "gladiator" rule, developed by Proffessor Armando Romeo in Italy, is helpful to understand the movements of the needle holder jaws in intracorporeal suturing. The superior jaw of the needle holder (arrow) acts like the thumb of Roman emperors, who determined the fate of gladiators by an "up" or "down" movement of the thumb. The superior jaw executes consecutive up and down movements to construct the intracorporeal knot.

manipulator could handle the uterus. The assistant surgeon who has only one free hand cannot handle exposing all the field hence laparoscopic suturing is helpful here.

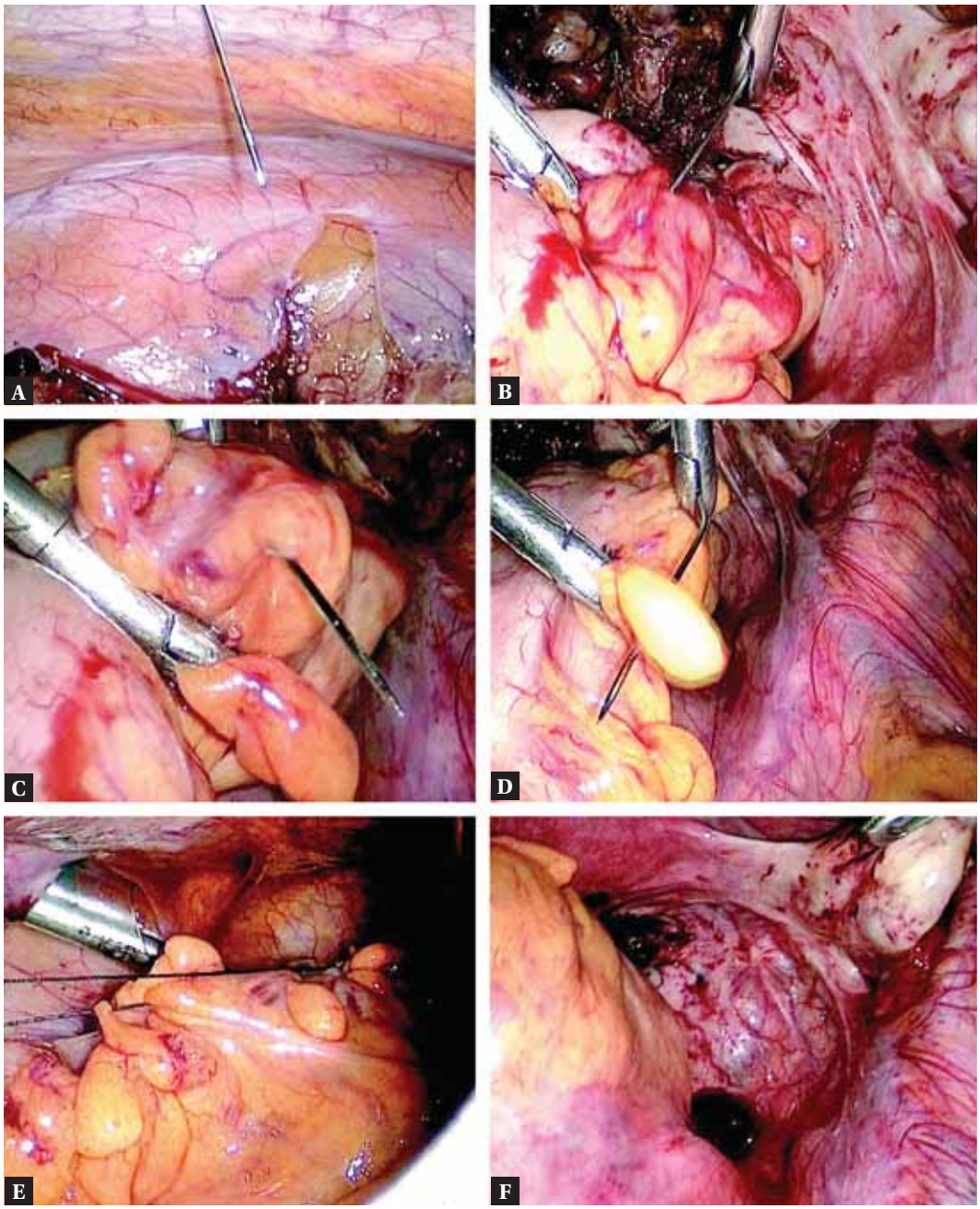
The ovaries, the uterus and the rectosigmoid colon are all be transfixed and pulled out of the field to increase exposure. (Figs. 5.9A to D). The uterus should be transfixed in its posterior wall with a 4-cm needle (Figs. 5.10A and B). In the rectosigmoid, a sequence of 4 to 6 right-sided epiploic appendices can be transfixed from caudal to cranial, allowing for traction of the rectosigmoid to the left side and, exposing the right side of the pelvis (Figs. 5.11A to F). Prolene® sutures are suitable for "running" inside the tissues without damaging them. Besides,



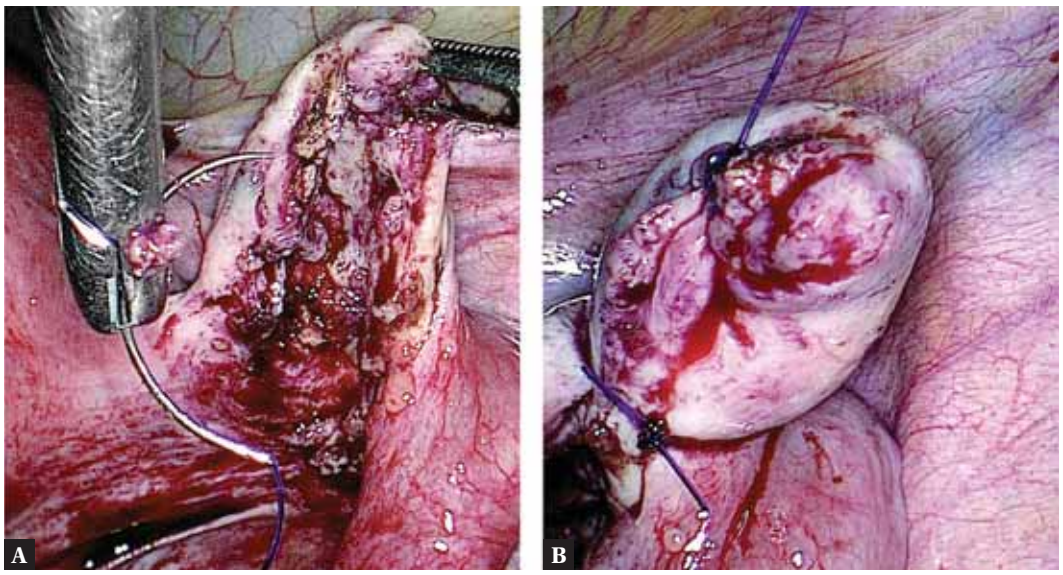
Figures 5.9A to D: Temporary oophoropexy is almost mandatory in DE surgery to improve exposure and access to the posterior pelvis. Sutures can be left in place and removed after seven days to diminish postoperative adhesions.



Figures 5.10A and B: Temporary hysteropexy obviates the need for a uterine manipulator to expose the posterior pelvis. It is very helpful for virgin patients. This suture can also be removed after seven days to decrease postoperative adhesions.



Figures 5.11A to F: Temporary enteropexy with a straight needle nylon suture (Nurolon®, Ethicon). We use the straight needle to transfix the rectosigmoid to the left superior quadrant of the abdomen and introduce the suture in the cavity. The same needle is used to transfix a sequence of 4 to 6 epiploic appendages in the right side of rectosigmoid. Finally, we exteriorize the needle and pull the suture, which is removed at the end of the procedure. Enteropexy is helpful to mobilize the rectosigmoid and increase surgical field exposure in the right side of the pelvis.



Figures 5.12A and B: Separate sutures can be used to approximate the ovarian borders and fasten healing after endometrioma excision.

Prolene® sutures in the uterus and ovaries can be left in place for 7 days as a manner of diminishing postoperative pelvic adhesions, which is highly effective.[2] There will be no difficulty in pulling them out after this period.

Suturing Methods for Different Organs

Ovary

After the excision of endometriomas, the ovary may be either left open, or its borders may be approximated for healing. For this purpose, 3-0 Mononylon® sutures can be an excellent option (Figs. 5.12A and B). Data comparing ovarian reserve and function after suturing are inconclusive.[3]

Bladder

Bladder endometriosis occurs in about 5% of women with DE. Typically, the lesion is located in the fundal, posterior part of the bladder, almost always above the trigone. Despite not infiltrating, stenting of the ureters might be necessary in some occasions for performing a safer suture.

Excision of disease will require full-thickness resection in most of the situations. Suturing of the bladder can be performed with two overlying running sutures in a mucosal and a seromuscular layers.

Running sutures are easier to be performed if we use our left hand (for surgeons standing on the left side of the patient) and begin it in the right border of the bladder (Figs. 5.13A to F). The assistant holds the suture, and the surgeon uses the assistant needle holder in his right hand to grasp the edges to be sutured.

Bowel

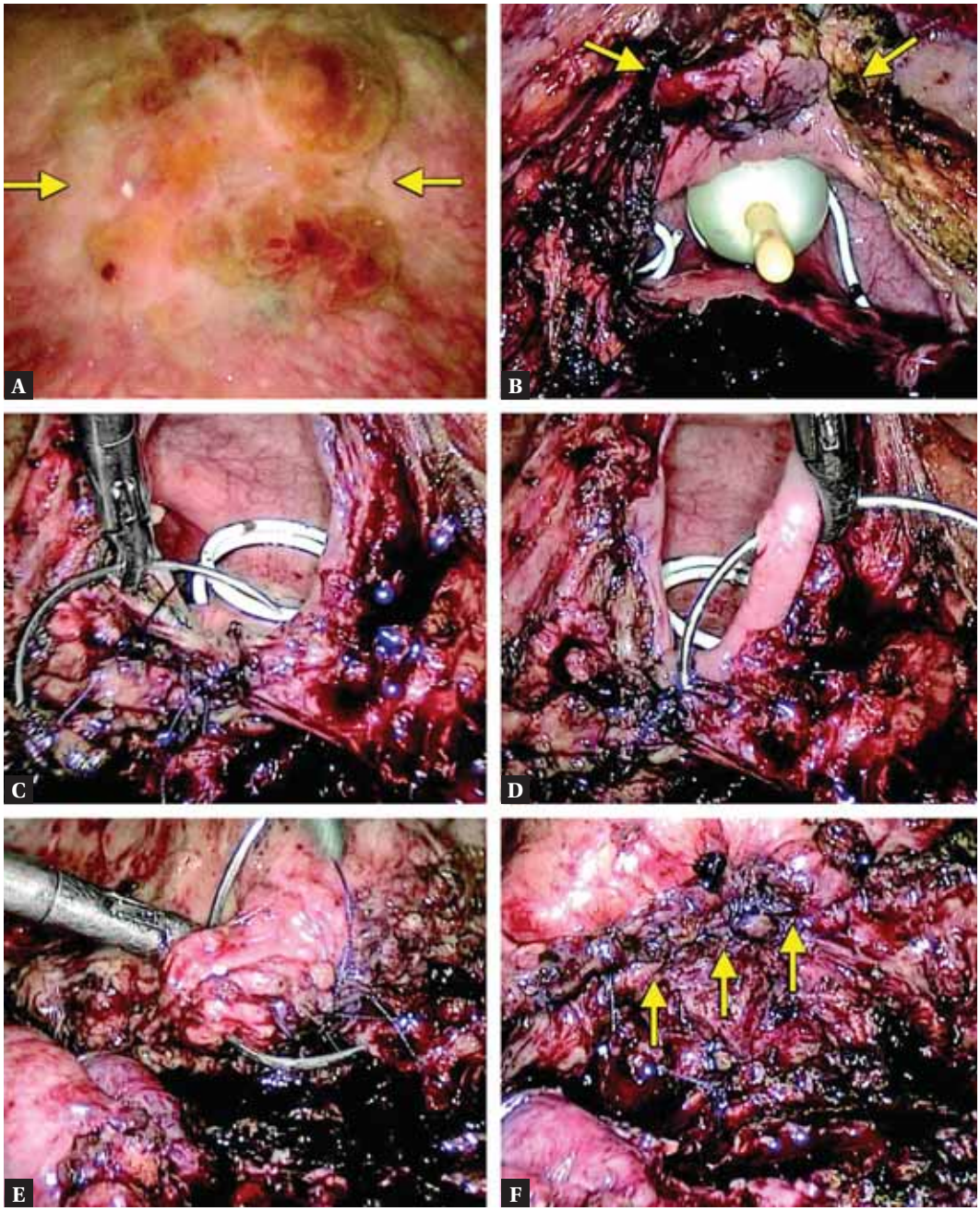
Bowel endometriosis is necessary for a complete treat-ment of the disease in about 25% of surgeries for DE,[4] and laparoscopic suturing is important for performing for bowel excision.

Rectosigmoid

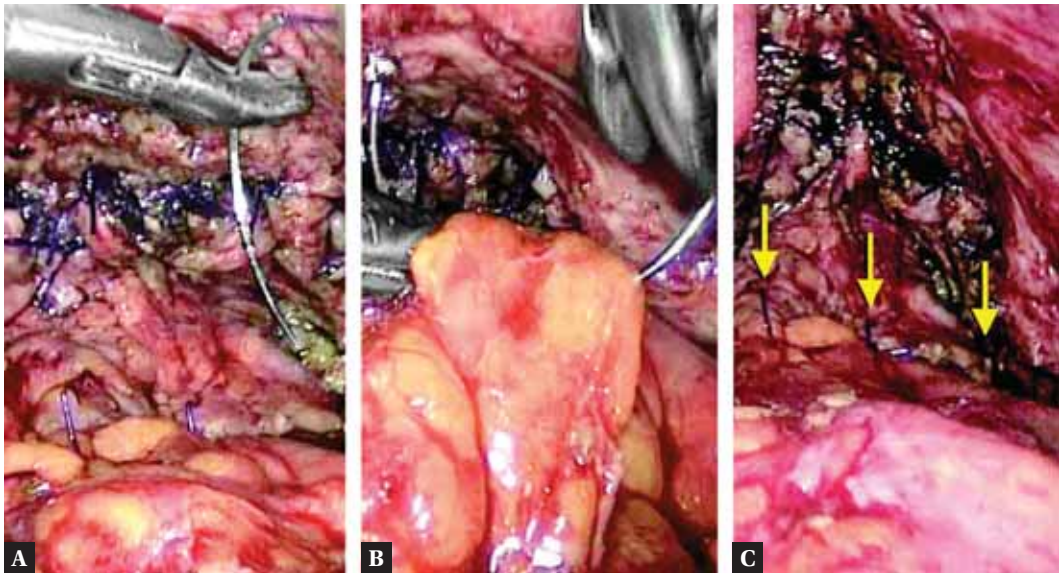
Rectosigmoid endometriosis can be excised by segmental resection where there is multifocal lesion or lesion greater than 3–4 cm. Mechanical stapling devices are a safe and helpful tool to perform segmental resections of rectosigmoid excision, and may obviate the need for extensive suturing in the bowel when performing the termino-terminal anastomosis. After finishing it, we may perform separate Prolene® 3-0, PDS® 3-0 or Vicryl® 3-0 sutures to reinforce the stapling line (Figs. 5.14A to C), although reinforcing sutures are not specifically recommended by the manufacturer. Sometimes, suturing becomes mandatory if there is a defect in the stapling line. In this situation, a two-layer suture to close the defect should suffice, and another integrity test should be performed afterwards.

Discoid resections are recommended for single recto-sigmoid endometriosis lesions measuring less than 3–4 cm. It can be performed either "manually" or using a laparoscopic circular stapler per anus.[5] The suture must be "water-tight" and meticulous. Complications such as fistulae or dehiscence are almost always caused by technical flaws.

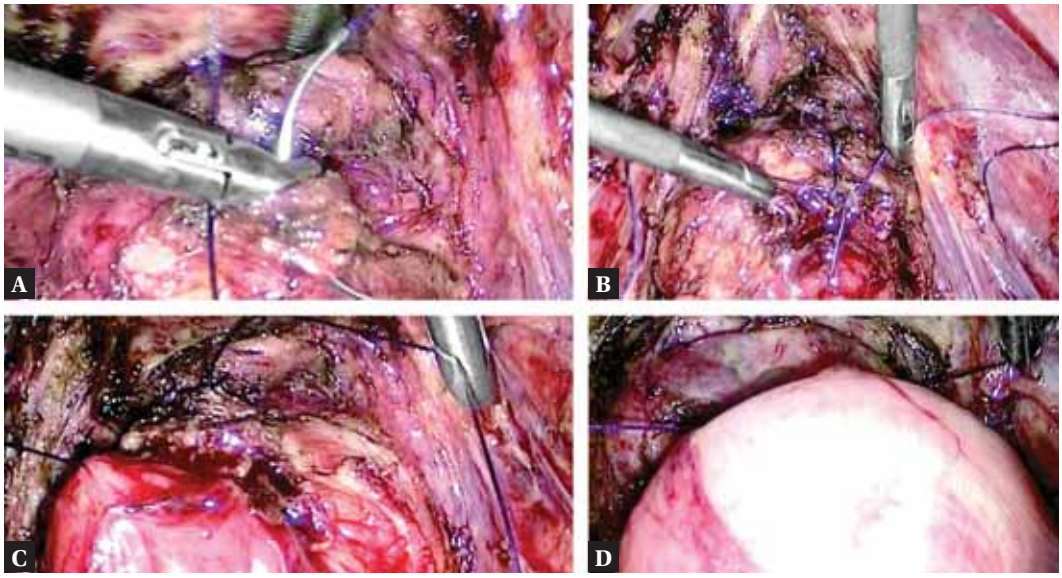
A very suitable, not a complex way to perform technique for rectosigmoid discoid resections is using the circular stapler, a technique in which we also need laparoscopic suturing. After excising all the endometriosis lesions in the pelvis, we isolate the endometriosis nodule in the anterior wall of the rectosigmoid. We use a Vicryl® 2-0 suture to transfix it from caudal to cranial, the limits being the healthy portions adjacent to the nodule. This part of the procedure is best performed with the left hand, for surgeons standing on the left side of the patient. We then perform a single intracorporeal knot, and pull the two edges of the suture to give traction to give the nodule inside the circular stapler passed per anus (Figs.5.15A to D). The stapler is fired and the lesion is excised. The stapling line will be limited to the anterior wall of the bowel, although in some occasions it might include its whole circumference.



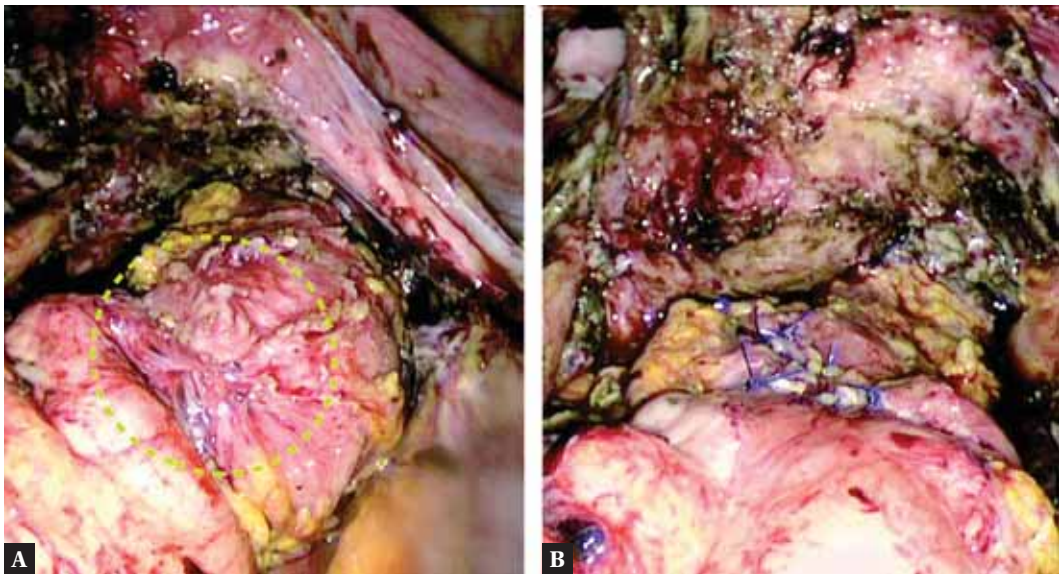
Figures 5.13A to F: Steps for cystorrhaphy after partial cystectomy for bladder endometriosis. (A) Cystoscopic; (B) Laparoscopic views of the nodule (arrows). Suturing of the base of the bladder close to the trigone should be performed "vertically" with the right hand in the central port; (C and D) The bladder dome should be sutured "horizontally" with the left hand; (E) The bladder can be entirely sutured by laparoscopy (arrows in F).



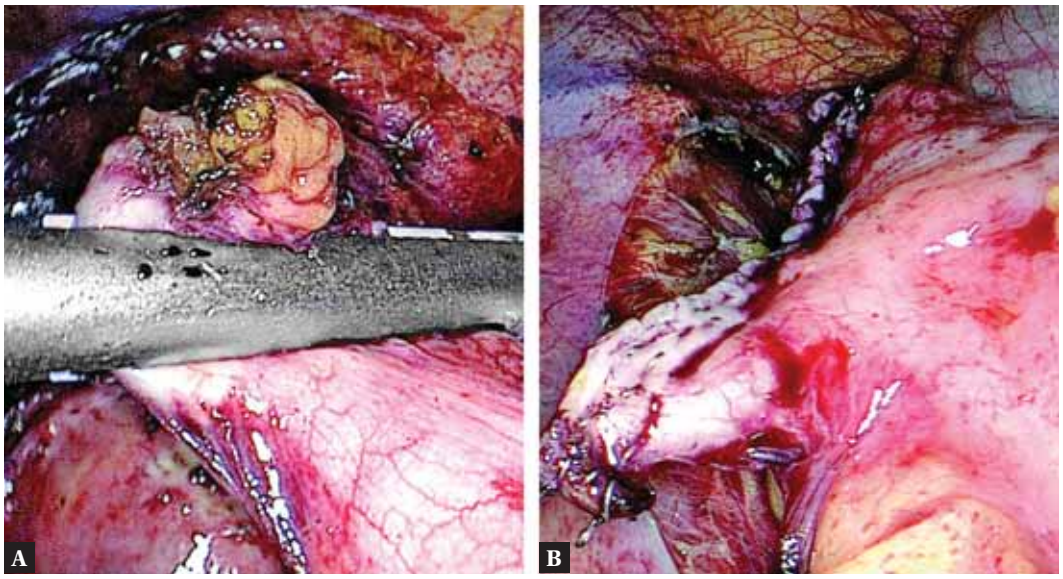
Figures 5.14A to C: A single layer of separate sutures (arrows) is helpful to reinforce the rectosigmoid anastomosis stapling line, after excision of endometriosis.



Figures 5.15A to D: Laparoscopic discoid anterior rectal wall excision with the circular stapler for endometriosis. A continuous suture is used to transfix an endometriosis nodule in the rectosigmoid. After constructing a single intracorporeal knot, the edges of the suture are used to pull the nodule inside a circular stapler, passed per anus.



Figures 5.16A and B: A single layer of separate sutures is necessary to repair the rectosigmoid defect after shaving excision of endometriosis.



Figures 5.17A and B: A laparoscopic linear stapler can be used to excise endometriosis in the cecum. A single layer of separate sutures can reinforce the stapling line afterward.

Lastly, laparoscopic suturing is needed to perform shaving resections of the rectosigmoid for endometriosis. Shaving resections are suitable for small lesions that do not penetrate the mucosal layer. Therefore, excision will be limited to the muscular layer of the bowel. A single layer of separate PDS® 3-0, Prolene® 3-0 or Vicryl® 3-0 sutures should be done to close the defect (Figs. 5.16A and B).

Ileum

Endometriosis in the terminal ileum may be excised either by shaving or segmental resections. A typical symptom of ileal endometriosis is cyclic epigastric pain that mimics gastritis,[6] or repetitive bowel occlusion that sometimes may lead to emergency surgery.[7]

Small lesions restricted to the antimesenteric border and that do not distort the anatomy can be excised by shaving resections, similarly to rectosigmoid shaving. On the other side, lesions that cause occlusion or that distort the circumference of the ileum must be excised by segmental resections. Laparoscopic stapling devices are best for this purpose, and suturing is sometime used to bring together the edges to be anastomosed, as well as to reinforce the stapling line suture.

Cecum

The lesions of endometriosis affecting cecum is generally located at and adjacent to the base of appendix. A laparoscopic linear stapler can be used to excise the lesion and appendix en bloc (Figs. 5.17A and B), and we may perform suturing to reinforce the stapling line.

Appendix Vermiformis

During laparoscopic excision of DE, laparoscopic appendectomy is very common. Abnormal appendixes may be identified in about 5–10% of the surgeries, and pathology will reveal endometriosis in most of them.[8] A first option is to construct three loops with a 90 cm cotton suture and to apply them to the appendix, 1 cm apart from each other, starting from its base. After coagulating the appendiceal vessels, pass one edge of the suture around the appendix and pull it out of the cavity, to construct an extracorporeal knot. The Röeder extracorporeal knot is the best option,1 because it is safe and strong and, the more you push it to the tissue, the stronger it gets

Another interesting option is to first mobilize the appendix and cecum from the lateral wall and pelvic brim, as enough as to exteriorize it through the umbilicus (Figs. 5.18A and B). Appendectomy is then performed as it would be performed by laparotomy. With this technique, there is no need for laparoscopic suturing.

Vagina

If the deep endometriosis infiltrate the muscular layer of the vagina, it becomes mandatory to perform a partial colpectomy to excise the disease. Suturing can be performed with a 3.5 cm curved needle Vicryl®1-0 suture, which can be introduced in the cavity transparietally, or by the vagina itself. Exposure is enhanced by hysteropexy (or using a uterine manipulator) and by a vaginal probe, which is very helpful to delineate the borders to be sutured (Figs. 5.19A to F).

Although not a treatment for DE, hysterectomies will sometimes be performed concomitantly during surgeries, especially for women with adenomyosis and who completed childbearing. In this situation, colporrhaphy can also be performed by laparoscopy.

Vessels Ligation

Many time major vessels involved in endometriosis sur-gery need to be ligated. Ovarian vessels while performing oophorectomy, uterine vessels while performing hys-terectomy, or any pelvic vessel are the major vessels which are possibly involved by DE. All major vessels can be ligated with an extracorporeal Röeder knot.

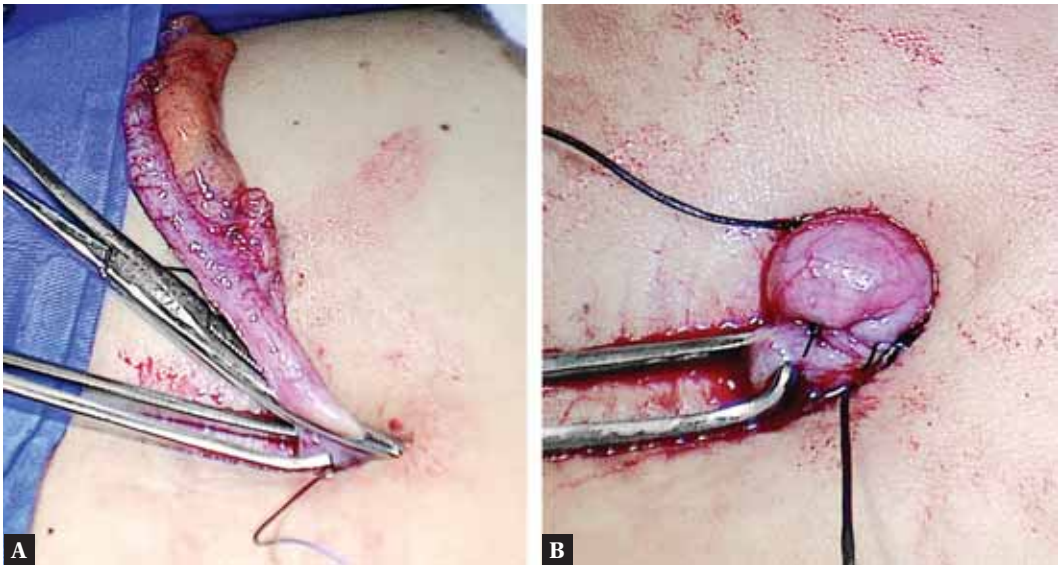
Iatrogenic Lesions

Laparoscopic suturing is helpful in treating iatrogenic injuries which occur during the excision treatment of DE Lesions in the bowel, bladder, ureter, vessels and nerves do occur in DE surgery, even when performed by experienced surgeons.

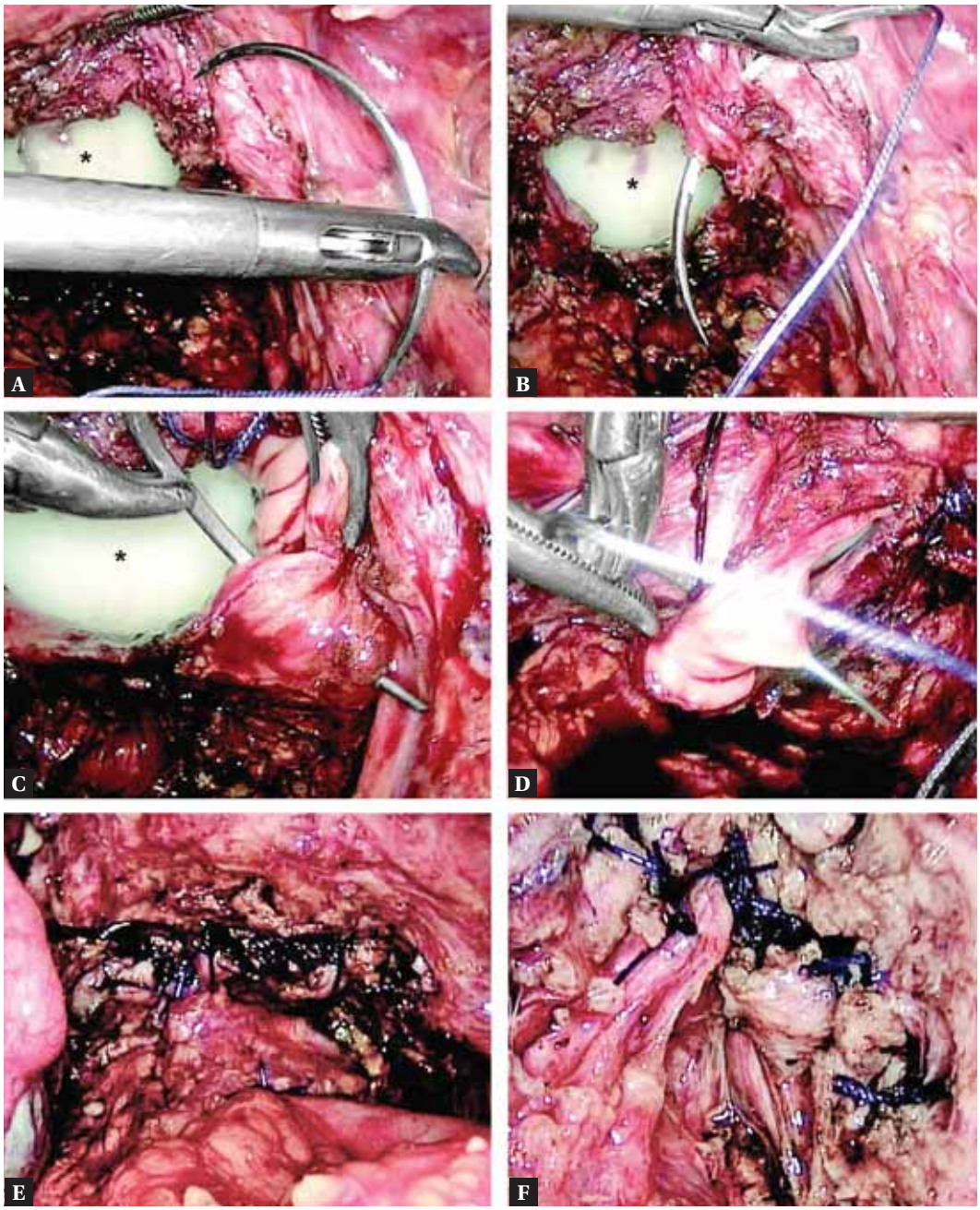
Bowel and bladder lesions can be sutured the same way as when DE lesions are excised from these organs, as cited above. A major vessel lesion, such as in the internal iliac vein, can be repaired continuously with 4-0 or 5-0 Prolene® sutures. Similarly, a sectioned ureter can be repaired by 60–90 days stenting and four separate sutures of Vicryl® 4-0 (Figs. 5.20A to D).

CONCLUSION

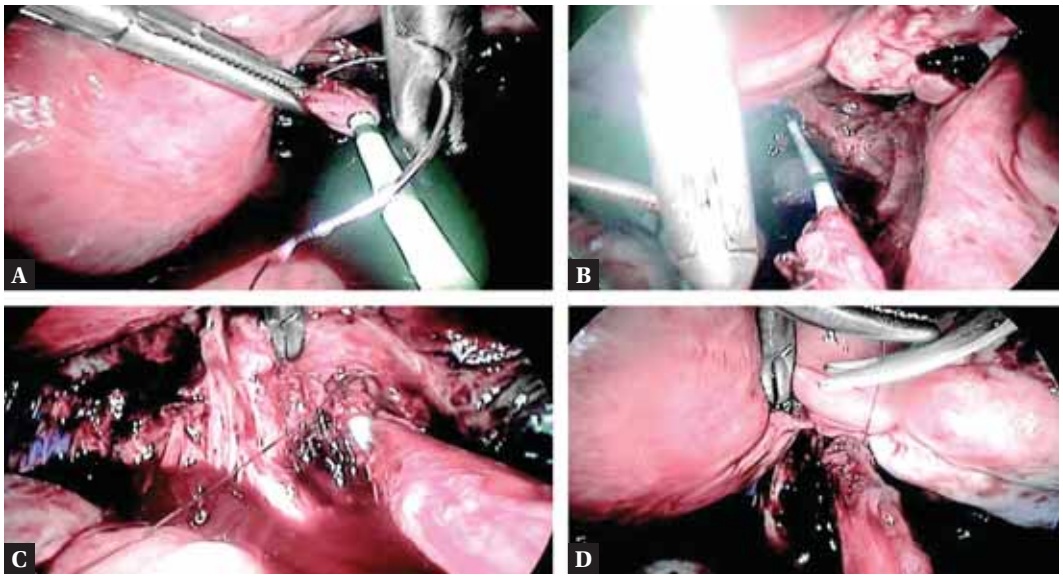
Laparoscopic suturing has many applications in DE surgery, like in other major laparoscopic procedures. Lap-aroscopy avoids the obvious burden of a large abdominal incision that not only requires significant care but also involves increased disability, cost, and pain for the patient. Mastering these skills is necessary for any surgeon willing to treat endometriosis surgically. Laparoscopic suturing can be learned at specific courses and



Figures 5.18A and B: During endometriosis surgeries, the appendix can be excised through the umbilicus after laparoscopic mobilization.



Figures 5.19A to F: After partial colpectomy, the vagina can be sutured by laparoscopy. (A to C) A vaginal probe (*) helps to delineate the borders to be sutured and increase exposure. Suture starts at the right edge, the surgeon standing on the left side of the patient using his or her left hand; (D) Suture finishes at the left edge, the surgeon using his or her right hand; (E and F) The vagina can be entirely closed laparoscopically.



Figures 5.20A to D: A sectioned ureter can be repaired completely by laparoscopy with 4 separate sutures and 60–90 days stenting.

workshops available worldwide, and they should be practiced and trained exhaustively in practical and animal models, even by the experienced surgeons.

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6

CHAPTER

Laparoscopic Hysterectomy in Endometriosis

INTRODUCTION

Hysterectomy is the most common gynecological procedure.[1] Most hysterectomies can be performed laparoscopically including those with severe endometriosis as well as with large myomas.[2-4] To tackle difficult hysterectomies, various techniques have been described previously, but the general use of these techniques is limited by the level of expertise needed for it.[5,6]

HYSTERECTOMY IN ENDOMETRIOSIS WITH FROZEN PELVIS

Introduction

Hysterectomy in frozen pelvis is considered to be a surgically difficult condition, whether it is done by laparotomy or laparoscopy. Frozen pelvis is defined as a surgical condition where reproductive organs and adjacent structures are distorted by extensive adhesive disease and fibrosis, which obscure the normal anatomical landmarks and surgical planes, making dissection extremely difficult and increasing the risk of injury to vital organs.[7] Common causes are infections, endometriosis and multiple previous surgeries, and other causes are ovarian carcinoma and radiotherapy. Surgery in frozen pelvis can result in serious complications like bowel and urinary tract injury. Most of these cases are referred to oncosurgeons who usually perform the surgery by an open retroperitoneal approach.[8,9]

Preoperative Investigations

The preoperative investigations in case of hysterectomy in endometriosis includes the following:

- To know the colorectal nodule and the extent of the disease, magnetic resonance imaging (MRI) pelvis should be done
- Transvaginal sonography is a must that should be done
- In some cases, the patient might show hydronephrosis or might suspect ureteric stricture due to involvement of cardinal ligament by endometriosis. In such cases, computed tomography-intravenous pyelogram (CT-IVP) may be required (Fig. 6.1)
- In patients with complaint of per rectal bleeding, to check rectal involvement in endometriosis, colonoscopy should also be done.

Preoperative Bowel Preparation

- A edentulous diet or soft diet is the one that reduces the requirement of chewing the food, as it is mechanically soft. The patient should be given a soft diet till afternoon which should be followed by clear liquid diet, one day prior to surgery. This is then to be followed by no diet at all by mouth for 8 hours prior to the surgery
- A preparation of peglec powder is to be given over 2–3 hours on previous evening. The preparation involves dissolving the pack in 2 L of water. The purpose of providing peglec powder is gastric lavage.

Essential Equipment

Following are the instruments that are required, apart from the standard equipments:

- Laparoscopic scissors—for surgeries

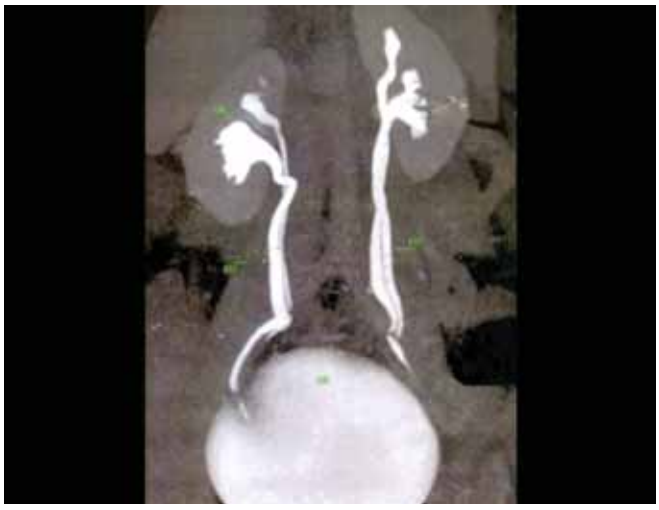


Figure 6.1: CT-IVP should be done preoperatively in every case of endometriosis with frozen pelvis to identify exact course of ureter, to see for hydroureter and hydronephrosis as well as any congenital anomaly of the ureter. This picture shows bilateral double ureter system.

- Rectal probe—to identify and mobilize the rectum
- Harmonic scalpel—for a better dissection
- Cystoscope and ureteric stents—to examine urinary bladder, urethra and ureter
- Vessel sealing system— for better hemostasis.

Position of Patient

Patient is placed in Lloyd-Davies position (Fig. 6.2).

Technique

Manipulator: Either Prashant Mangeshikar's uterine manipulator or Clermont-Ferrand uterine manipulator can be used.

Port Placement

- One primary 10 mm port should be placed intraumbilically
- Three secondary 5 mm port placement should be done at left iliac fossa, right iliac fossa (both lateral to midclavicular line) and in midline (Fig. 6.3). Middle port is a very multifaceted port as it is helpful for dissection on both sides in cases of frozen pelvis in endometriosis.

Steps of Laparoscopic Hysterectomy

- Inspection of pelvis: In cases of frozen pelvis, thorough inspection of pelvis is very important to be carried out (Figs. 6.4 A and B)
  - Small bowel adhesions to anterior abdominal wall and the adhesions to the uterus are present in case of previous surgery. For small bowel adhesions, sharp dissections are preferred. No energy sources are used for the small bowel dissection. Also in advance cases, rectosigmoid colon is densely adherent to the posterior wall of uterus
  - Ureters are supplanted medially in case of advance endometriosis
  - Apart from pelvis, inspection of abdominal cavity should also be done. In some cases, appendix is low and adherent to right adnexa (tubo-ovarian mass). Sometime tip of appendix is also involved by endometriosis (Fig. 6.5)

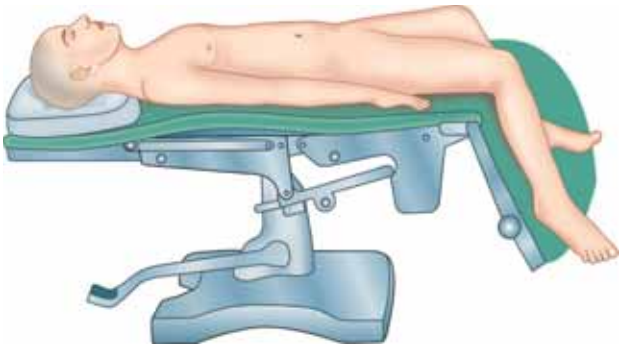


Figure 6.2: Patient in Llyod-Davies position.

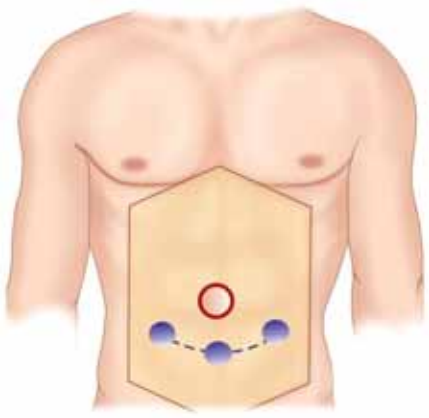
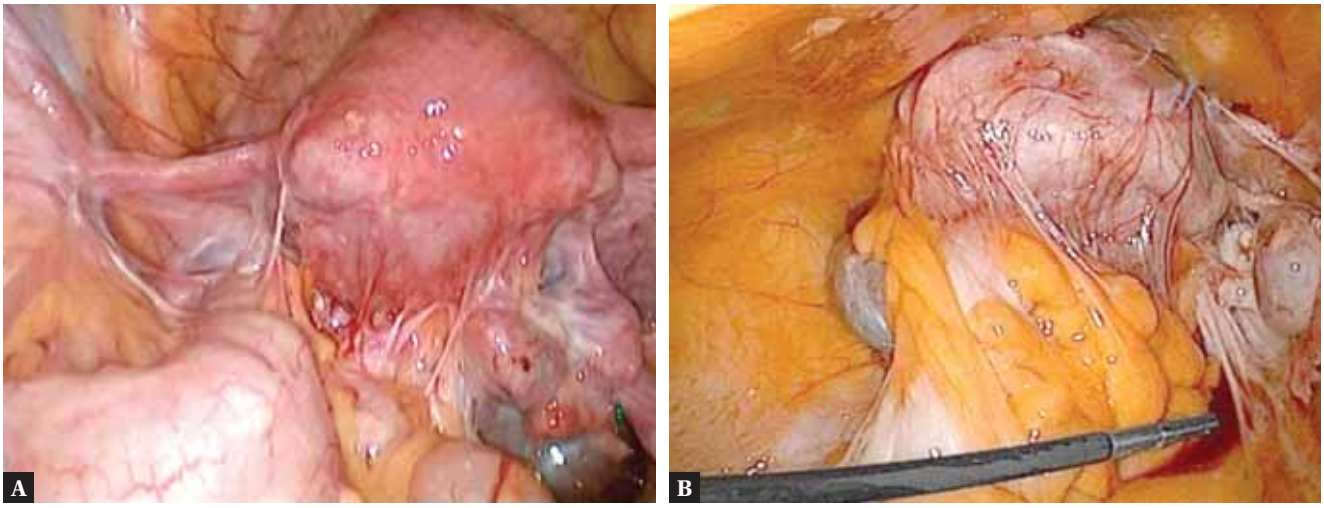


Figure 6.3: Port placement in patient.

  - Omentum, diaphragm, small intestine, and large intestine should also be inspected for endometriotic implants. Also we look liver for liver bed adhesions
- Aim of dissection is to start from virgin (retroperitoneal area) to nonvirgin area (pathological site posterior to the uterus, adnexal area and both paracolic gutters)



Figures 6.4A and B: Laparoscopic panoramic view of endometriosis with frozen pelvis.

- Dissection is indirectly facilitated using injection pitressin (1:200 mL dilution) which is injected posteriorly in the uterus to reduce bleeding and avoid the staining of the tissue with blood (Fig. 6.6)
- It is usually started laterally by mobilization of the mesentery of sigmoid colon on left side and entering retroperitoneal space (Fig. 6.7)
- The level of pelvic brim is the most common site to identify ureter, as it crosses internal and external iliac vessels. To avoid injury to the ureter, the retroperitoneal spaces are opened at the level of pelvic brim and lateral mobilization of ureters are and dissection is done till it enters ureteric tunnel. Dissection is done parallel to the ureter as it becomes much easier. Sometimes, fiberoptic ureteral catheter is used to exactly see the course of the ureter. This is followed bytubo-ovarian mass excision or salpingo-oophorectomy (Figs. 6.8 to 6.14)
- The step is followed by entering the retroperitoneal space where origin of the uterine vessels is identified. Identifying uterine vessels, the only tortuous vessels in the pelvis traversing the pararectal space is easy. Uterine vessels are ligated at their origin using vessel sealing system, and avoiding injury to the ureter is taken care of (Figs. 6.15 and 6.16)
- Round ligaments are then coagulated and are then cut using 5 mm ligature
- With the help of either harmonic scalpel or by sharp dissection (in cases of previous cesarean section), the bladder is mobilized, once the uterus is retroverted (Fig. 6.17)
- To separate rectum from the posterior wall of the uterus, scissors can be used for posteriorly sharp dissection to flush

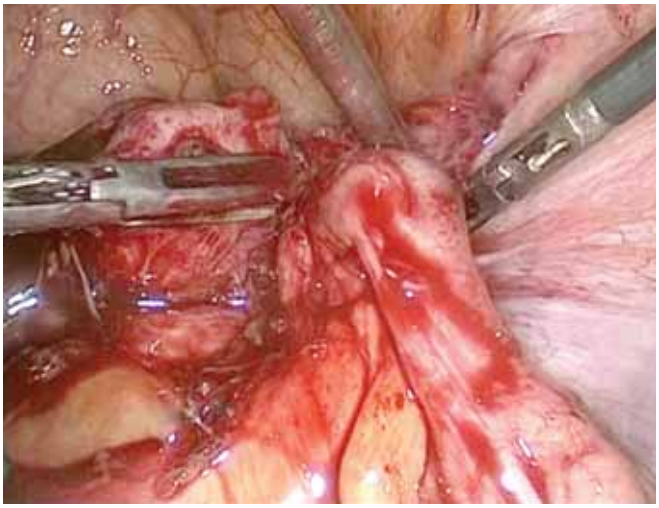


Figure 6.5: Sometimes appendix is adherent to right adnexa.

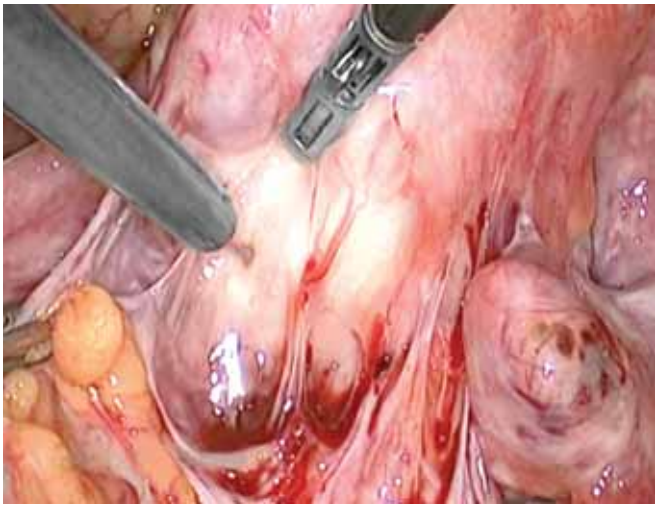


Figure 6.6: Vasopressin (1:200 mL dilution) injected in the uterus to reduce bleeding to avoid staining of the tissue during dissection.

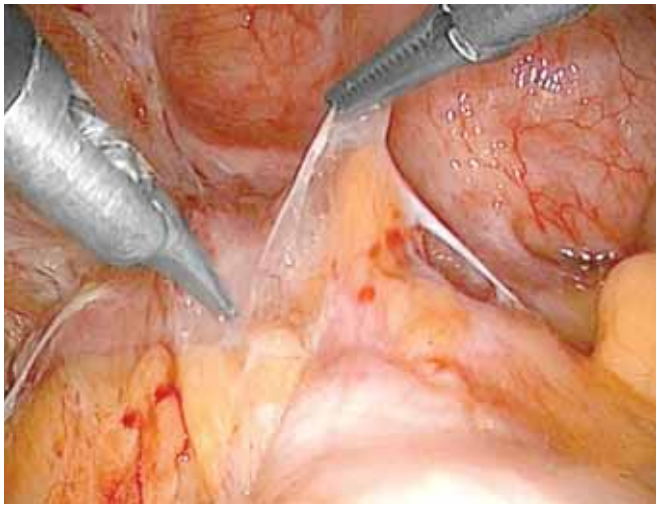


Figure 6.7: Lateral mobilization of sigmoid colon should be commenced by sharp dissection.

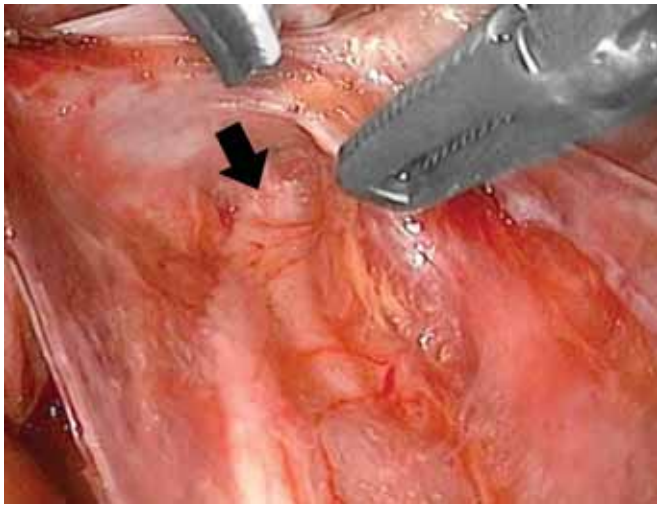
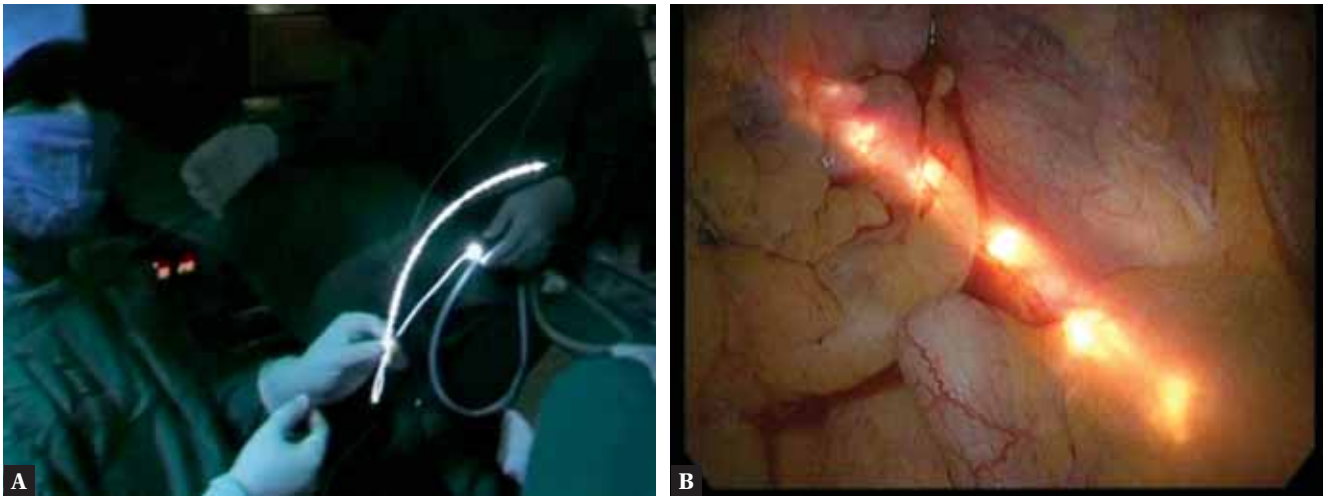


Figure 6.8: Always start dissection laterally by opening retroperitoneal space (virgin area). Identify the course of ureter at the site of pelvic brim.



Figures 6.9A and B: Fiberoptic ureteric catheter—Illumination effect of the catheter helps to find the pathway of the ureter.

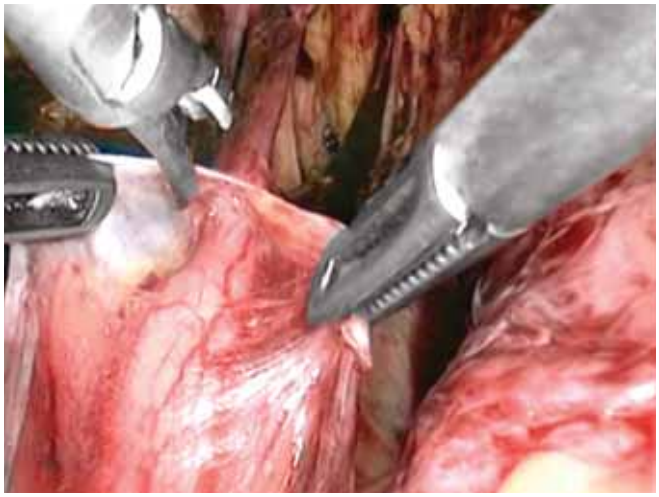


Figure 6.10: Mobilization of the ureter in retroperitoneal space. Do dissection parallel to the ureter.

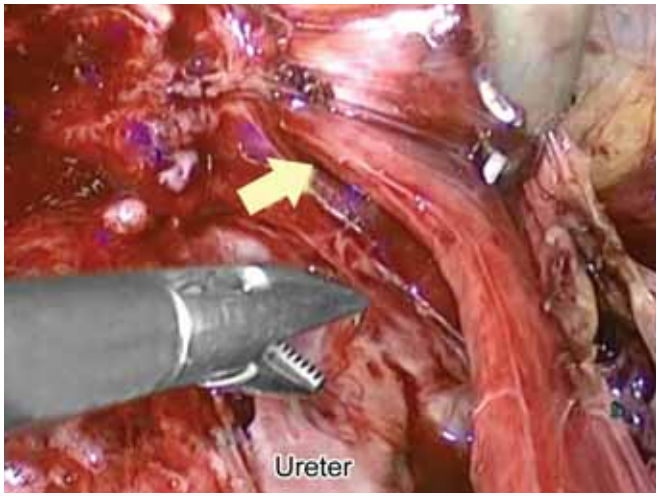


Figure 6.11: Ureter should be mobilized after which salpingo-oophorectomy should be performed.

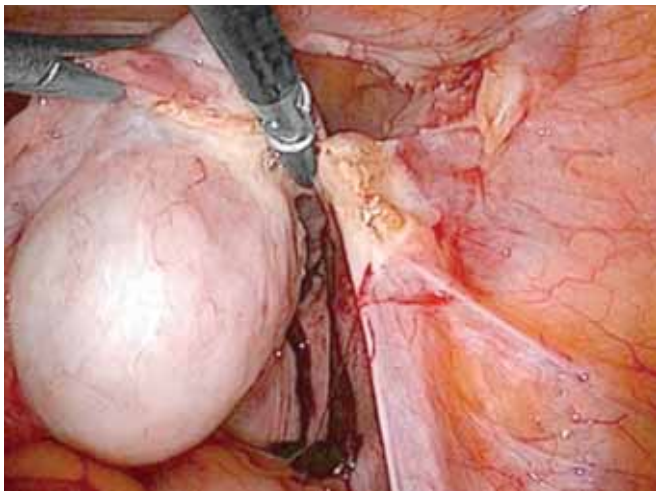


Figure 6.12: Salpingo-oophorectomy should be done after ureter mobilization.

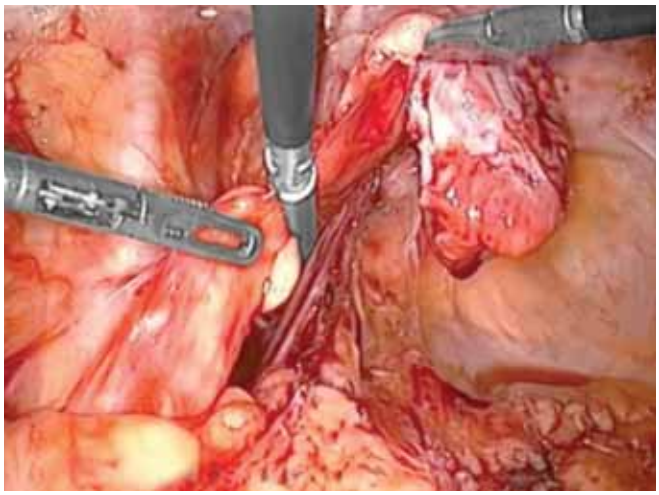


Figure 6.13: Left tubo-ovarian mass excision after ureter mobilization.
.

to the uterus inside the colorectal nodule. Care should be taken to remain inside the colorectal nodule to avoid injury to the rectum. No usage of energy source should be there to avoid thermal injury to the rectum. Once hysterectomy is completed, colorectal nodule should be left on the rectum and should be excised (Fig. 6.18)

- Subsequently steps of intrafascial hysterectomy are followed. Anterior displacement of the uterine vessels anteriorly occurs due to axis rotation of the uterus. After proper skeletonization, uterine vessels are again cut flush to the uterus on both sides. Cardinal ligament and uterosacral ligament are also coagulated and then cut subsequently (Fig. 6.19)
- After insertion of the Prashant Mangeshikar's uterine manipulator (Fig. 6.21A) or Clermont Ferrand uterine manipulator (Fig. 6.21B) and removal of the specimen vaginally, colpotomy (Fig. 6.20) is done using 5 mm harmonic scalpel or harmonic hook
- Excision of colorectal nodule is done after completion of intrafascial hysterectomy. Two techniques are therefore recommended for excision of the colorectal nodule: either shaving of the nodule followed by insertion of rectal probe or complete excision of the nodule by circular stappler is recommended. Shaving technique with scissors is preferred as it gives less morbidity postoperatively (Figs. 6.22 to 6.25)
- Due to involvement of cardinal ligament by endometriosis in some cases, there is presence of ureteric stricture. To excise the endometriotic nodule for the purpose of relief of external compression over the ureter, ureteric tunnel dissection is carried out. In few cases, because of severe ureteric stricture,

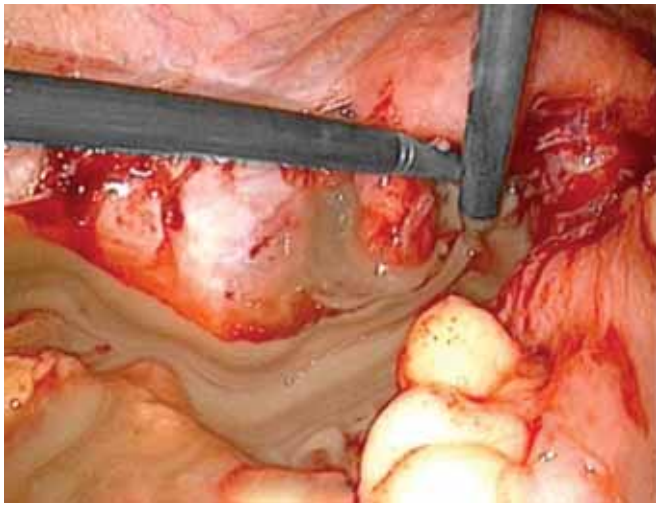


Figure 6.14: Left tubo-ovarian abscess following ovarian endometrioma aspiration. Salpingo-oophorectomy should be done.

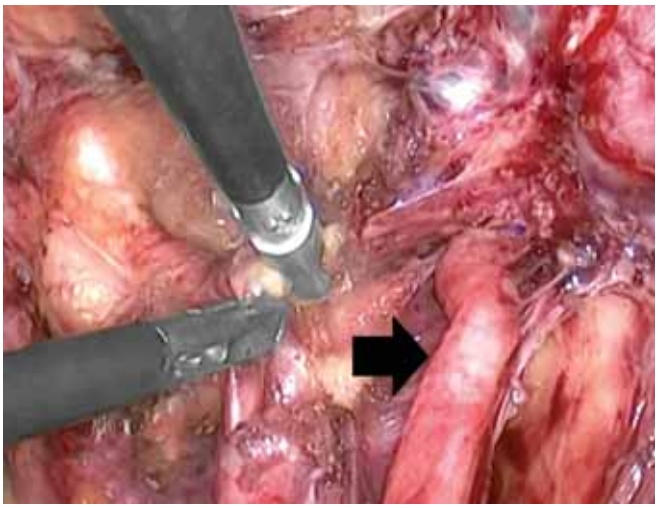
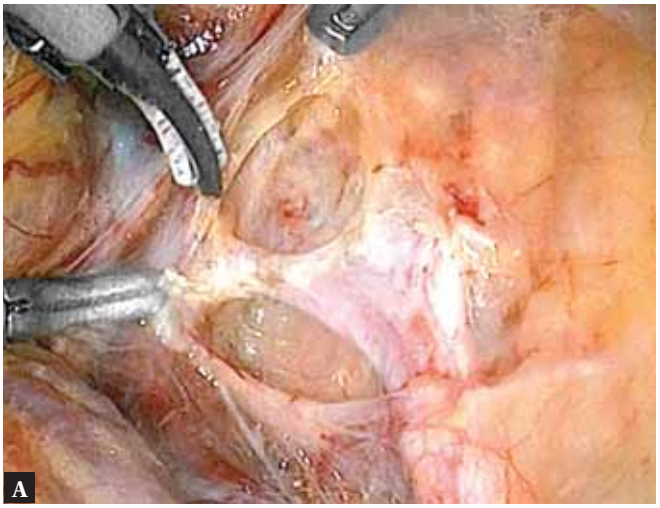
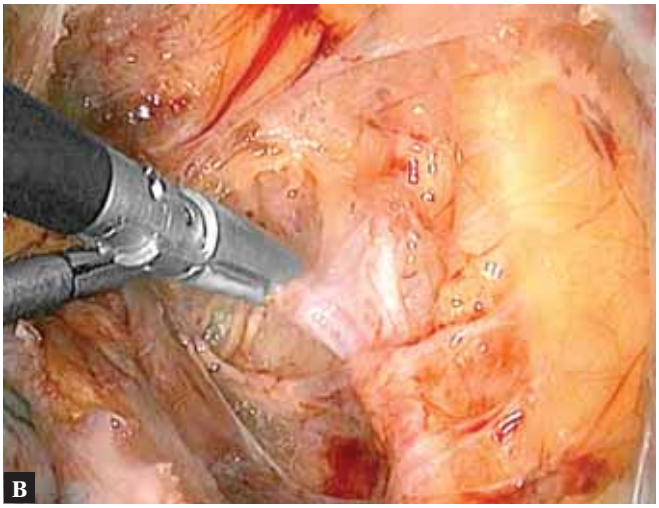


Figure 6.15: Uterine vessels ligated at their origin using 5 mm ligasure after doing ureteric dissection. They are only tortuous vessels crossing the para-rectal space. This figure arrow shows hydroureter (dilated ureter) due to stricture at the site of cardinal ligament in ureteric tunnel.





Figures 6.16A and B: Uterine vessels ligated at their origin.

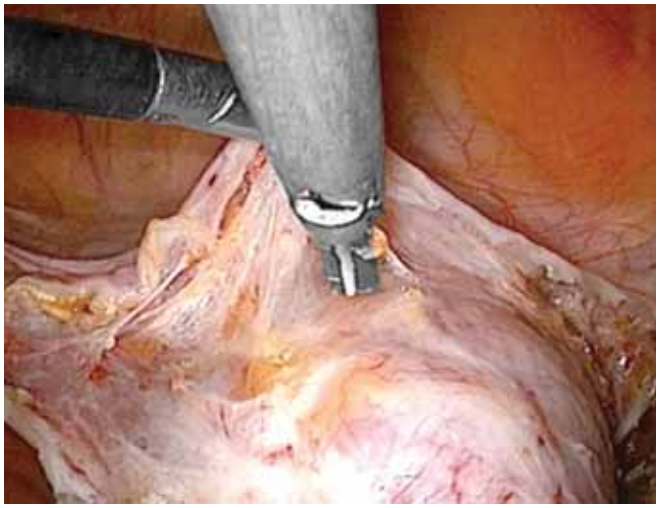


Figure 6.17: Bladder mobilization.

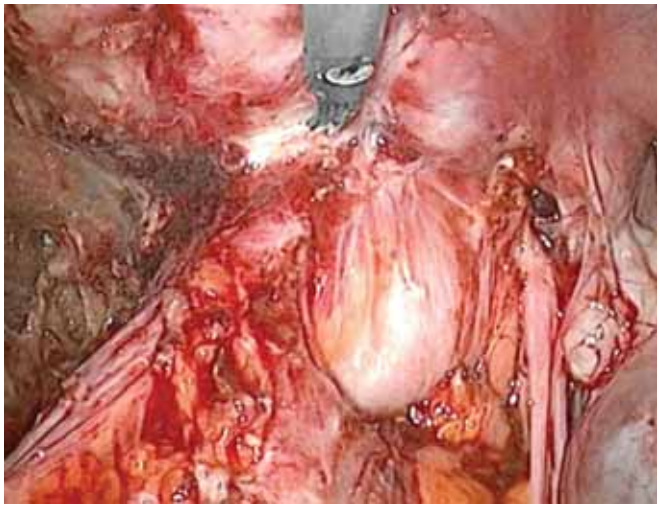


Figure 6.18: Posteriorly dissection done flush to the uterus to avoid colorectal injury. Try to bring nodule on the colon. Colorectal nodule is removed after completion of hysterectomy.

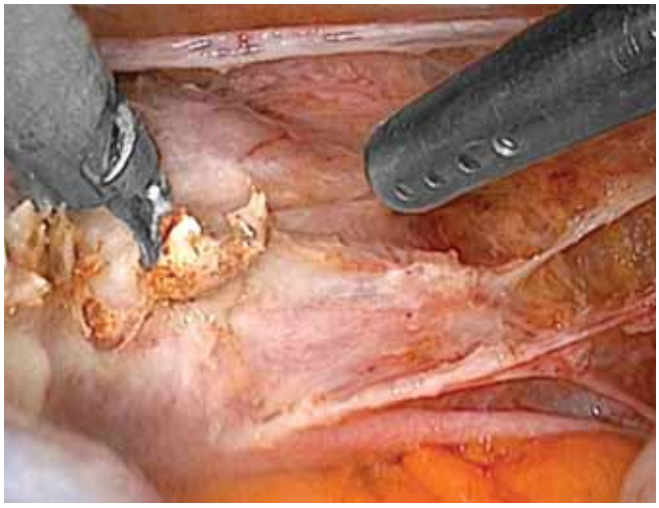


Figure 6.19: Uterine vessels ligated and cut using harmonic scalpel flush to the uterus.

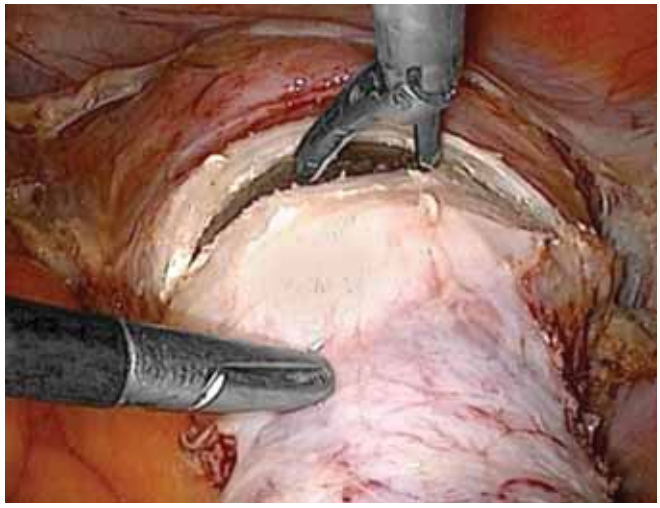
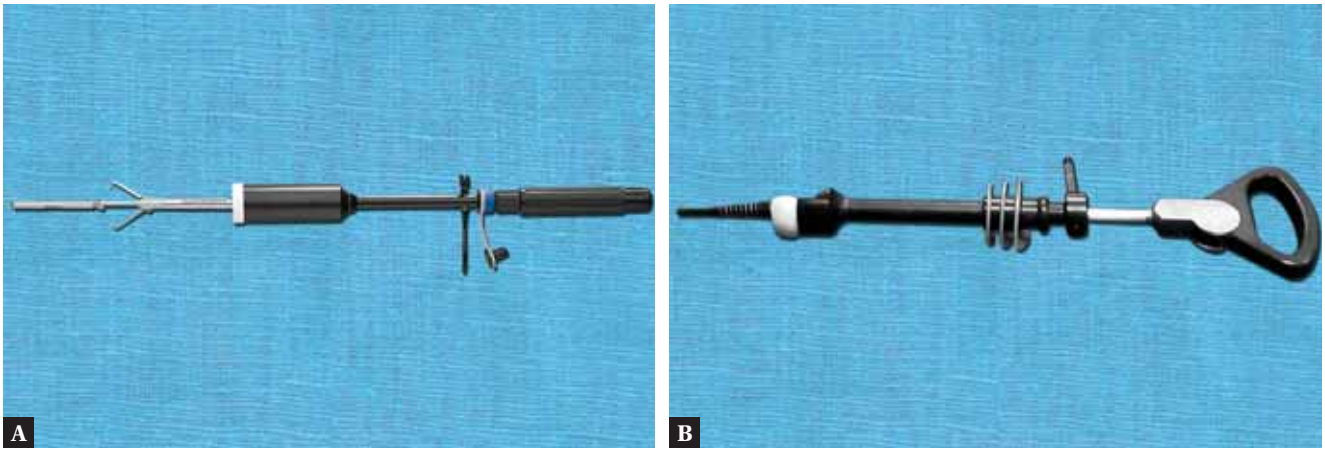


Figure 6.20: Colpotomy with 5 mm harmonic salpel or harmonic hook.



Figures 6.21A and B: (A) Prashant Mangeshikar's uterine manipulator; (B) Clermont-Ferrand uterine manipulator.

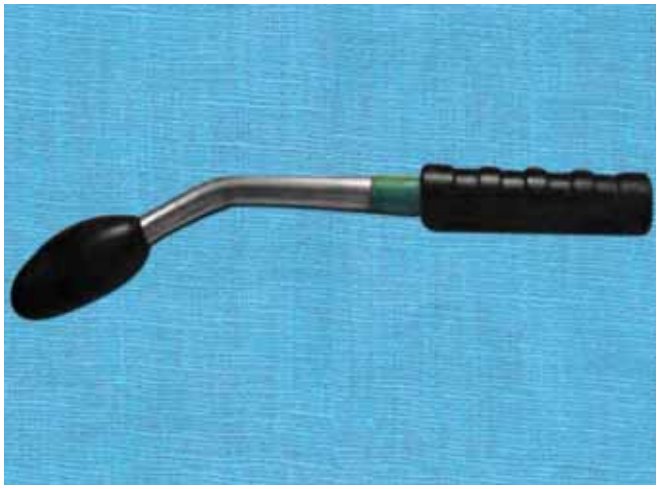


Figure 6.22: Rectal probe should be introduced before shaving of the colorectal nodule.

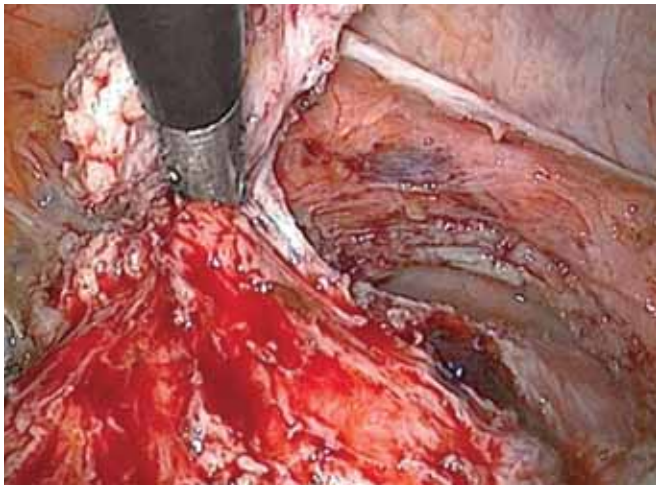


Figure 6.23: Shaving of the colorectal nodule should be done after.

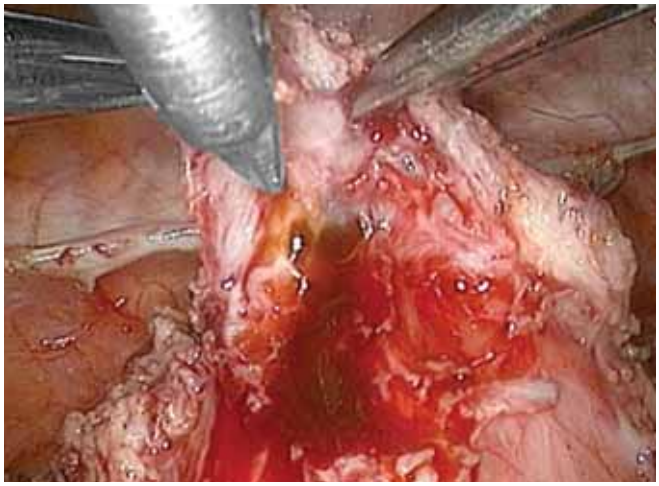


Figure 6.24: Shaving of the colorectal nodule with scissors. Sometimes we find choky material coming out from the nodule (lacunae of colorectal nodule).

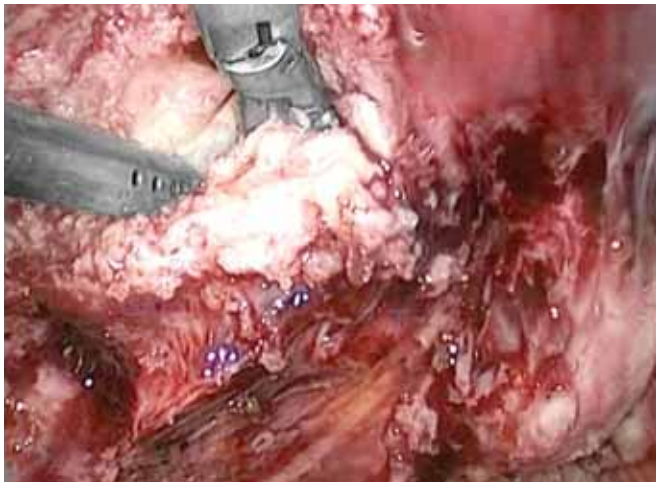


Figure 6.25: Shaving of the colorectal nodule with harmonic scalpel.

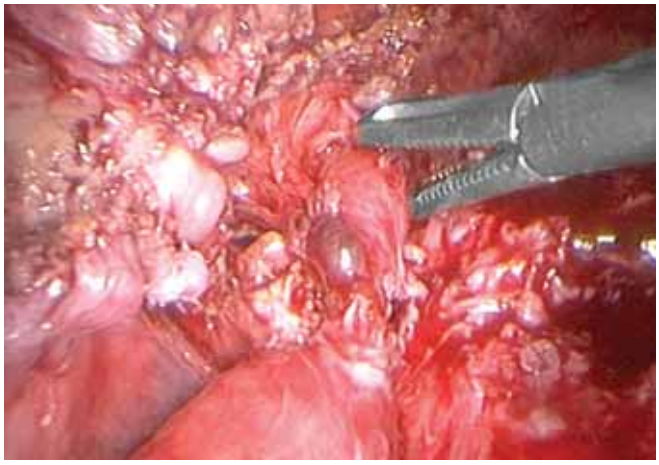
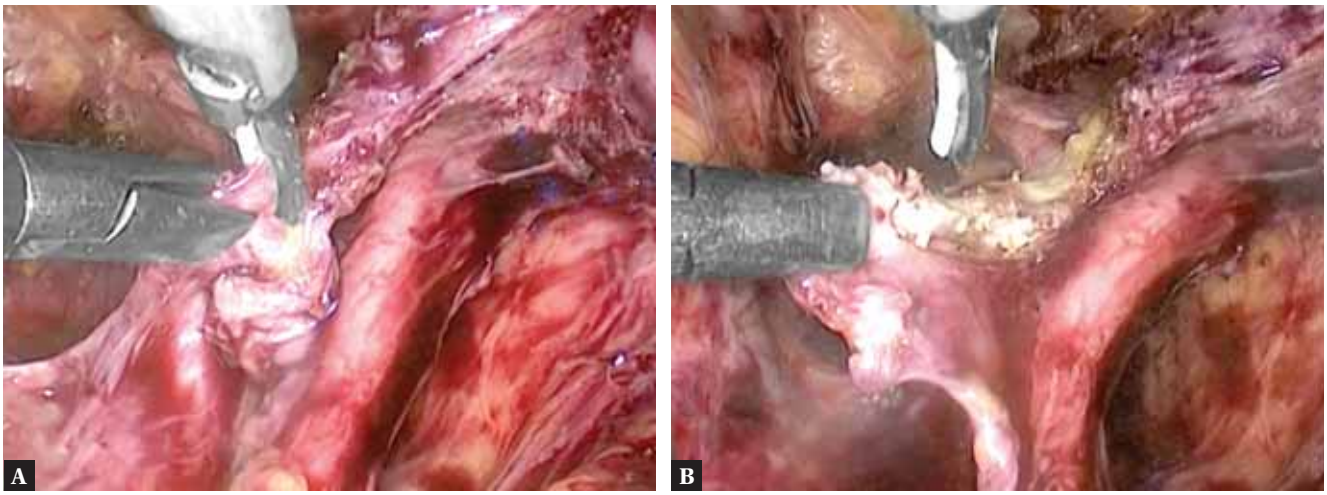


Figure 6.26: Ureteric stricture at the level of the cardinal ligament. Ureteric tunnel dissection is done to excise the endometriotic nodule.

excision of the diseased portion of the ureter and uretero-ureteral anastomosis is done. Ureteric stenting should be carried out post-procedure and stent should be kept for 6 weeks (Figs. 6.26 to 6.29)

- Vault is then closed laparoscopically by contralateral intracorporeal suturing using Vicryl no.1 (Fig. 6.30)
- Colorectal integrity test is done (air enema test) (Fig. 6.31). Pelvis is filled-up with normal saline and air is pushed from below inside the rectum to see bubbling of the air in the pelvis to rule out rectal injury. Since sharp dissection with scissors is preferred, primary suturing with Vicryl 2–0 is done for rectal injury. But if any energy source which leads to injury of the colon, is used, then primary suturing along with colostomy is required.

Similarly to see for bladder mucosal involvement in endometriosis as well as to see urine spurts from both ureteric orifices, cytoscopy is must. If there is presence of bladder mucosal involvement, then excision of the bladder mucosa and resuturing of the bladder wall with Vicryl 3–0 is preferred.



Figures 6.27A and B: Endometriotic nodule causing ureteric structure excised at the level of the cardinal ligament.

- Hemostasis is confirmed, If oozing persists from the raw surfaces in pouch of Douglas (POD), laparoscopic bilateral internal iliac artery ligation is preferred to be done. It leads to reduction in pulse pressure by 85% which then helps in blood clot formation distal to ligation (Figs. 6.32 and 6.33). Sometimes SURGICEL SNoW (J&J) is kept over the raw area to achieve hemostasis
- Intraperitoneal drain and Foley catheter is preferred in each case.

Postoperative Management

- It is preferred to keep patient nil by mouth till she passes flatus as extensive dissection is done for colorectal nodule
- There might be requirement of glycerin syringe per rectally to relieve the gaseous abdominal distension
- Complete blood count (CBC), serum electrolytes, and serum creatinine are routinely done postoperatively next day
- Patient is usually discharged within 48–72 hours once urine and stool is passed by her normally

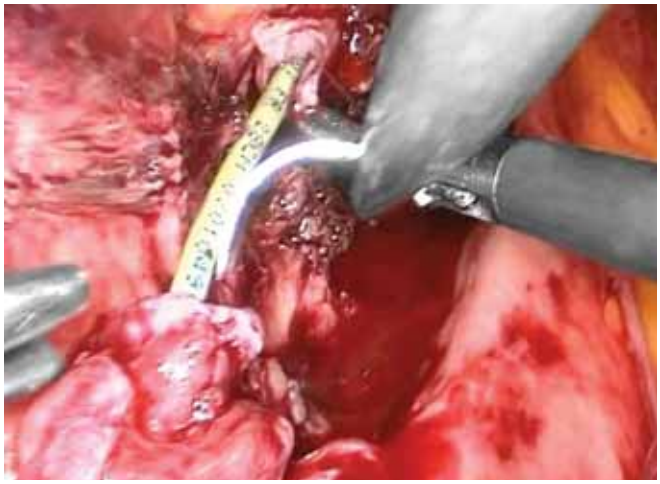
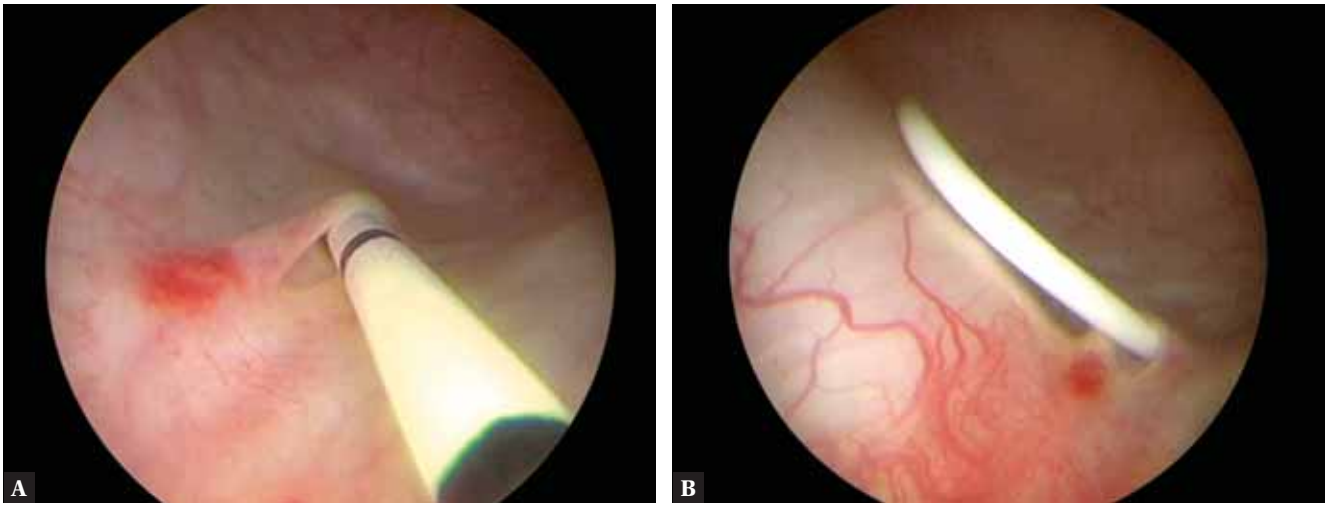


Figure 6.28: Severe ureteric stricture with large area of ureter involvement along with mucosa, resection followed by uretero-ureteral anastomosis should be done.



Figures 6.29A and B: Ureteric stenting should be done after the procedure and stent should be kept for 6 weeks.

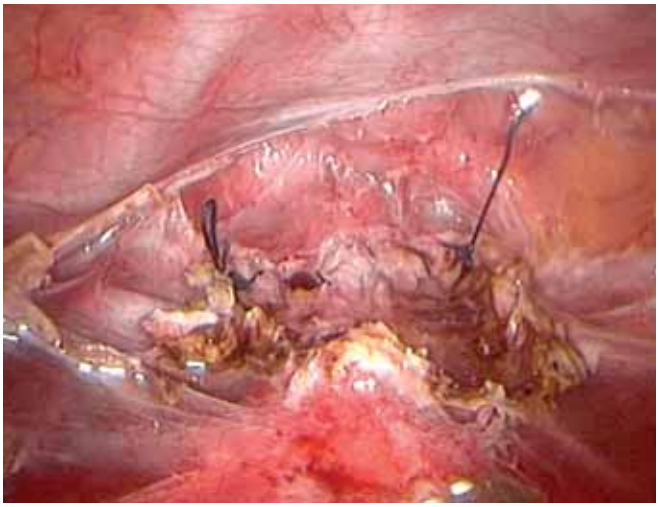


Figure 6.30: End result: Vault suturing by contralateral intracorporeal suturing technique using Vicryl no.1 after excision of the colorectal nodule.

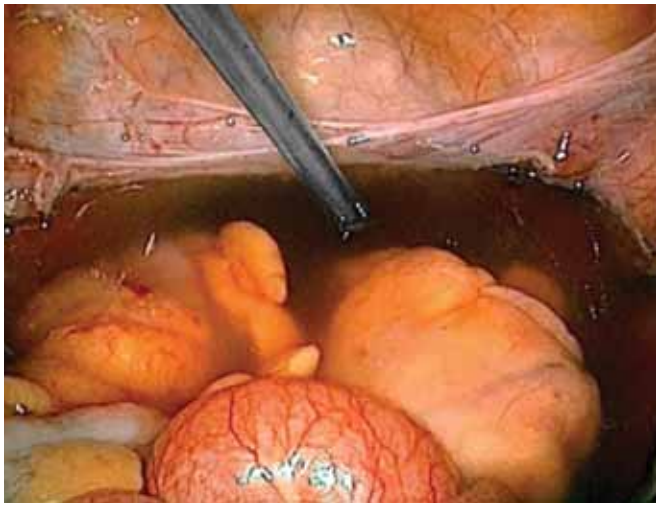


Figure 6.31: Colorectal integrity test.

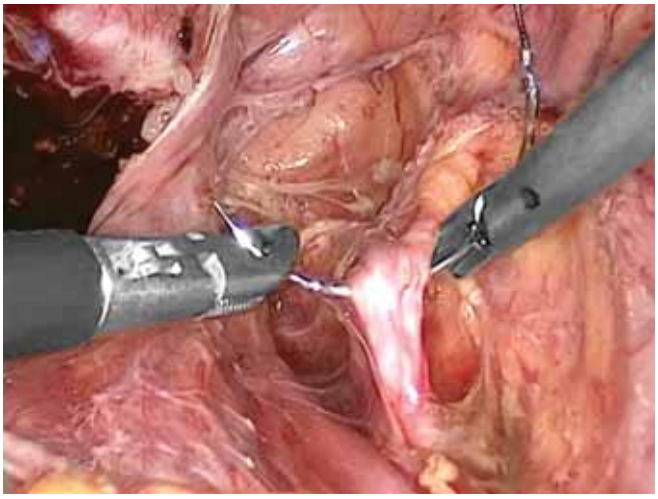


Figure 6.32: Bilateral internal iliac artery ligation may be required if bleeding persists from raw surfaces. It reduces pulse pressure by 85% which helps in blood clot formation.

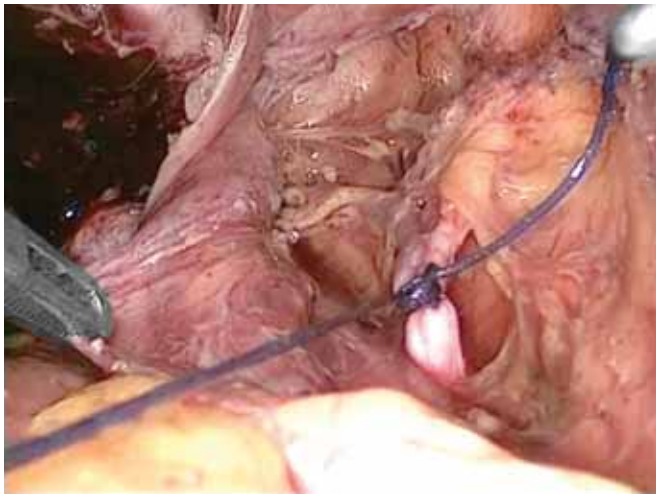


Figure 6.33: Bilateral internal iliac artery ligation may be required if bleeding persists from raw surfaces. It reduces pulse pressure by 85% which helps in blood clot formation.

- Analogues of gonadotropin-releasing hormone (GnRH) are given postoperatively to treat the microimplants of endometriosis. This is done especially in cases where the ovaries have been preserved.

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7

CHAPTER

Medical Management of Endometriosis

INTRODUCTION

Endometriosis is an estrogen-dependent multifactorial, multi-faceted disease described by the proliferation and presence of functional endometrial glands and stroma outside the uterine cavity. It is a common, benign, recurrent chronic gynecological disorder in routine clinical practice. The incidence of endometriosis is 20–30% in women with subfertility and 40–60% in women with dysmenorrhea1 and it affects 5–10% of women in reproductive age.

The origin of the disease is still indefinite and few of the most popular mechanisms that have been proposed are:

- Retrograde menstruation
- Celomic metaplasia
- Immune tolerance
- Adhesion
- Transplantation proliferation by abnormal inflam-matory cytokine profile in peritoneal fluid.

For the association of endometriosis and infertility several mechanisms have been proposed and include altered peritoneal function resulting in impaired folliculo-genesis and oocyte quality, pelvic anatomy distortion, immunologic dysfunction, and impaired implantation.

Endometriosis affected women may be asymptomatic or characteristically suffer from infertility or chronic pelvic pain. The heterogeneous clinical picture leads to difficulty and delay in making the diagnosis. Most studies report a mean duration of 8–10 years between the onset of symptoms and the diagnosis.[2]

MEDICAL MANAGEMENT (TABLE 7.1)

Though it is impossible to get rid of disease from root but can happen naturally or after a pregnancy. The treatment for endometriosis therefore aims at reducing or suppressing the disease so that the patient becomes symptom free or achieves a pregnancy. The choice of treatment and planning is based on various factors such as:

- Size
- Location
- Extent of the disease
- Type and severity of the symptomatology mainly pain, infertility and age of the patient.

The treatment can be divided into two categories: (1) surgical and (2) medical.

Surgical Management

Surgical interventions can be broadly classified as conservative when reproductive potential is retained, semiconservative when reproductive ability is eliminated but ovarian function is retained and radical when the uterus and ovaries are removed. Surgical management has its own disadvantages as it cannot be performed repeatedly and is a more invasive and expensive approach.

Originally the disease was felt to be best treated surgically and with the progressive development of operative laparoscopy the treatment of endometriosis could be instituted at the time of

TABLE 7.1: Medical interventions for the treatment of endometriosis.[3]

The medical interventions within each one of these categories			
Analgesia/anti-inflammatory agents	**Suppression of ovulation/estrogen**	**Direct action in endometriotic deposits**	**Immunomodulation**
NSAIDs*	Contraceptive pill* Danazol* Gestrinone* GnRH agonists* add back HRT AIs* (+ direct action)	LNG-IUS* Progesterone antagonists** SPRMs*** AIs* (+ estrogen suppression) ER ligands*** Angiogenesis inhibitors** Statins**	Inflammatory modulators***

*Currently available and sufficient evidence to recommend usage
** currently available but insufficient evidence to recommend usage
*** product(s) in development (basic science or phase I, II, III trials)

(NSAIDs, nonsteroidal anti-inflammatory drugs; GnRH, Gonadotropin-releasing hormone; HRT, hormone replacement therapy; LNG-IUS, levonorgestrel-releasing intrauterine system, ER, estrogen receptors; SPRMs, selective progesterone receptor modulators)

diagnosis, resulting in a more efficient but not necessarily more effective therapy. However, as the complexity and chronicity of endometriosis has been recognized, the pendulum has been swinging relentlessly towards medical options and it is now accepted that medical treatment that can induce a generalized suppression of the disease is necessary.[4,5]

Medical Management

This includes either a nonhormonal or hormonal medical therapy.

HORMONAL TREATMENT

The rise and fall of hormones during the menstrual cycle causes endometrial implants to bleed, thicken and break down. Hormones play an important role in reducing or eliminating the pain of endometriosis many times. However, hormonal therapy may slow down the growth and prevent the formation of new implants of endometrial tissue thus it is not a permanent cure for endometriosis though.

Advantages of Hormonal Therapy

- It is suitable administration to patients who are either surgically unfit or are refusing surgery
- It is less invasive and less expensive
- It can be used as adjuvant with surgical treatment both preoperatively and postoperatively and can be given for long duration.

The commonly prescribed hormonal agents are outlined in Table 7.2.

Oral Contraceptive Pill (Fig. 7.1)

Inclusive of minimal and mild stages of disease for pain control, oral contraceptive pills (OCPs) are the most commonly used drugs in endometriosis. OCPs induce atrophy of ectopic endometriotic implants by initial decidualization creating a pseudo pregnancy like situation. In endometriotic implants OCPs increase the apoptosis.[7] But for deep and severe endometriotic lesions they are not a permanent cure, only induce temporary disappearance of active lesions.[8] Patients with advanced stage disease are also being treated by OCPs as per few reports.[9] OCPs can be administered in a cyclic or a continuous regimen, without a break for withdrawal menses. Both regimens have comparable effects. The choice of regimen can be according to patient's preference. Continuous regimen is preferred for its decreased frequency of menses especially for women who fail to achieve pain relief with cyclic combined oral contraceptive therapy. Also better clinical results have been shown with continuous rather than cyclic administration.[10] There are no differences between the existing formulations in pain relief potency. OCPs having 30–35 g of ethinylestradiol can be used with good results. Formulations with a higher dose like 50 μg of ethinylestradiol have no added advantage.[11] Long-term OCP therapy can be a reliable adjuvant postoperative measure to prevent or reduce frequency or severity of anatomical relapse of endometriosis and recurrent dysmenorrhea.

Medical treatment of women with chronic pelvic pain suspected to be related to endometriosis should begin with a trial of nonsteroidal anti-inflammatory drugs (NSAIDs) or OCP or a combination of both. Selection of a first-line medical therapeutic agent should be based on the nature of the pain (cyclic or noncyclic), contraindications to NSAIDs or OCP, desire for contraception, and other factors. If an adequate pain relief is obtained from NSAIDs or OCP (individually or in combination), then a maintenance management regimen should be considered. If first-line therapy with OCP and NSAIDs fail to improve symptoms within a reasonable time (3–6 months), a second-line therapy with GnRH agonists and add-back should be tried, for a time. If second-line therapy fails, the clinician should reconsider other causes of pain and laparoscopy. This plan for the management of pain and endometriosis (Flowchart 7.1) was ratified by consensus panels made up of practicing gynecologists from both the United States and Europe.[12, 13]

Recently, the American College of Obstetricians and Gynecologists Committee on Adolescent Care wrote a Committee Opinion regarding endometriosis in adolescents which has also changed the diagnosis and treatment of endometriosis.[14] They recommend that lap-aroscopic evaluation be offered to adolescents under the age of 18 years only if they have persistent pain while taking OCP and NSAIDs given their safety profiles. In fact, most experts think it is reasonable to begin with this first-line empiric therapy but it has been reported that 50–70% of adolescents with pelvic pain not responding to combination hormone therapy (such as OCP and NSAIDs) have endometriosis at the time of laparoscopy.[14] Therefore, while the need for an early diagnosis and treatment of endometriosis during adolescence has been emphasized,[14] there is often a long delay in the diagnosis and treatment of the condition and it has been suggested that in the long-term there may be psychologic and social disadvantages associated with delaying diagnoses.[15] On the other hand, it is not known how the use of OCP masks the diagnosis and no studies have shown that early intervention limits specific disease outcomes. In this regard, it must be emphasized that there are no data available regarding medical therapy for prevention of disease progression or for prevention of future pain and fertility preservation, a fact to be considered mainly in asymptomatic women in whom endometriosis is discovered incidentally.[16]

TABLE 7.2: Hormonal agents used in the treatment of endometriosis.

Drug	*Effect*
Oral contraceptives	Causes atrophy of endometrium
GnRH agonists	Downregulates HPO axis
Androgens	Inhibits steroidogenesis
Aromatase inhibitors	Reduces estrogen synthesis
GnRH antagonists	Blocks the GnRH receptor directly
Progesterone antagonists	Prevents progesterone from exerting action
Selective progesterone receptor modulator	Induces reversible amenorrhea by selective inhibition of endometrial proliferation
Levonorgestrel releasing intrauterine system	Induces the endometrium to become inactive and atrophic

(GnRH, Gonadotropin-releasing hormone; HPO, hypothalamic pituitary ovarian)

Oral contraceptive pills are widely used as first-line treatment for painful symptoms associated with endometriosis and they are also used for maintenance treatment following GnRH agonist therapy. However, as previously stressed,[18] it is evident that the medical treatments currently available do not cure endometriosis, independently of the hormonal milieu induced and the presence of amenorrhea. Ectopic endometrial implants survive, although in atrophic form, ready for reactivation when suspension of the treatment occurs. A more rationale therapeutic objective might be simple limitation of the growth of eutopic and ectopic endometrium; hypomenorrhea obtained with OCP containing a prevalent progestogen component and low estrogen doses, could reduce the amount of retrograde menstruation and endometrial synthesis of prostaglandins, with decreased myometrial contractility and pelvic pain. This could give patients with endometriosis an acceptable quality of life. However, the relationship between early OCP use and risk of endometriosis as well as specific disease outcomes remains to be determined.

Progestins

Progestins induce decidualization in endometriotic tissues and then they cause atrophy by proliferation inhibition. They also deplete the estrogen receptors and inhibit their activation. Also progestins could induce conversion of potent estrogens (estradiol) to weaker products (estrone). With higher dosage, progestins cause inhibition of matrix metalloproteinase. Progestins formulations are available for oral, parenteral, as intrauterine devices and implants (Box 7.1). The clinical response to progestins is like the OCPs. Side effects like breakthrough bleeding and reversible bone loss can occur. Breakthrough bleeding can be managed with short time, low-dose estrogen administration.

Dienogest (DNG) is a progestin of 19-nortestosterone derivative with a good oral bioavailability. Progesterone receptor-binding affinity is higher for DNG than for progesterone. It has low affinity for the androgen receptor and almost negligible affinity for the estrogen receptor, glucocorticoid receptor and mineralocorticoid receptor.

An oral DNG dose of 1 mg/day is required for inhibition of ovulation in cyclic women. DNG is as effective as triptorelin as a therapy after surgery for the treatment of endometriosis.

Also, DNG is as effective as intranasal buserelin acetate for the relief of pain associated with endometriosis.[19]

Mifepristone (Progesterone Antagonist)

Mifepristone (RU 486) is an oral progesterone receptor antagonist and has a high affinity for progesterone and glucocorticoid II receptors. It also has a direct inhibitory effect on human endometrial cells[20] and can modulate the estrogen and progesterone receptor expression in both eutopic and ectopic endometrium. Among a series of studies conducted on various doses of mifepristone in women with endometriosis, a minimum dose of 50 mg over a period of six months demonstrated a significant resolution in visible endometriotic lesions and improvement in clinical symptoms.[21] Another study using a low dose of 5 mg mifeprestone failed to demonstrate a change in the lesion size although clinical improvement in pain was observed. The authors concluded that this dose was too low for an acceptable clinical efficacy.[22] The antiglucocorticoid effect raises significant concerns of the long-term use of this drug especially with doses over 200 mg per day.

Selective Progesterone Receptor Modulators

Selective progesterone receptor modulators (SPRMs) are progesterone receptor ligands with a high degree of endometrial selectivity. They exhibit agonist/antagonist effects based on the target tissue.[23] They have the potential to induce reversible amenorrhea through selective inhibition of endometrial proliferation, a direct effect on endometrial blood vessels and the potential to suppress endometrial prostaglandin production in a tissue specific manner without the systemic effects of estrogen deprivation, providing a rationale for the treatment of endometriosis-related pain.[24]

Asoprisnil: It is the first SPRM to reach an advanced stage of clinical development for the treatment of endometriosis. Asoprisnil can suppress both the menstrual cycle and endometrial growth.[25] A study using different doses of Asoprisnil showed that 5 mg is the minimum effective dose for pain relief in subjects with endometriosis.[26] No serious, drug-related adverse events have been reported during the treatment or follow-up period of the various studies conducted.

Levonorgestrel-releasing Intrauterine System

Levonorgestrel is a frequently used steroid, both as a component of oral contraceptive pill as well as subdermally implanted contraceptive devices. The intrauterine device is a T-shaped system which releases levonorgestrel locally. The additional benefits of this local therapy have been observed in the treatment of menorrhagia and in the prevention of endometrial proliferation during post-menopausal estrogen therapy. The timed release of this drug per day with a gradual reduction of the daily delivered dose over time induces the endometrium to turn atrophic and inactive. This mode of delivery is a useful treatment option in patients with endometriosis, adenomyosis, chronic pelvic pain, and dysmenorrhea and menorrhagia. This is an excellent strategy for long-term management of women with endometriosis in view of no modifications in estrogen levels and few hypoestrogenic side effects.[27]

Androgens

Danazol is a synthetic isoxazole derivative chemically related to 17a-ethinyltestosterone and was the first approved treatment of endometriosis in the United States. The mechanism of action is believed to be suppression of midcycle LH surge and PG

Box 7.1: Different progestins used for medical treatment of endometriosis.

- Oral route
  - Norethisterone acetate
  - Cyproterone acetate
  - Dienogest
- Intramuscular route
  - Medroxiprogesterone acetate
- Intrauterine route
  - Levonorgestrel-releasing intrauterine device (IUD)

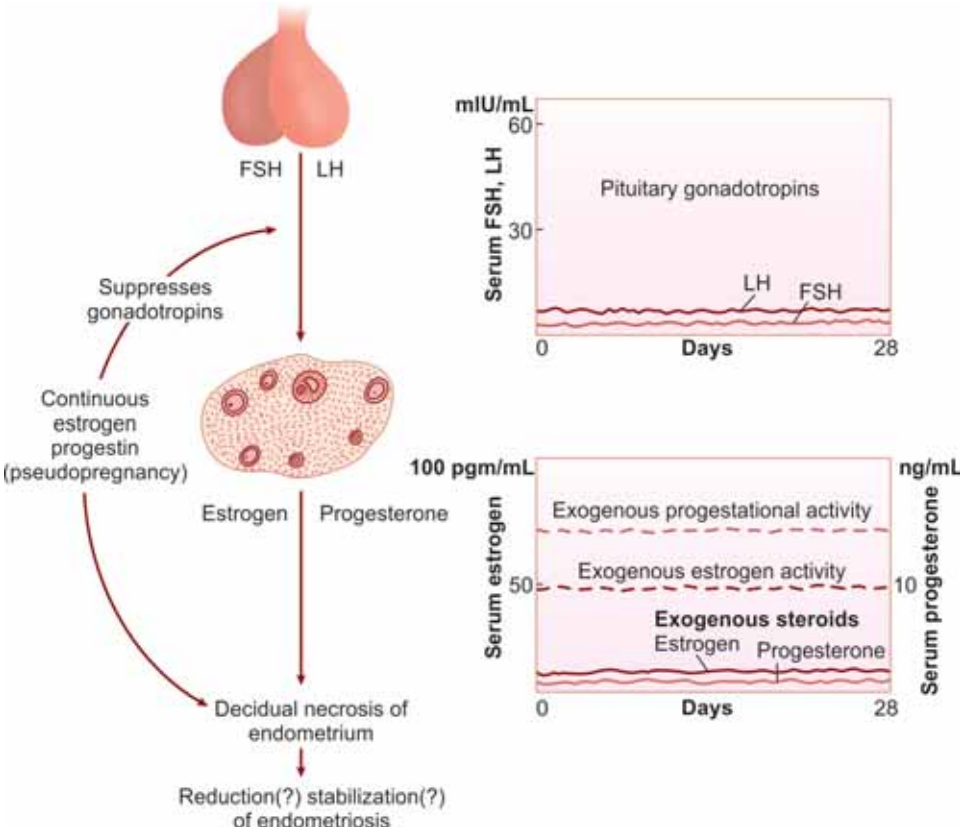
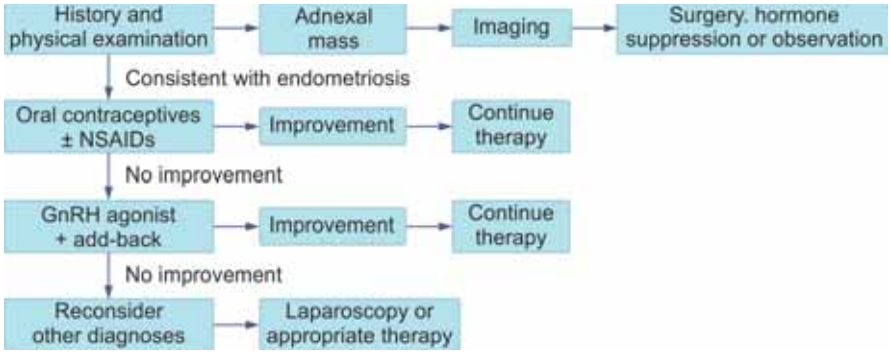


Figure 7.1: Effects of continuous estrogen-progestin therapy on the pituitary-ovarian axis. Gonadotropin release and ovarian steroidogenesis are suppressed with the exogenous estrogen and progestin, causing decidual necrosis of the endometrium.[6]

(FSH, follicle stimulating hormone; LH, luteinizing hormone)

Flowchart 7.1: Recommended strategy for the management of women with endometriosis and pain symptoms.[17]



(NSAIDs, nonsteroidal anti-inflammatory drugs; GnRHa: gonadotropin-releasing hormone agonists)

F2a production in ovary creating a chronic anovulatory state. It creates a hypoestrogenic, hyperandrogenic state, inducing endometrial atrophy.

Many nonrandomized studies have shown improvement in pain associated with endometriosis, in 66 to 100% of the women evaluated and clinical trials have also demonstrated that both danazol and GnRH agonists were equally effective in reducing both the growth of endometriotic implants and endometriosis-related symptoms during the treatment phases of the trial.[28]

At the recommended dose of 400–800 mg/daily, danazol has significant side effects precluding its long-term use. Oily skin, acne, hirsutism, irreversible voice deepness, variation in lipid profile, vaginal atrophy and hot flushes distress patients. Due to its teratogenic potential, this medication should be taken in conjunction with effective contraception only.

Gestrinone (ethylnorgestrienone; R2323) is an antiprogestational agent prescribed in Europe for the treatment of endometriosis. Gestrinone equals the effectiveness of danazol and of GnRH agonists for relief of endometriosis-related pain.

Clinical management of endometriosis with danazol: Medical treatment of endometriosis with danazol is indicated when the predominant manifestation of endometriosis is adenomyosis for both patients seeking pain relief and patients desiring fertility. Medical treatment is also indicated when pain returns after surgical treatment. When medical treatment is used for the purpose of pain relief a 6-month course of either danazol or GnRH will provide continued relief of pain for approximately 18 months after the cessation of treatment, providing E2 levels are adequately suppressed. The time until return of pain symptoms is approximately the same after laparoscopic laser or electrocautery of endometriosis implants. If pain is not relieved after the first month of medical treatment surgery should be considered instead. In the author's experience and that of his gynecological teachers forty plus years earlier, surgical treatment of endometriosis for relief of pain should include uterosacral ligament transection, uterosacral ligament reattachment to the posterior lower uterine segment, uterosacral ligament plication with non-resorbable suture to elevate the uterus out of the cul de sac, and if the surgeon has been trained in the procedure, presacral neurectomy. The advantages of danazol over GnRH for pain relief are less severe hypoestrogen side effects; less lose, if any, of bone density, and a more rapid onset of estrogen suppression. The onset of E2 suppression and endometriotic lesion regression is immediate for danazol compared to a delay of 10–21 days for GnRH because of an initial flare up of serum E2 levels. The disadvantages of danazol for pain relief are the need to take a pill 3 or 4 times a day, a tendency to weight gain although this averaged only 2.2 pounds in 3 months, and usually mild androgenic effects.

Initiating and monitoring danazol: Danazol treatment should be initiated during menses. Treatment must be started no later than the fifth menstrual cycle day to insure ovarian suppression and preferably earlier as is true for hormonal contraception.[29] Patients who could become pregnant should use nonhormonal methods of contraception until ovulation suppression is assured. Suppression of ovulation can be assumed of the E2 level is < 50 pg/mL.

Edgardo Somigliana starts with an initial dose of 200 mg danazol every 8 hours for women with mild or moderate endometriosis who weigh less than 150 pounds (68 kg). Patients with severe or extensive endometriosis and those with lesser stages, who weigh more than 150 pounds (68 kg), should be given 200 mg every 6 hours initially. I evaluate serum E2 levels initially and 3 weeks after the initial dose and after any change in dose. My therapeutic goal is for E2 levels to be < 20 pg/mL in patient with severe and extensive endometriosis, and < 40 pg/mL in patients with moderate endometriosis.

The determination of serum E2 levels is essential when either danazol or GnRH agonist are used to treat endometriosis. The author measures serum E2 levels the day treatment is initiated and again 3–4 weeks latter to determine if levels are suppressed. I sometimes measure E2 levels earlier if a patient has symptoms of excess androgen or hypoestrogenism so that I can decrease the frequency of danazol administration if E2 levels are adequately or more than adequately suppressed. When decreasing the total daily dose of danazol it can be given as 200 mg 3 instead of 4 times daily or 2 instead of 3 times daily. A 100 mg danazol pill is also available that can be given 2–4 times daily. In no case should danazol be given less than twice daily if treatment is to be effective. E2 assay results much more than other hormones assays give varying results according to the assay technique.

Gonadotropin-releasing Hormone Agonists

Releasing hormone agonists are synthetic drugs resistant to degeneration in body which differ from the naturally occurring GnRH agonists by there amino acids sequence and have a longer half-life than native GnRH.

When administered continuously, an initial flare effect is followed by downregulation of pituitary, leading to suppression of FSH and LH production, menstruation and ovulation. A low estrogenic environment thus achieved, inhibits the proliferation in endometriotic implants. A long-term follow-up study of patients treated with a GnRH agonist alone for six months revealed a 53% recurrence of disease/symptoms two years after treatment.[30]

However, GnRH agonists administered in a pulsatile fashion activate the gonadotrophs to both synthesize and release LH and FSH.

Adverse effects include hot flushes, vaginal atrophy and dryness, headache and other vasomotor signs and symptoms. Prolonged use of GnRH agonists is associated with reduced bone mineral density necessitating appropriate investigations and add-back therapy.

LHRH-analogs: Agonists and Antagonists

In the past 30 years, more than 3,000 analogs of lutei-nising hormone releasing hormone (LHRH) have been synthesized.[31-33] Agonistic analogs, such as triptorelin, leuprolide, goserelin and buserelin, which are 50–100 times more potent than LHRH and available as depot preparations have become well-established therapeutic tools for the treatment of sex steroid dependent diseases such as endometriosis.[31,32,34] Potent antagonistic analogs of LHRH, such as cetrorelix, ganirelix, degarelix have also been synthesized.[35,36]

Dosage and timing of administration: The dose of LHRH agonist used for the treatment of endometriosis varies with the specific compound and mode of delivery. For patient convenience depot preparations should be used (Table 7.3). If dosed adequately, no difference with respect to efficacy was noted between the different compounds.[37]

TABLE 7.3: Luteinizing-hormone releasing hormone agonists and antagonists.

Analog type	*drug*	*dose*
Agonist	Goserelin	3.6 mg/month; 10.8 mg/3 months
Agonist	Triptorelin	3.75 mg/month
Agonist	Leuprolide	3.57 mg/month
Agonist	Buserelin	6.6 mg/2 months; 9.45 mg/3 months
Antagonist	Cetrorelix	0.25 mg/day; 3 mg
Antagonist	Cetrorelix-pamoate	52 mg
Antagonist	Ganirelix	0.25 mg/day

Since LHRH agonists initially induce an increase of the levels of gonadotrophins and estradiol, endometriosis related symptoms may become worse at the initial phases of therapy. However, there are three ways to avoid this unwanted effect.

1. One way is to start with the LHRH agonist in the midluteal phase instead of the follicular phase of the cycle.[38,39] Thus, due to high progesterone levels at that time of the cycle, the flare–up effect of the gonadotrophins and subsequently of estradiol is prevented. One shortcoming of this approach is the fact that administration of the LHRH agonist may co incide with an inadvertent pregnancy.
2. A second approach may consist of the pretreatment with progesterone or oral contraceptives for several weeks prior to the administration of the LHRH agonist.[39]
3. A third way to avoid the flare-up effect is the co-treatment with an LHRH antagonist for the first week after the administration of the LHRH agonist.

Treatment of endometriosis-related symptoms: LHRH analogues are currently one of the most widely used medical therapies for endometriosis.[40] As the endometrial implants are estrogen-sensitive, chronic administration of LHRH- agonists inducing medical menopause can be successfully used for the management of endometriosis. LHRH analogs used for the treatment of endometriosis include nafarelin, buserelin, histrelin, goserelin, tripto-relin and leuprolide, which are about equally effective.[37,41] Most patients achieve symptomatic relief within a month of starting therapy. Treatment of women with endometriosis leads to relief of abdominal pain, and reduction in endometrial implants.

The most common adverse events occurring during a therapy with LHRH agonists are hypoestrogenic symptoms such as hot flushes, sleep disturbances, vaginal dryness and decrease of libido.[42] Other nonspecific side effects such as joint pain, headache and mood changes may also occur. However, the decrease in bone-density that occurs as a side effect of hypoestrogenism after 3–6 months is a major source of concern and limits the duration of therapy with LHRH-analogs. Although, the recurrence rates after a therapy with LHRH agonists are similar to surgery and endometriosis can be diagnosed clinically with a positive predictive value of more than 90% if patient history and pelvic exam are suggestive, LHRH-agonists are used commonly prior to surgery, in order to reduce the size and activity of the endometriotic lesions, after surgery to prevent or delay the recurrence and prior to IVF/ET to improve the pregnancy rate.[43]

Antagonists of LHRH in the treatment of endometriosis: A long-term medical treatment for endometriosis would be desirable because of a high recurrence rate after surgery. LHRH antagonists act through a dose-dependent receptor blockade. A fine tuning of the suppression of estradiol should therefore, be possible with LHRH antagonists, and it has been speculated that in this approach hormonal replacement therapy could be avoided. Most available administration forms of LHRH antagonists provide short-term (daily or every third-day) dosing as infertility treatment.

Due to the absence of an initial flare-up effect, a long-term intermittent therapy with LHRH antagonists seems to be a new option for the treatment of endometriosis. The antagonist could thus be given at doses that do not lead to suppression of estrogen to castration levels and another treatment cycle could be initiated if symptoms reappear. Development of LHRH antagonists as depot preparations or orally active non-peptidic LHRH antagonists may be of use for such treatment.

Antagonists of Growth Hormone-releasing Hormone (GHRH) in the Treatment of Endometriosis

One recent publication showed that growth hormone and its splice variant SV-1 receptor may play a role in endo-metriosis or development of endometriosis. Consequently, it is possible that antagonistic analogs of GHRH could find an application in the treatment of endometriosis alone or in combination with LHRH analogs.[44]

Gonadotropin-releasing Hormone Antagonists

In view of the concerns about initial flare effect, probable exacerbation effect on endometriosis, long interval between initiation and efficacy, and intolerable side effects in some patients, GnRH antagonists became a suitable substitute for GnRH agonists. The antagonistic properties of GnRH exert their effect by competing with endogenous GnRH for pituitary binding sites. GnRH antagonists interfere with the basic activation process of the GnRH receptor, blocking the receptor dimerization synthesis and secretion of LH and FSH. Given the high binding affinity, relative abundance and long half-life of the antagonist, these molecules monopolize the GnRH receptors. These characteristics offer the advantage of these agents acting faster with better efficacy and patient compliance compared with GnRH agonists.

The usual recommended dose of Cetrorelix injection is 3 mg subcutaneously weekly and has shown clinical efficacy without pseudo menopausal side effects.[45] A pilot study in 15 women receiving a treatment protocol with 3 mg of Cetrorelix subcutaneously weekly for eight weeks reported a symptom-free period during the study period, with regression in endometriosis occurring in more than half of the cases and the degree of endometriosis declining to a mild stage on second look laparoscopy.

Oral GnRH antagonists have been recently studied in the treatment of endometriosis. Elagolix used weekly showed effective suppression of gonadal hormonal pro-duction.[46] Although still investigative, these agents have the potential to improve patient comfort and compliance.

Aromatase Inhibitors

Luteinizing hormone can stimulate androgen substrate production from theca cells and conversion into estrogen by

FSH induced aromatase activity in granulosa cells. Aromatase catalyzes the conversion of C19 steroids to estrogens (estrone and estradiol). In view of the in situ presence of aromatase in these tissues, blockage of aromatase activity in these endometriotic sites with an aromatase inhibitor is a rational approach to medical treatment of endometriosis. Aromatase inhibitors act both locally on endometriotic implants, as well as on all estrogen producing sites including ovary, brain and adipose tissue. The aromatase inhibitors are classified into type I and type II and the enzyme activity is permanently blocked due to an unbreakable bond between the inhibitor and enzyme protein.

Prolactin Secretion Inhibitors

Elevated level of serum prolactin had been found in endometriosis like other stressful condition. Interestingly the mean serum prolactin levels are higher in advance stages in endometriotic patients. Quinagolide, a dopamine agonist, could be a potentially effective option for treatment of endometriosis either by reducing prolactin levels (like other dopamine agonists) or by reduction in VEGF receptor (a main factor for angiogenesis). This could decrease the size of peritoneal lesions or eradicate all endometriotic implants.

NONHORMONAL THERAPY

Nonsteroidal Anti-inflammatory Drugs

They are analgesics which inhibit the cyclooxygenase (COX) enzymes thereby inhibiting the production of prostaglandins and alleviating cramps. The first of the drugs with this mode of action was aspirin (acetylsalicylic acid), which was introduced in 1899.

Traditional NSAIDs inhibit both COX-1 and COX-2 (Table 7.4), and in so doing not only decrease inflammation and pain, but also promote gastrointestinal tract damage and bleeding. Inhibitory potency and selectivity of conventional first-generation NSAIDs for COX-1 and COX-2 vary greatly. However, at therapeutic concentrations none of the currently marketed NSAIDs spare gastric COX-1 activity. It is estimated that 25% of patients using NSAIDs experience some kind of side effect, with 5% developing serious health consequences (massive GI bleeds, acute renal failure, etc.). The occurrence of side effects varies with the traditional NSAIDs.

Prostaglandins whose synthesis involves the cyclooxygenase-I enzyme, or COX-1, are responsible for maintenance and protection of the gastrointestinal tract, while prostaglandins whose synthesis involves the cyclooxygenase-II enzyme, or COX-2, are responsible for inflammation and pain.

NSAIDs and Endometriosis

Classically, the main indications for the medical therapy of endometriosis have been dysmenorrhea, pelvic pain, and dyspareunia.

Management of Pain Related to Endometriosis

The three most commonly suggested mechanisms for pain production in endometriosis are: (1) production of substances such as growth factors and cytokines by activated macrophages and other cells associated with functioning endometriotic implants; (2) the direct and indirect effects of active bleeding from endometriotic implants; and (3) irritation or direct invasion of pelvic floor nerves or direct invasion of those nerves by infiltrating endometriotic implants, especially in the cul-de-sac.

Simple analgesics (e.g. paracetamol, aspirin) can be used to relieve mild to moderate pain in endometriosis, there being no consistent evidence of significant differences in effectiveness between these first line alternatives.

Dysmenorrhea secondary to endometriosis is, however, frequently treated by NSAIDs as the first option, despite the paucity of randomized controlled trials.

CONCLUSION

The current treatments mainly focus on inhibiting estrogen and its receptors which are not useful for every patient with endometriosis as estrogen is only one of the factors responsible for the development of the disease. There is a need to develop an effective therapy which not only suppresses estrogen levels but also inhibits inflammatory cytokines and angiogenesis.

A better understanding of the molecular mechanisms of endometriosis and well-conducted prospective, rando-mized clinical trials comparing various therapies will help in better disease therapy in the future.

TABLE 7.4: History of the prostaglandin E pharmacotherapy.[47]

Date	*Breakthrough*
Ancient times	Parts of the willow tree used to relieve pain and inflammation
1897	Acetylsalicylic acid isolated, identified and synthesized
1899	Bayer Company first marketed aspirin
1963	Indomethacin synthesized, followed by several other synthetic and semisynthetic NSAIDs
Mid-1970s	Investigations into development of aromatase inhibitors begins
1971	NSAIDs such as aspirin exert their actions primarily by inhibiting the production of prostaglandins
1976	COX enzyme purified
1984	COX enzyme shown to increase in inflamed tissue
1988	COX enzyme shown to be stimulated by interleukin -1
1988	COX enzyme cloned
1990	COX shown to be induced by endotoxin and prevented by glucocorticoids, but dexamethasone does not affect baseline prostaglandin formation, so postulated a second COX enzyme
1991	Second COX gene discovered and isoform cloned: COX-2
1999	Launch of COX-2 selective inhibitors: rofecoxib and celecoxib
2002	Second-generation COX-2 selective inhibitors: valdecoxib, parecoxib and etoricoxib

(COX: cyclooxygenase NSAIDs: nonsteroidal anti-inflam-matory drugs)

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8

CHAPTER

Newer Medical Treatment in Diagnosis and Management of Endometriosis

INTRODUCTION

Endometriosis affects an estimated 10% of women in the reproductive age group, rising to 30–50% in women with infertility and/or pain.[1] This equates to approximately 100 million women across the world, during the prime of their lives, whose physical, mental and social well-being are impacted by the disease, potentially affecting their ability to finish an education and maintain a career, with effect on their relationships, social activities and fertility.

Endometriosis is more common in women with:

- Müllerian anomalies: resulting in outflow obstruction[2]
- Prolonged menstruation and shorter cycles: cycle of 27 days or less.[3]

PATHOGENESIS

Retrograde Menstruation

The most accepted theory for the pathogenesis of endo-metriosis is retrograde menstruation. During menstruation it gives rise to spill of endometriotic lesions in abdominal cavity.[4] Endometriosis appears to be a multifactorial genetic disorder. Receptiveness of endometriosis depends on the complex interaction of genetic, immunologic, hormonal and environmental factors.[5] Endometriotic lesions are developed from the endometrial cells, which are spilled from retrograde menstruation, and get attach to the peritoneal surface. Invasion of these endometrial cells occur into the mesothelium, after which there is production of inflammatory cells and angiogenesis.[6] Endometriosis is an estrogen–dependent disease and, therefore, the endometriotic lesions are also estrogen dependent. The absence of estrogen in conditions like ovarian downregulation and menopausal condition decreases the size and impact of endometriotic lesions.[7]

INDICATIONS

In substantial number of cases, it is asymptomatic. The most common symptoms of endometriosis are given in Box 8.1. Endometriosis presents also as intermittent pyrexia and also affects fertility of the women.[8] Endometriosis could negatively impact development of oocyte, embryogenesis or implantation even in mild condition. Advancement of the disease leads to pelvic adhesions, distorting the normal anatomy of pelvic, impair tuboovarian function and leads to infertility.[9]

DIAGNOSIS

Diagnosis of endometriosis is difficult because of the nonspecific nature of many of its symptoms. Pelvic inflam-matory disease or irritable bowel syndrome can also be the reason of pelvic pain in women other than endometriosis.[8] For the accurate diagnosis of endometriosis one requires:

Medical History

- Relationship of dysmenorrhea and gynecological operation
- Menstruation
- Reproduction
- Family history
- Operation history.

Gynecological Examination

- Tender and enlarged adnexal masses
- Localized tenderness in uterosacral ligaments
- Palpable tender nodules in rectovaginal septum or uterosacral ligaments
- Pain with uterine movements
- Fixation of adnexa or uterus in a retroverted position.

Box 8.1: Symptoms of endometriosis.

- Dysmenorrhea
- Dyspareunia
- Dyschezia
- Dysuria
- Backache
- Acute abdominal pain
- Premenstrual syndrome
- Menstrual bleeding with menorrhagia
- Cyclic hematuria during menstruation.

- Should be done during early phase of the periods endometrial implants are likely to be the largest and deep infiltrating disease is more easily detectable.

Auxiliary Examination

Imaging

- Transvaginal sonography
  - Gold standard in imaging for pelvic pathologies
  - Helps in identifying an ovarian endometrioma
  - Helps to identify the causes of pelvic pain other than endometriosis.
- Computed tomography: Provides additional information about the disease
- Magnetic resonance imaging:
  - Provides additional and confirmatory information
  - Added benefit of imaging in multiple planes—axial, coronal or sagittal images
  - Useful noninvasive tool in the diagnosis of deep endometriosis
- Endorectal sonography
- Barium enema
  - Possible to differentiate between cases
  - Bowel is simply displaced by a pelvic endometrioma or with bowel involvement.
- Sigmoidoscopy.

Laboratory

- Serum CA-125
- Serum CA-19-9
- Serum protine
- PP14
- Serum antiendometrial antibodies.

Laparoscopy and laparotomy are also conducted and recent advances in imaging technology have improved nonoperative diagnosis of endometriosis.

The principal objective in treating endometriosis is to establish symptom-relief management (Flowchart 8.1).

TREATMENT OF PAIN ASSOCIATED WITH ENDOMETRIOSIS

Nonsteroidal Anti-inflammatory Drugs

There is inconclusive evidence to show whether nonsteroidal anti-inflammatory drugs (NSAIDs) are effective in managing pain caused by endometriosis.

Hormonal Treatment

Progestogens

First choice for the treatment of endometriosis and the effect of treatment can only be evaluated after 3–6 months of therapy.

Desogestrel: It is now being looked as an alternative treatment and to reduce pain associated with endometriosis levonorgestrel intrauterine system (LNG-IUS) is considered.

GnRH agonists: Treatment for 3 months with a gonadotropin-releasing hormone (GnRH) agonist may be as effective as 6 months in terms of pain relief.

Combined oral contraceptives (COCs): Cyclic regimen to women with endometriosis was found as effective as GnRH agonist treatment for relief of dyspareunia and nonmenstrual pain as assessed by a pain scoring system. Continuous low-dose OCs was more effective than cyclic OCs in controlling endometriosis. Pain has been reduced by 70–100% by the use of medroxyprogesterone acetate (MPA), dydrogesterone or norethindrone acetate.

Danazole: Proved to be effective in pain management; side effects prevent it from becoming a favorable option.

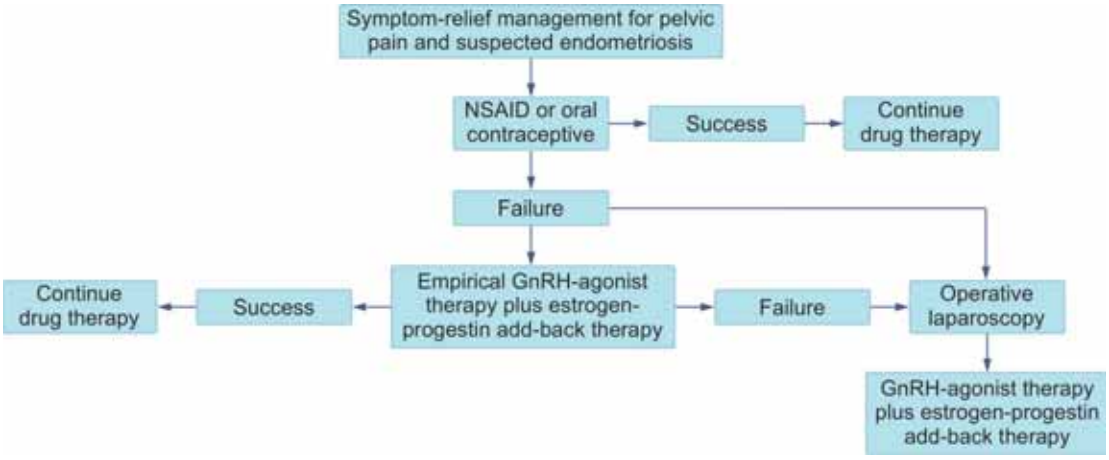
Antiprogesterone

These agents induce chronic anovulation and thereby reduce pain (for e.g. gestrinone and mifepristone).[10-12]

NEWER TREATMENT MODALITIES

In view of the side effects associated with established medical methods for the treatment of endometriosis, new approaches

Flowchart 8.1: Pelvic pain and suspected endometriosis.



are being evaluated. These include inhibitors of aromatase and angiogenesis, matrix metalloproteases modulators, estrogen receptor β agonists, as well as proge-sterone receptor modulators (PRMs). This chapter will focus on various new treatment options for endometriosis.

The Vaginal Ring

The vaginal ring is a small, thin, flexible rubber ring that fits inside the vagina. Once in place, it releases a combination of estrogen and progestin (hormones). Similar to OCPs and the patch, the vaginal ring may be used to treat symptoms of endometriosis by controlling your menstrual cycle. Like the patch, this is also used cyclically.

The COC Patch

The patch is a type of hormone therapy that looks like a square adhesive bandage. It contains hormone in similar to birth control pills and is worn on the skin. Each hormone patch lasts 1 week. After 3 weeks of usage, there would be a patch-free week.

Aromatase Inhibitors

Aromatase enzyme is a target for selective inhibition of estrogen synthesis. The inhibition of local estrogen production in endometriotic implants is an attractive option for the management of endometriosis. The main side effects are hot flashes and gastrointestinal side effects (Table 8.1 and Boxes 8.2 and 8.3).

GnRH Antagonist

GnRH antagonists have been used for the treatment of pelvic endometriosis. However, they have been as widely accepted as GnRH agonists.

Selective Progesterone Receptor Modulators

Selective progesterone receptor modulators (SPRMs) suppress estrogen-dependent endometrial growth and induce reversible amenorrhea. Progesterone treatment commonly causes breakthrough bleeding by inducing fragility of the endometrial blood vessels. The SPRMs have spiral arterioles as the target and causing stabilization of the endometrial blood vessels.

Mode of Action of SPRMs

Endometriosis is an estrogen dependent condition and the beneficial effects of treatment with PRMs reported are probably related to their antiproliferative effects which have been well-described in the primate endometrium[6] and in rodent mammary tumors.[13] In the latter model, progesterone was strongly proliferative. The PRMs mifepristone and CDB-4124 differed in their antiproliferative activity with CDB-4124 showing strong reduction in the number of tumor cells positive for the proliferation marker Ki-67 but mifepristone demonstrated no such activity.[13]

PAs and SPRMs are associated with an increase in ER, PR and androgen receptor (AR).[14] Androgens suppress estrogen-induced endometrial proliferation. The increase in AR consequent to PRMs could thus produce these unexpected antiproliferative effects. Further evidence of the role played by androgens in this antiproliferative effect is the observation that the pure antiandrogen, flutamide, blocks the antiproliferative effects of the PRMs ZK137316 and ZK230211 in the endometrium.[14] The effect on the AR appears to be a likely mechanism explaining the antiproliferative effect although it may also be related to the fact that the PRA isoform inhibits estrogen receptor gene transcription induced by progestins and PAs.[15]

Aromatase expression in endometriosis implants is markedly increased compared to eutopic endometrium and this leads to an increase in estradiol. Mifepristone blocks medroxyprogesterone acetateinduced aromatase activity in endometrial stromal cells.[16]

The enzyme, 17β hydroxysteroid dehydrogenase (17βHSD) type 2, catalyses the conversion of E2 to the biologically inactive E1. Progesterone is the most potent stimulator of this enzyme in the eutopic endometrium during the secretory phase of the cycle but is unable to induce this enzyme in endometriosis[17] and this suggests the presence of progesterone resistance. This is most likely a consequence of overexpression of the repressive PRA and downregulation of the stimulatory PRB.[18]

Matrix Metalloprotease Modulators

Several of the MMPs are dysregulated in endometriosis and it has been suggested that inhibition of MMP activity may be used to treat this disease. Cell specific mRNA expression of MMP3 and MMP7 is elevated in the eutopic endometrium of women with endometriosis during the secretory phase whereas they are absent in normal women.[17] Together with the absence of 17β-HSD type 2 in endometriosis, this increase in MMP3 and MMP7 is further evidence of the presence of progesterone resistance.

Antiangiogenesis Therapy

Antiangiogenesis therapy has been investigated in rodents, and demonstrated that angiostatic agents prevent the development of endometriosis-like lesions in the chicken chorioallantoic

TABLE 8.1: Different generations of aromatase inhibitors.

Generation	Nonsteroidal aromatase inhibitors	Steroidal aromatase inhibitors (Sometimes called suicidal inhibitors of the aromatase enzyme)
	Work by temporary (reversible) inactivation of the aromatase enzyme	Work by permanent (irreversible) inactivation of the aromatase enzyme
First generation	Aminoglutethimide (Cytadren®)	N/A
Second generation	Rogletimide Fadrozole	Formestane
Third generation	Letrozole (Femara® 2.5 mg/tablet) Anastrozole (Arimidex® 1mg/tablet) Vorozole	Exemestane (Aromasin® 25 mg/tablet)

Box 8.2: Problems associated with early generations aromatase inhibitors.

Pharmacodynamic:

- Low potency in inhibiting the aromatase enzyme particu- larly in premenopausal women (very low potency)
- Lack of specificity in inhibiting the aromatase enzyme with significant inhibition of other steroidogenesis enzymes leading to medical adrenalectomy.

Pharmacokinetic:

- Not all members are available orally (some require parentral administration
- Variable bioavailability after oral administration
- Variable half-life that changes with the period of administration due to induction of its metabolism.

Clinical:

- Poorly tolerated on daily administration with more a third of patients discontinued treatment due to adverse effects
- Significant side effects related to both the aromatase inhibi- tors, e.g. drowsiness, morbilliform skin rash, nausea and anorexia, and dizziness and side effects secondary to the steroids used for replacement therapy, e.g. glucocorticoids
- Interaction with alcohol with significant potentiation of its action
- Significant interactions with other medications, e.g. cou- marin and warfarin
- Need for replacement therapy due to medical adrenalec- tomy, e.g. glucocorticoid and mineralocorticoid replacement
- Long-term possible carcinogenesis (at least in animals).

Box 8.3: Advantages of third generation aromatase inhibitors.

Pharmacodynamic advantages:

- Extreme potency in inhibiting the aromatase enzyme (up to thousand times potency of the first generation aminoglutethimide)
- Very specific in inhibiting the aromatase enzyme without significant inhibition of the other steroidogenesis enzymes. This is true even at high doses
- Absence of estrogen receptor depletion.

Pharmacokinetic advantages:

- Orally administered (other routes of administration are also possible, e.g. vaginal and rectal)
- Almost 100% bioavailability after oral administration
- Rapid clearance from the body due to short half-life, (~ 8 hours for the aromasin ® to ~ 45 hours for the Femara® and Arimidex®)
- Absence of tissue accumulation of the medications or any of their metabolites
- No significant active metabolites.

Clinical advantages:

- Well tolerated on daily administration for up to several years (in post-menopausal women with breast cancer) with few adverse effects
- Few mild side effects
- Very safe without significant contraindications
- Absence of significant interactions with other medications
- Very wide safety margin (toxic dose is several thousand times higher than recommended efficacious therapeutic dose)
- Relatively inexpensive.

membrane. The future challenge is to successfully utilize it in women suffering from pelvic endometriosis. Estradiol is a potent stimulus of angiogenesis through the direct increase of vascular endothelial growth factor (VEGF) expression.[19] VEGF is elevated in the peritoneal fluid of women with endometriosis and is expressed in endometriotic lesions.[17] VGEF is one of the main stimuli for angiogenesis in this disease and PRMs have been shown to suppress VGEF in human and cynomolgus endometrial tissue samples.[20,21]

Immunomodulators

Four compounds with immune-enhancing properties have been investigated cytokines, interleukin-12 and interferon a-2b, and two synthetic immunomodulators, the guanosine analog loxoribine and the acetyl-choline nicotine receptor agonist levamisole.

Chinese Herbal Medicine

Although clinical studies on herbs in the literature show promising effects, conclusive clinical evidence of the efficacy of medical herbs in the treatment of pain associated with endometriosis is yet to be proved (Tables 8.2 and 8.3).

Vascular Endothelial Growth Factor Targeted Conditionally Replicative Adenoviruses

The virus showed a similarly low tropism to the liver and eutopic endometrium in vitro and in mouse model. In a clinical setting, VEGF-targeted CRADs could be administered into the abdominal cavity after laparoscopic resection of deep infiltrating endometriosis.

Statins

Statins may be effective in the treatment of endometriosis, targeting growth and invasiveness of ectopic endometrial tissues as well as inflammation and oxidative stress associated with this condition.

Formation of endometriotic implants requires ectopic attachment and proliferation of endometrial stroma and glands. Prominent features of endometriosis include inflammatory reaction, increased oxidative stress and intense angiogenesis surrounding the implants.[22]

The rationale for considering statins as a promising treatment of endometriosis is based on several considerations.

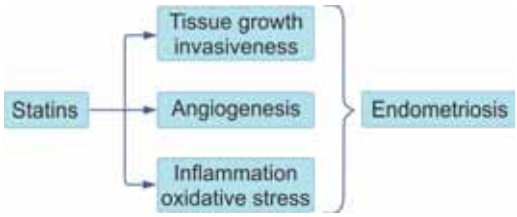
- Statins are competitive inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, a rate-limiting step of the mevalonate pathway. The inhibition of HMG-CoA reductase depletes down-stream products of the mevalonate pathway, especially isoprenyls.[23] Depletion of isoprenyls decreases activity of small GTPases such as Ras and Rho resulting in decreased signaling of important growth-regulating pathways.[24]
- Inhibition of HMG-CoA reductase may reduce another downstream product, dolichol, which is required for maturation of type I IGF-I receptor, and hence may decrease the mitogenic effect of IGF-I on endometrial stromal cells.

- Statins can interfere with angiogenesis, which is necessary for the development of endometriotic implants. In addition, statins possess anti-inflammatory and immune-modulatory properties, which may reduce the inflammatory reaction associated with endometriosis.

Another and related aspect of the actions of statins pertains to their anti-oxidant properties. Proliferation of endometrial stroma is stimulated by moderate oxidative stress, but inhibited by a broad range of antioxidants.[25] Statins may reduce oxidative stress by decreasing activity of a small GT-Pase, Rac, which is essential for generation of reactive oxygen species (ROS) by NADPH oxidase.[26] In addition, statins possess intrinsic antioxidant activity.[27]

The hypothesis that statins may be used in the treatment of endometriosis is also supported by the evidence that in several tissues, such as vascular smooth muscle, products of the mevalonate pathway have been shown to facilitate isoprenylation of small GPTases and thus activate signal transduction pathways promoting growth while inhibition of the mevalonate pathway by statins decreases growth and exerts antioxidant effects (Flowchart 8.2).[23,28]

Flowchart 8.2: Proposed role of statins in treatment of endometriosis.



SURGICAL TREATMENT

Role of Surgery in Adolescents

Endometriosis should be considered in adolescents presenting with bilateral complex ovarian masses regardless of their size. Laparoscopy should be considered if adolescents with chronic pelvic pain, who do not respond to medical treatment (NSAIDs, OCPs) since endometriosis is very common under these circumstances. Minimal to mild endometriosis according to the American Society for Reproductive Medicine (ASRM) classification is the most common stage of the disease in adolescents.

Menstrual outflow obstructions such as Müllerian anomalies may cause early development of endometriosis in adolescents. Physicians treating adolescents with endometriosis should adopt a multidimensional approach:

- Surgery
- Hormonal manipulation
- Pain medication
- Mental health support
- Complementary and alternative therapies
- Education in self-management strategies.

Surgical Treatment for Endometriosis-associated Pain

Depending upon the severity of disease found, ideal practice is to diagnose and remove endometriosis surgically.

TABLE 8.2: Botanicals used in the treatment of endometriosis.

English name	*Pinyin name*	*Literal name*	*Botanical name*	*Pharmaceutical name*
Bupleurum	Chai Hu	Kindling of the barbarians	Bupleurum chinense DC.	Radix Bupleuri
Chinese angelica	Dang Gui	State of return	Angelica sinensis	Radix Angelica Sinensis
Cattail pollen	Pu Huang	Cattail pollen	Typha angustifolia	Pollen typhae
Cinnamon twigs	Gui zhi	Cinnamon twigs	Cinnamoomum cassia	Ramulus Cinnamomi
Cnidium	Chuang Xiong	-	Ligusticum chuanxiong	Rhizoma Ligustici
Corydalis	Yan Hu Suo	-	Corydalis turtschaninovii	Rhizoma Corydalis
Curcuma	Yu Jin	Constrained metal	Curcuma aromatica	Radix Curcumae
Cyperus	Xiang Fu	Aromatic appendage	Cyperus rotundus	Rhizoma Cyperi
Dahurian angelica	Bai Zhi	White rootlet	Angelica Dahurica	Radix Angelicae Dahuricae
Frankincense	Ru Xiang	Fragrant breast	Boswellia carterii	Gummi Olibanum
Licorice root	Gan Cao	Sweet herb	Glycyrrhiza uralensis	Radix Glycyrrhizae
Myrrh	Mo Yao	-	Commiphora myrha	Myrrha
Persica	Tao Ren	Persia seed	Prunus persica	Semen Persicae
Poria	Fu Ling	-	Poria cocos	Poria
Red peony root	Chi Shao	Bright red peony	Paeonia veitchii Lynch	Radix Paeoniae Rubrae
Rhubarb	Da Huang	Big yellow	Rheum plamatum L.	Radix et Rhizoma Rhei
Salvia root	Dan Shen	-	Salvia miltiorrhiza	Radix Salvia Miltiorrhizae
Scutellaria	Huang Qin	-	Scutellaria baicalensis	Radix Scutellaria
Sparganium	San Leng	Three edges	Sparganium stoloniferum	Rhizoma Sparganii
Turmeric	Jiang Huang	Ginger yellow	Curcuma longa L	Rhizoma Curcumae Longae
White peony root	Bai Shao	White peony	Paeonia lactiflora Pall	Radix Paeonia Alba

TABLE 8.3: Botanicals and their anti-inflammatory effects.

Botanicals	*Major active component*	*Antioxidant*	*COX-2↓*	*Cytokines ↓*	*NF-kB ↓*
Bupleurum	Triterpenoids			+	+
Chinese angelica	Ferulic acid	+		+	
Cattail pollen	Palmitic acid			+	
Cinnamon twigs	Cinnamonaldehyde		+	+	+
Cnidium	Alkaloids				
Corydalis	Tetrahydropalmitine			+	
Curcuma	Curcumin	+	+	+	+
Cyperus	Cyperene	+			
Dahurian angelica	Coumarins		+	+	+
Frankincense	Boswellic acids			+	+
Licorice root	Triterpenoids		+	+	+
Myrrh	Terpenoids	+		+	
Persica	Essential oils			+	
Poria	Pachymose		+	+	
Red Peony	Paeoniflorin	+			
Rhubarb	Emodin			+	+
Salvia root	Tanshinone	+			+
Scutellaria	Baicalin		+	+	+
Sparganium	Essential oils			+	
Turmeric	Curcumin	+	+	+	+
White peony root	Paeoniflorin		+	+	+

Peritoneal Lesions

Diagnostic laparoscopy, without complete removal of endometriosis, has been found to alleviate pain in 50% of patients.

Surgical options for the treatment of endometriosis include the use of unipolar or bipolar cautery, laser ablation using potassium-titanyl-phosphate (KTP), CO_2, or neodymium-yittrium-aluminum-garnet lasers, and excision techniques, but no randomized trials have evaluated their comparative efficacies.

Ablation of endometriotic lesions reduces endome-triosis-associated pain compared with diagnostic laparo-scopy. Ablation of endometriotic lesions plus laparoscopic uterine nerve ablation (LUNA) in minimal- moderate disease reduces endometriosis-associated pain.

Moderate-to-Severe Degree of Endometriosis

If the endometriosis-related adhesions are part of an inflammatory fibrosis, they should be removed carefully. Radical procedures such as oophorectomy or total hysterectomy are indicted only in severe cases. If a hysterectomy is performed, the cervix should be extirpated as persistent pain in remaining cervix is common due to endometriosis in the cervix or endometriosis in the uterosacral ligaments.

TREATMENT OF ENDOMETRIOSIS-RELATED INFERTILITY

Suppression of ovarian function to improve fertility in minimal-mild endometriosis is not effective and should not be offered for this indication alone. The only hormonal treatment offered for endometriosis is dihydrogesterone as it does not suppress ovulation.

Ablation of endometriotic lesions plus adhesiolysis to improve fertility in minimal-mild endometriosis is effective compared with diagnostic laparoscopy alone.

Excision surgery for endometriomas provides for a more favorable outcome than drainage and ablation with regard to recurrence of the endometrioma, recurrence of pain symptoms, and in women who may subsequently undergo fertility treatment, insufficient evidence exists to determine the favored surgical approach.[29]

Excisional cystectomy is the preferred method to treat endometrial cysts for both pain and fertility and may be aided by the use of mesna and initial circular excision. An absorbable adhesion barrier, 4% icodextrin solution, and a viscoelastic gel are safe and effective products to help prevent adhesions in laparoscopic surgery to treat endometriosis.

Laparoscopic cystectomy for ovarian endometriomas is better than drainage and coagulation.

Ovarian reserve determined by anti-Müllerian hormone (AMH) is less diminished after the three-step procedure compared with cystectomy of endometriomas.[30] Tubal flushing with oil soluble media in infertile women is associated with a significant increase in clinical pregnancy rates. The effect is more pronounced in women with endometriosis.

CONCLUSION

The advances in management of endometriosis are quite substantial with newer medical treatment available. Dienogest

and GnRH analogues have come out to be a large role in controlling endometriosis. Development of newer technologies in laparoscopy is also the reason for controlling recurrences and management of these diseases. Assisted reproductive techniques (ARTs) are useful in treating infertility associated with endometriosis. Grade I and II endometrioses are best treated with controlled hyperstimulation and IUI. The best result for Grade III and IV can be given to patient by ARTs.

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9

CHAPTER

Endometriosis in Infertility

INTRODUCTION

Endometriosis is widely accepted as a cause of infertility, especially when the disease is severe. It is defined as a chronic and recurrent disease that is characterized by the presence and proliferation of functional endometrial glands and stroma outside the uterine cavity.

Endometriosis generally affects every part of a woman's reproductive system including ovarian function, the quality of the oocyte, embryo development as well as implantation, uterine function, and the endocrine system that arranges the reproductive process and results in infertility or spontaneous pregnancy loss (Fig. 9.1).

Current treatments are stacked with menopausal-like side effects. Many of these side effects cause cessation or chemical alteration of the reproductive cycle, neither of which is favorable in achieving a pregnancy.[1]

It has been suggested by some classical studies that 25–50% of infertile women have endometriosis and that 30–50% of women with endometriosis are suffering from infertility. Thus, it is difficult to quantify the true prevalence of endometriosis, as the literature reports very wide ranges have been reported in the literature.[2,3]

An ongoing source of controversy constitutes the efficacy of medical and surgical treatment of endometriosis-associated infertility and pelvic pain. A complete resolution of endometriosis is not yet possible and current therapy has three main objectives:

1. Reduction of pain
2. Increase in the possibility of pregnancy
3. Delaying recurrence for as long as possible.

There is possibility that a consensus will never be reached on the optimal treatment of minimal and mild endometriosis. The combined approach [operative laparoscopy with a gonadotropin-releasing hormone (GnRH) agonist] should be

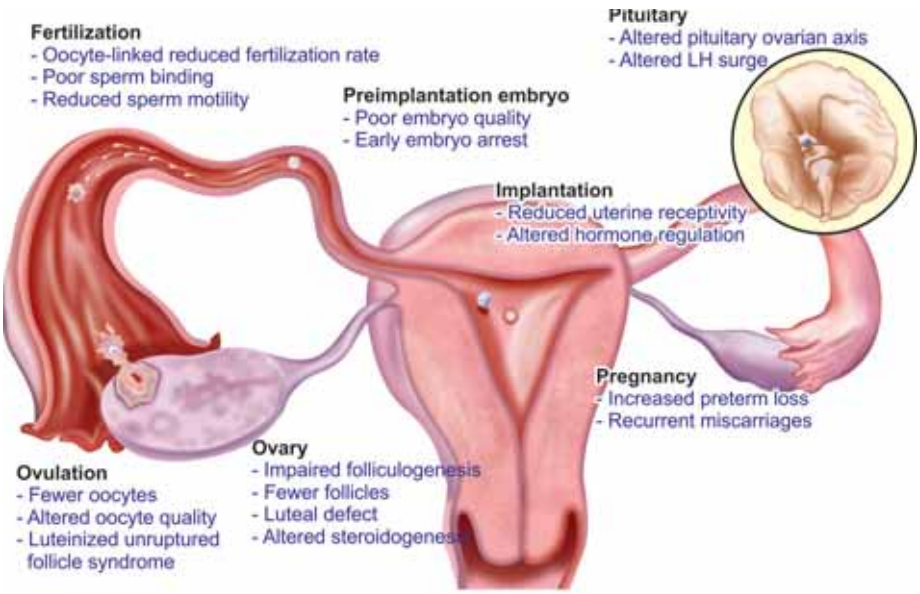

Figure 9.1: Factors associated with reduced fecundity in women with endometriosis.[1]

considered as "first-line treatment" in case of moderate and severe endometriosis-associated infertility.[4]

Reports from literature following surgery suggest that the mean pregnancy rate (PR) of 50% provides scientific proof that to impart the patients the best chance of conceiving naturally, operative treatment should first be undertaken.

PATHOPHYSIOLOGY OF INFERTILITY IN PATIENTS WITH ENDOMETRIOSIS

The pathophysiology of infertility in patients with endometriosis has been illustrated in Box 9.1.

DIAGNOSIS AND STAGING

Endometriosis is a type of heterogeneous disease with two types of peritoneal lesions: typical and atypical. These lesions range from a single 1 mm peritoneal implant to 10–12 cm sized endometriomas and cul-de-sac obliteration. A number of significant findings suggestive of endometriosis could be yielded from a history and a physical examination. These findings might include: cyclic or chronic pelvic pain, dyspareunia, dysmenorrhea, a fixed retroverted uterus, an adnexal mass, and uterosacral ligament nodularity, thickening, or tenderness. Additionally, ultrasound can aid help to the clinicians in establishing a presumptive diagnosis of an ovarian endometrioma but cannot reliably image peritoneal implants of disease.

For a definitive diagnosis of endometriosis in current clinical practice, there is a requirement for surgical procedure such as laparoscopy. Whenever the diagnosis is not apparent on visual inspection at surgery, the histologic evaluation is warranted. When there is a conflict of whether a laparoscopy should be performed or not on a woman presenting with a complaint of infertility, both the likelihood of the diagnosis of endometriosis as well as potential benefit of treatment should be considered.

The classification of endometriosis is based on visual findings. It is generally simple and concise for an easy implementation in routine practice. Also, it is sufficiently analytical and descriptive to allow clear comparison of anatomicopathological modifications with time or following treatment. However, no correlation is found between classification systems and the type or severity of symptoms or the chance of conception that is followed by therapy.[6]

The severity of the disease is generally assessed by describing the findings at surgery or quantitatively, using a classification system similar to the one developed by the American Society for Reproductive Medicine (ASRM). The staging system as described by the ASRM classification system for endometriosis is the most widely one.[2,7]

Attempts have been made in effort to develop a standardized classification to objectively assess the extent of endometriosis, since the extent of endometriosis can vary widely between individuals. The initial classification system attempted to provide a scoring system to describe the pathologic extent of disease. The classification system is initially created by the American Fertility Society (AFS) 1979, and has been subsequently renamed the ASRM, which was then subsequently revised by the AFS in 1985. This revision was then differentiated between superficial and invasive disease. Unfortunately, studies revealed that no prognostic information with respect to subsequent fertility or severity of pelvic pain was provided by both of these classification systems. In 1996, the ASRM further revised the endometriosis classification system (ASRM, 1997), in an attempt to further correlate surgical findings with clinical outcomes.

According to this system, endometriosis is classified as:

- Stage I (minimal)
- Stage II (mild)
- Stage III (moderate)
- Stage IV (severe).

The revised 1996 classification was provided for description of endometriotic lesion morphology as white, red, or black.

Endometriosis fertility index (EFI) is a simple, robust, and validated clinical tool that predicts pregnancy rates (PRs) for patients after surgical staging of endometriosis. The EFI is very useful in developing treatment plans in infertile patients with endometriosis.[8]

Box 9.1: Pathophysiology of infertility in patients with endometriosis.[5]

Mechanisms responsible for infertility in patients with endometriosis
Mild-to-moderate

• Changes in peritoneal fluid
  ○ Increased prostaglandin levels
  ○ Increased number of macrophages
  ○ Increase in volume
  ○ Reduced sperm motility and binding
  ○ Presence of interleukins and tumor necrosis factor
• Ectopic endometrium abnormalities
• Myometrial and peristalsis abnormalities
• Follicular environment and embryo quality
  ○ Increased progesterone and interleukin-6
  ○ Decreased vascular endothelial growth factor
• Ovulation disorders
  ○ Anovulation
  ○ Hyperprolactinemia
  ○ Abnormal follicular genesis
  ○ Premature follicular rupture
  ○ Luteinized unruptured follicles
  ○ Luteal phase defect
• Pelvic pain
• Immunological abnormalities
  ○ Antigen-specific B-lymphocyte activation
  ○ Non-specific B-lymphocyte activation
  ○ T-lymphocytes
  ○ Anti-endometrial antibodies
• Spontaneous abortion
• Implantation disorders

Moderate-to-severe
• Fimbrial distortion or even occlusion can occur • Adhesions with the distortion of pelvic architecture interfering with the release of the oocytes and the tubal pick-up of these oocytes • Tubal narrowing and constriction • Proximal tubal obstruction

TREATMENT

There are some primary aims of endometriosis treatment which have been discussed as followed:

- Restoration of normal anatomy
- Removal or reduction of ectopic endometrial implants
- Alleviation of symptoms
- Reducing disease progression
- Enhancing fertility.

A broad spectrum of therapeutic options, that includes expectant management, medical, and surgical interventions (which could be alone or in combination), as well as assisted reproductive technology (ART), has been used to address the clinical sequelae of endometriosis. However, in endometriosis-associated infertility, the efficacy of these options with regard to achieving conception success remains considerably variable and remains inadequately explored.[8]

MEDICAL TREATMENT OF ENDOMETRIOSIS

Usage of hormonal treatment for 6 months for suppression of ovarian function, reduces endometriosis-associated pain. Recurrence of symptoms is common following medical treatment of endometriosis.[9] Recurrent symptoms require long-term or repeated courses of medication. Treatment with gonadotropin-releasing hormone agonist (GnRHa) analogues, such as leuprolide, is limited to only 6 months. This is because these agents induce a hypoestrogenic state that substantially decreases the bone marrow density. The addition of add-back therapy is an option, but regimens are both complicated and costly, and no single add-back therapy has yet been recommended for all women treated with GnRHa.[10] Long-term usage of daily oral combined oral contraceptives (COCs) can be safely recommended, although the high frequency of dosage may be inconvenient for some women. COCs are often used daily and continuously (without a pill-free interval) for 6–9 months as a treatment for endometriosis pain.

Combination Oral Contraceptives

The agents have been considered a cornerstone for the treatment of pain that is associated with endometriosis. The mode of action of these drugs is by inhibiting gonadotropin release, decreasing menstrual flow, and decidualization of the implants. In cases of women who fail to achieve pain relief with cyclic COC therapy, the continuous regimen may be preferable for its decreased frequency of menses. The reseeding of refluxed endometrial tissue is prevented because oral contraceptives are capable of reducing menstrual flow and retrograde menstruation. Furthermore, the risk of endometrioma development may be reduced by the inhibition of ovulation induced by oral contraceptive pill (OCP). Induction of atrophy of the endometriotic implants, downregulation of cell proliferation and increase in apoptosis in endometrial tissue by OCP have also been demonstrated.[11] Therefore, OCP therapy might prevent implant growth and reduce the endometriosis-related pain, since there is correlation between pain and the cyclic microbleeding within the endometriotic lesions.[12]

Those women who are undergoing conservative surgery for symptomatic endometriosis, in those women long-term administration of OCP seems to be a valuable adjuvant postoperative measure. Since both continuous and cyclic administrations are found to be similarly effective in reducing endometriosis recurrence, the choice of the regimen can be modulated according to patient preferences.[13]

Progestins

Progestins or synthetic progestogens (having similar effects to progesterone) are known to antagonize estrogenic effects on the endometrium, causing initial decidualization and then leading to subsequent endometrial atrophy. However, there is a lot of debate regarding mechanism of action of progestins on endometriosis.[14] The different progestins are capable of terminating the proliferation in endometriotic implants and lead to induction of regressive change to certain degrees, but they are not able to heal endometriosis because endometriosis is a chronic and recurrent disease. Progestins—especially non-androgenic progestins—are well-tolerated and have only few side effects; they can be used repeatedly or continuously over a long period of time.

Administration of progestins have been done in the treatment of endometriosis in numerous ways and it includes oral progestins, depot medroxyprogesterone acetate (DMPA), the newer selective progesterone receptor modulators (SPRMs) and a levonorgestrel-releasing intrauterine device.

Levonorgestrel Intrauterine System

The levonorgestrel intrauterine system (LNG-IUS) has been used effectively as a contraceptive and treatment for menorrhagia. This system works by releasing a steady low-level of the levonorgestrel, progestogen. The LNG-IUS has been shown to be an effective treatment for endometriosis-associated pain along with reduction in the size of rectovaginal nodules and improvement in the staging.

Selective Progesterone Receptor Modulators

There are certain molecules called progesterone-receptor molecules that bind the progesterone receptors and then activate or inactivate and show activities of a progesterone agonist and antagonist both.

One common SPRM is mifepristone (RU486). It is an abortifacient that predominantly possessing anti-progestational activity. Through various studies in women with endometriosis it was found to be reducing pelvic pain and extent of endometriosis, when it is used for 6 months at oral dosages of 50 mg daily.[15] Asoprisnil (J867) is also an SPRM that induces amenorrhea and endometrial atrophy.

Androgens

Danazol

A chronic anovulatory state is created by the predominant mechanism of action that appears to be suppression of midcycle luteinizing hormone (LH) surge. Danazol creates a hypoestrogenic, hyperandrogenic state that leads to induction of endometrial atrophy in endometriotic implants. A recommended dosage of danazol of 600–800 mg daily is to be given. Unfortunately, significant androgenic side effects develop at this dosage and include acne, hirsutism, adverse serum lipid profiles, hot flashes, and even deepening of voice.

Gonadotropin-releasing Hormone Agonists

Pituitary desensitization and subsequent loss of ovarian steroidogenesis occurs due to GnRH administration. A pseudo-menopausal state is created during treatment and removal of the stimulation normally provided to the endometriotic implants occurs by the hypoestrogenic environment alongwith loss of ovarian estradiol production. The effectiveness of GnRHa therapy to improve pain symptoms in women with surgically-confirmed endometriosis has been demonstrated by numerous studies.

The use of a GnRHa with "add-back" (estrogen and progestogen) therapy protects against loss of bone mineral density (BMD) during treatment and for up to 6 months after treatment.

Add-back therapy involves taking one of the following medications at the same time as a GnRHa: a low-dose progestin, a low-dose estrogen or tibolone (a synthetic steroid mimicing the activity of estrogen and progesterone in the body). In a meta-analysis, BMD was found to be significantly higher in women with uptake of progestogen and estrogen as "add-back" compared with a GnRHa alone. Also, hypoestrogenic adverse effects were found to be significantly less severe in the women who received "add-back".

Aromatase Inhibitors

Aromatase is locally produced by endometrial tissue, and it is the enzyme responsible for estrogen synthesis. Similar hypoestrogenic side effect profiles as GnRHa is found in aromatase inhibitors, but it hold promise in severe, refractory cases of endometriosis.

Any of the primary biological mechanisms responsible for the disease process does not get affected by hormonal manipulation. Consequently, medical treatment does not always provide complete pain relief and some women fail to respond at all.

The development of non-daily hormonal delivery options (intravaginal, transdermal, and subcutaneous injectable) has potentially increased the convenience and consistent use of estrogens/progestins over the long-term for many women. The DMPA reduces endometriosis pain effectively, with significantly less impact on BMD as compared to a GnRH analog and it has been shown in randomized clinical trials. Other treatments are also there, like SPRMs, aromatase inhibitors, and selective estrogen receptor modulators (SERMs) are considered to promising prospective by virtue of their ability to target endometriotic implants more specifically rather than systemically reducing estrogen levels, but their efficacy has not yet been assessed fully in clinical studies.[9]

Treatment of Endometriosis Associated Infertility (Box 9.2)[16]

To improve the quality of life for many patients with endometriosis, medical management has been demonstrated. Unfortunately, the medical therapies for endometriosis almost exclusively limit reproductive options due to their contraceptive effects. Some modalities, such as DMPA, even though are very effective for treatment of symptoms, may show lasting effects of ovulation suppression beyond the duration of treatment.

A Cochrane review of 23 trials that included over 3,000 women demonstrated no difference in PRs with preceding ovulation suppression with oral contraceptives, progestins, or danazol in subfertile women with endometriosis.[17] Therefore, in treatment of symptoms of endometriosis before and after pregnancy, OCPs, progestins, and GnRHa can be very effective, but pretreatment with these agents does not improve the fecundity and therefore implementation of medical management will only delay attempts at conception.[18]

SURGICAL TREATMENT OF OVARIAN ENDOMETRIOMAS

For the purpose of conservative laparoscopic treatment of endometriotic cysts, several techniques have been proposed.

Cyst Drainage

There is involvement of a high-risk of recurrence of 80–100% which is considered as the major problem of cystic drainage associated with laparoscopy, as it is with ultrasound-guided aspiration.

It is at present accepted that simple drainage by laparoscopy should not be used to treat endometriomas.

Laparoscopic Excision of Endometriotic Cyst

A more favorable outcome than drainage and ablation, is provided by excisional surgery for endometrioma. This is in with regard to the recurrence of the endometrioma, recurrence of symptoms, and subsequent spontaneous pregnancy in women who were previously subfertile and should be the favored surgical approach.[19]

This technique is considered to be a first-line choice for the conservative treatment of the endometriotic cysts.

Technique

Resection of endometriomas (Figs. 9.2 to 9.4)

Once the endometrioma is drained of its chocolate-colored fluid, the cyst wall is then opened further and inspection is done

Box 9.2: Treatment of endometriosis-associated infertility.

- Medical treatment is considered to be effective for relieving pain that is associated with endometriosis but does not improve productivity.
- In case of minimal-to-mild endometriosis: Ablation of endometriotic lesions along with adhesiolysis to improve fertility is effective as compared to diagnostic laparoscopy alone.
- In case of moderate-to-severe endometriosis: No randomized controlled trials or meta-analyses are available to predict whether surgical excision enhances pregnancy rates (PRs) or not.
- A surgical approach, by normalization of the pelvic anatomic distortion and by adhesiolysis, can lead to enhancement of the fertility. More severe/advanced forms require a multidisciplinary approach.
- Laparoscopic cystectomy for ovarian endometriomas with a diameter greater than 4 cm improves fertility as compared to drainage and coagulation.
- Coagulation or laser vaporization of the endometriomas without excision of the pseudocapsule is found to be associated with a significantly increased risk of cyst recurrence.

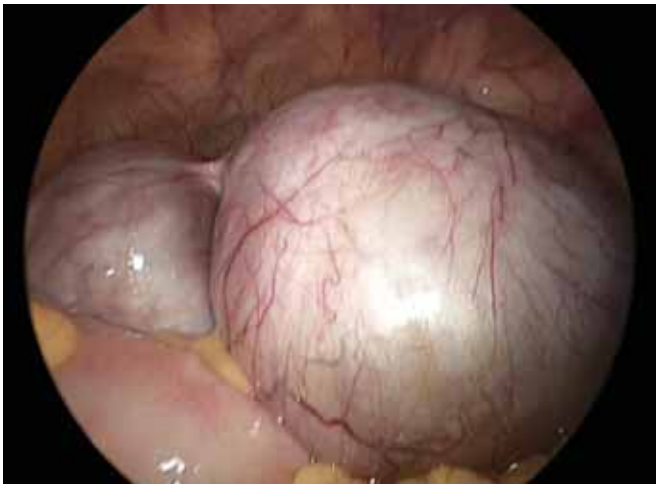

Figure 9.2: Large endometriotic cysts.

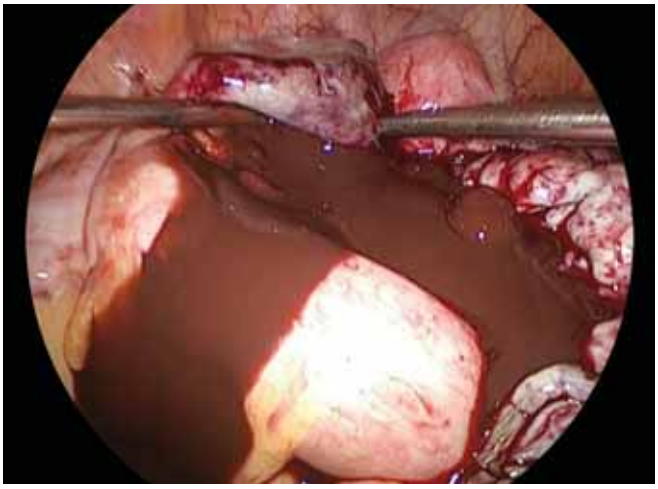

Figure 9.3: Chocolate-colored fluid drained.

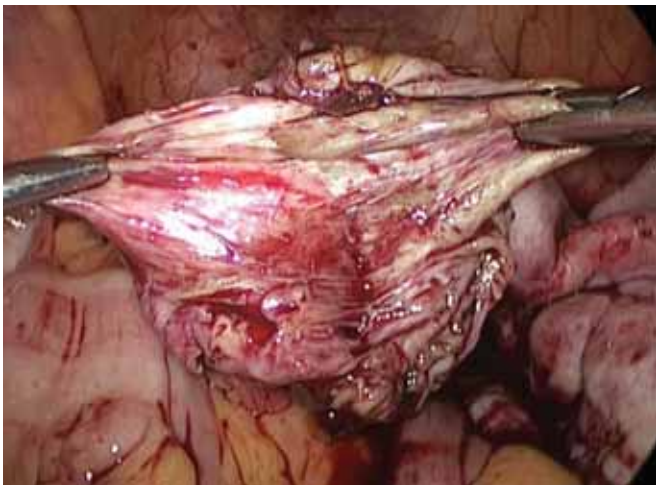

Figure 9.4: Cyst wall excision.

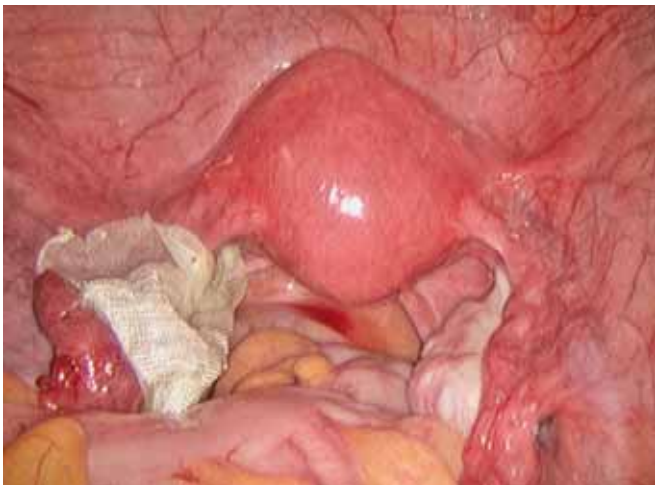

Figure 9.5: Placement of adhesion barrier (Interceed).

to examine the surface. The surface is often found to be laden with implants of deep and superficial endometriosis.

To create a space between the wall and the underlying stroma, the edge of the incised wall is grasped and retracted. From that space, it is progressively stripped from the ovary.

The two hallmarks of dissection are traction and counter-traction. For the purpose of resection of the ovarian stromal attachments that adhere cohesively to the cyst wall, the technique of sharp dissection can be used. It is continued until the entire cyst wall is removed.

The ovarian crater at all times shows bleeding, after the wall of the cyst is removed. This is because blood vessels supplying the wall have been separated and opened. Identification and coagulation of each vessel individually, is recommended, thus inflicting minimal thermal damage to the surrounding stroma.

Suturing: Based on the largeness of the defect and whether the edges of the crater spontaneously come together or not, the approximation of the edges, preferably with fine absorbable suture is decided, once complete hemostasis has been achieved.

Adhesion prevention: De novo adhesion formation in endometriosis is done in following way: An alteration in the function of peritoneal macrophages, lymphocytes, and natural killer cells is found in women showing endometriosis. Furthermore, growth factors and inflammatory mediators in the peritoneal fluid, that are produced mainly by the peritoneal macrophages, are altered in case of endometriosis. This indicates a role for these immune cells and mediators in the pathogenesis of adhesion formation.[20]

During surgery, the subsequent postoperative adhesions formation is influenced by the disruption of the peritoneal surface, adhesiolysis, and the local inflammation of endometriosis. Synthetic barriers prevent adhesion. Interceed (TC7) is an oxidized regenerated cellulose compound which requires no suturing, can be cut as necessary, can be applied laparoscopically, and is absorbable. It is a Food and Drug Administration (FDA) approved adhesion barrier to be used in laparotomy. It forms a gelatinous protective coat within 8 hours and is absorbed within 2 weeks. Since TC7 is a procoagulant and causes fibrin deposition at sites of incomplete hemostasis, therefore it must be applied after hemostasis is achieved (Fig. 9.5).

The Combined Technique (Stripping and Ablation)

Based on the cystectomy technique, a large part of the endometrioma wall is first excised, after which using diathermy, the remaining 10–20% of the endometrioma wall close to the hilus is desiccated.

The volume of the ovary remains similar to that of the contralateral normal ovary, after the combined technique. The antral follicle count on 2nd to 5th day, shows the same number of antral follicles. Thus, it proves that the technique is not deleterious to the ovary.[21]

An acceptable alternative is bipolar coagulation to carry out aspiration, drainage and destruction of the cyst wall, in case when cystectomy is technically difficult.[22]

Adjuvant Medical Treatment[23]

Laparoscopic procedures, either preoperatively or postoperatively are combined with medical treatment for endometriosis. The theoretical advantages of medical treatment before surgery include reduced inflammation, vascularization and shrinkage of implants. These effects may then contribute to much easier, quicker, and less traumatic surgery, with more chance of complete eradication of the disease and a reduced risk of postoperative adnexal adhesions. On the other hand, under medical suppression, there could be regression of small endometriotic foci temporarily and thus escape laparoscopic recognition and ablation could be escaped. There is decrease in endometriosis classification scores by presurgical medical therapy decreases, but there is no demonstration that this leads to better outcomes for infertile patients.

Recurrence of Endometriosis[24]

A distinctive tendency to recur after conservative surgery is possessed by endometriosis. The recent trend toward delaying pregnancy and the persistence of pathogenic mechanisms result in a considerable rate of postoperative disease and symptoms relapse. This gradually increases throughout the years.

For those patients who present with clinical recurrence, three risk factors were found:

1. Previous history of endometriosis
2. Stage IV revised American Fertility Society (rAFS) classification
3. Score of rAFS (total, adhesions, and implants' scores).

In addition, two main risk factors were detected for reintervention:

1. Endometrioma size
2. Total rAFS score.[25]

Recently, Guo (2009)[26] calculated that the disease relapse rate is higher than 20% at 2 years and 40–50% at 5 years. The relapse of endometriosis and its consequences on reproductive performance may be particularly detrimental, owing to gonadal as well as peritoneal damage that is caused by both recurrent disease and repeated surgical trauma. Moreover, the patients are exposed to frustration, repetitive suffering, multiple courses of medical therapy and risk of serial surgery due to pain symptoms relapse.

According to studies GnRHa or postoperative OCPs treatment have been associated with a major reduction in the risk of endometrioma recurrence. Ovarian stimulation is a risk factor for the recurrence of dysmenorrhea. Chronic pelvic pain is also related to the adhesions score at laparoscopy and a prior operation for endometriosis.

A protective effect against pain and endometrioma recurrence is shown by pregnancy.

Assisted Reproduction in Endometriosis

In cases when other treatments prove to be unsuccessful then assisted reproduction techniques could be useful when endometriosis-associated infertility is unexplained or a consequence of pelvic distortion is there. In women showing mild or moderate endometriosis with patent, mobile fallopian tubes and ovaries, in that case intrauterine insemination with or without ovarian hyperstimulation may be considered. A crucial role is played by ovarian responsiveness to hyperstimulation in determining the success rate of in vitro fertilization (IVF). The prognosis is considered to be worse if despite the use of elevated dosages of gonadotropins, the woman develops few follicles.[27]

In vitro fertilization is appropriate treatment especially if:

- There is compromization in tubal function
- Male factor infertility
- Other treatments have failed in moderate-to-severe endometriosis: A prolonged treatment with a GnRHa before IVF should be considered and discussed with patients.

MANAGEMENT OF OVARIAN ENDOMETRIOMA BEFORE IN VITRO FERTILIZATION

In the management of ovarian endometrioma before in vitro fertilization (IVF) treatment, two questions needs to be be answered, which are:

- Are the results of IVF impaired due to the presence of the endometrioma?
- Should endometriomas be operated in patients scheduled for ART or not?

Impact of Endometrioma on Ovarian Responsiveness

The formation of endometriotic cysts could be considered as a reason behind reduced ovarian reserve. Women with endometriomas show follicular depletion in the ovaries that has been related to oxidative stress. This oxidative stress can induce necrosis in early follicles and apoptosis of the oocytes in vitro. The damage that is produced to the ovary by the endometrioma may be quantitative rather than qualitative. It could be suggested that fewer or a small number of oocytes could be retrieved after the ovarian stimulation has occurred in IVF cycles but with a relatively unaffected quality.[28]

Impact of Surgery in Endometrioma-related Infertility

Due to removal of healthy ovarian tissue and due to vascular injury, the surgical removal of endometriomas can prove to be damaging to the ovaries. This finally results in a reduced ovarian reserve and a lower response to gonadotropins in IVF cycles. Although endometriomas could be detrimental to the ovarian reserve, the current evidence indicates an even lower ovarian reserve observed after surgery. Also, according to different studies, after surgical removal of endometriomas, there has been a reduced response of the ovaries to gonadotropins. The quality of

the oocytes retrieved in IVF cycles is not improved after surgery. Patients undergoing an operative procedure might extend the time to pregnancy. In specific or special circumstances such as pelvic pain or difficult access to growing follicles, surgery should be expected. But it should not be offered to every single patient with endometrioma-associated infertility.[28]

Effect of Surgery on Ovarian Reserve

As assessed by the levels of serum anti-Müllerian hormone (AMH), a decreased ovarian reserve could be associated with ovarian cystectomy for endometriomas. Furthermore, the severity of endometriosis and the bilaterality of endometriomas are significantly related to the rate of decline of the serum AMH level. While performing a cystectomy for bilateral endometriomas and even for unilateral endometrioma with severe adhesion surrounding the ovary, the decrease in ovarian reserve should be taken into account.[29]

To Touch or not to Touch?

In ovarian endometrioma, with diameter of greater than or equal to 4 cm, laparoscopic cyst excision leads to improvement in access to follicles and it might possibly improve ovarian response, but the counseling of the woman should be done regarding the risks of reduced ovarian function after the surgery has taken place.

Operating a cyst beyond 3 or 4 cm, and all decisions related to it are arbitrary. Surgeons should keep this in mind that if all healthy growing follicles may be reached without damaging the endometrioma, there is no requirement of surgery for cyst over 4 cm or even 5 cm, in asymptomatic patients. However, when the growing follicles get hidden by the smaller cysts, especially when the ovary is fixed, then in this case it may require intervention.[27]

Thus, it could be said that if oocyte collection is not hindered then ovarian endometrioma need not be removed. If there is a requirement for removal, then excision has been demonstrated to yield better results as compared to that of ablative surgery. However, in women undergoing IVF, when excision is difficult because of a poor surgical plane between the cyst wall and the surrounding ovarian tissue, then fenestration and selective ablation of the endometrioma bed should be considered. Along with the recurrence rate of endometrioma, the ablation technique is increased, however, the outcome of IVF is not impaired by the presence of endometrioma. The purpose of reproductive surgery in this context is to improve fertility, and not to eradicate the disease, as in case of women with chronic pelvic pain.[30]

STAGE OF ENDOMETRIOSIS AND SURGERY OUTCOME

To improve fertility in minimal-to-mild endometriosis, ablation of endometriotic lesions plus adhesiolysis is found to be effective as compared with diagnostic laparoscopy alone. Moderate-to-severe endometriosis may be treated with surgery to restore normal anatomy and tubal function. However, there are no well-designed trials that examines the role of surgery for subfertility in women with severe endometriosis. Alternatively, the patients with infertility and endometriosis are considered to be the candidates for fertility treatments such as controlled ovarian hyperstimulation, intrauterine insemination and IVF.

ENDOMETRIOSIS AND INFERTILITY: GUIDELINES BY THE PRACTICE COMMITTEE OF AMERICAN SOCIETY OF REPRODUCTIVE MEDICINE 2012

- The age of the female, duration of infertility, pelvic pain, and stage of endometriosis should be considered while formulating a management plan
- The benefit of laparoscopic treatment of mild endometriosis is insufficient to recommend laparoscopy solely to increase the likelihood of pregnancy
- When laparoscopy is being performed for other indications, then ablating or excising visible lesions of endometriosis could be considered by the surgeon safely
- In younger women (those who are under the age of 35 years) with stage I or stage II endometriosis-associated infertility, expectant management or ovulation induction or intrauterine insemination can be considered as first-line therapy
- For women of 35 years of age or more, a much more aggressive treatment, such as intrauterine insemination or ovulation induction or IVF may be considered
- In women with stage III or stage IV endometriosis-associated infertility, possible laparotomy or conservative surgical therapy with laparoscopy may prove to be beneficial
- Resection or ablation, rather than drainage should be included in surgical management of endometrioma. Resection is considered a preferred mode of treatment
- For women with either stage III or stage IV endometriosis who fail to conceive following a conservative surgery or due to advancing reproductive age, then IVF-embryo transfer (ET) is considered to be an effective alternative.[2]

CONCLUSION

Endometriosis significantly impacts, every part of the reproductive process, in a negative manner. Since every patient is not bound to experience the same symptoms, therefore, infertility associated with endometriosis can prove to be even more puzzling. Hence, all the patients does not respond to therapies in the same way, making treatments particularly difficult to develop.

Medical as well as surgical treatments for endometriosis show different effects on a woman's chances of conception, either spontaneously or via ARTs. A woman's age, pelvic pain, duration of infertility, and the stage of endometriosis are taken into account while formulating an infertility treatment plan.

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CHAPTER

Endometriosis and Assisted Reproduction Techniques

INTRODUCTION

Endometriosis is one of the most inexplicable and mysterious conditions in gynecology. It is characterized by the presence and proliferation of both endometrial glands and stroma outside the uterine cavity. Endometriosis is one of the most frequently investigated disorders in gynecology. Despite that, there remains a lack of consensus on various issues related to its pathophysiology and treatment. The relationship between endometriosis and infertility is well known, as there is higher overall prevalence of disease reported in infertile women, but the exact mechanism remains unclear and also a cause and effect relationship has not been established, especially in the early stages of the disease.[1] Recent scientific reports based on sound laboratory and clinical research have helped advance the understanding of mechanisms involved in the endometriosis disease process. It has also been seen that not all women with endometriosis are infertile or need assisted reproduction techniques (ART). In fact, many women with endometriosis are fertile and successfully reproduce. Thus, infertile women who have been diagnosed with endometriosis should begin ART, in a reasonable period of time, considering that they will probably have lower chances of conceiving naturally on their own. Thus in this chapter, we will discuss how the treatment of endometriosis patients with ART is helpful in improving the chance of viable pregnancy.

RELATIONSHIP BETWEEN ENDOMETRIOSIS AND INFERTILITY

Like discussed before, the relationship between early endometriosis and infertility is unclear. There is a body of indirect evidence of the association between infertility and endometriosis. In prospective studies, normal fertile women have a much lower incidence of endometriosis than those who are infertile.[2,3] Many factors have been described as a cause of decreased fertility found in endometriosis patients without tubal involvement. Lower fecundity has been demonstrated in animal models with surgically induced endometriosis.[4-6] Women with minimal endometriosis entering a donor insemination program have significantly-reduced cycle fecundity.[7] Some of the potential causes of infertility include defective folliculo-genesis, poor oocyte quality, luteinized unruptured follicle, altered tubal permeability and functionality, diminished sperm motility in the uterus, reduced oocyte fertilization, slower embryo cleavage, and reduced embryo implantation. Many women with endometriosis are fertile and successfully reproduce. Nevertheless, their fecundability or chances of achieving pregnancy per month seem to be reduced, as endometriosis may have adverse effects on several aspects of reproductive physiology, including folliculogenesis, ovulation, sperm motility, fertilization, and embryo quality.

ENDOMETRIOSIS AND ART

Relationship between endometriosis and ART is still more debated. Many studies have suggested the lower success rate of ART in women who have endometriosis.[8-10] But some studies do not support this fact.[11]

It is tough to understand studies involving ART, as usage of a high dose gonadotropin-releasing hormone (GnRH) analogs and gonadotropins with consequent morphologic abnormalities in endometrium, extended luteal phase support and transfer of more than one embryo, make direct comparison between stimulated and natural cycles extremely difficult.[12]

GnRH Analog Therapy in ART Cycles in Women with Endometriosis

It the pregnancy and endometriosis are related, then logically pregnancy rate should improve after endo-metriosis is treated. Women with moderate and severe endometriosis have been found to have a significantly lower pregnancy rate in ART cycles than women with tubal disease and an improvement in the rate is noted with the use of a GnRH analog.[13,14] Two recent studies demonstrated the benefits of prolonged down-regulation with GnRH analogs before initiation of in vitro fertilization (IVF) in patients with endometriosis.[15,16]

Folliculogenesis and Ovulation in Endometriosis

IVF is an effective tool which has been now being used for women with endometriosis and has enabled us to gain clinical knowledge of factors implicated in endometriosis-associated infertility. Anovulation, or luteinized unruptured follicle (LUF)

syndrome may occur when, despite ovulatory changes, such as a luteinizing hormone (LH) surge and a rise in progesterone concentration, the egg is not released from the follicle. The LUF syndrome has been noted in some women with endometriosis,[17] but it is also known to occur in normal fertile women.[18] It is not clear whether the LUF syndrome is a consistent change or sporadic event during ovulatory function, or whether it is associated with endometriosis.

Impaired fertilization is thought to be an adverse effect of endometriosis. Reduced fertilization rates in women with endometriosis have been reported as compared to those with tubal or unexplained infertility.[19,20] It is possible that lower fertilization rates in oocytes derived from women with endometriosis are a consequence of altered folliculogenesis. In women with endometriosis Follicular fluid from has been shown to stimulate the proliferation of endometrial stromal cells in culture.[21] Moreover, there is reduced estradiol concentrations during the preovulatory phase, reduced estradiol and progesterone concentrations in the early luteal phase, impaired follicular growth[22] and altered LH surge profiles have also been noted.[23]

Other than gonadotropins and ovarian steroids, growth factors and other chemical messengers are important for folliculogenesis and oocyte maturation.The interleukins IL-1b and IL-6, and vascular endothelial growth factor (VEGF) are responsible for a number of effects in the ovary. The serum concentration of IL-6 was found to be significantly increased during natural, but not stimulated cycles of women with endometriosis.[24]

Embryo Quality and Uterine Receptivity in Endometriosis

Embryo quality may be altered in women with endo-metriosis. Clinical observations suggest that implantation rate may be diminished in these patients. For successful implantation, complex interactions between embryonic and uterine cells must occur. There remains some controversy whether endometriosis affects implantation and pregnancy rates during IVF cycles.[25-28] Earlier studies, focused on oocyte quality, have noted a decreased pregnancy rate in endometriosis patients using either their own oocytes or donated oocytes from women with endometriosis.[29] When these patients received oocytes from women without endometriosis, there is no decrease in implantation rate or ongoing pregnancy rate. These observations suggest that poor oocyte quality may lead to a decreased implantation and pregnancy rate in women with endometriosis and not to a defect in the endometrium. To have a clearer answer to the question, whether oocytes derived from the ovaries of women with endometriosis have a reduced ability to implant, the quality of embryos derived from women with endometriosis was investigated. In a retrospective study, the number of blastomeres and degree of fragmentation of embryos derived from women with endometriosis were analyzed, and compared with data from embryos derived from women with tubal infertility.[30] After 72 hours in culture, there was a significant decrease in the number of blastomeres, and a significant increase in the percentage of embryos that arrested in the endometriosis group. The data thus collected suggests that the poor embryo quality may be the main factor contributing to lower implantation rates in women with endometriosis. Confirmatory evidence comes from oocyte donation programs, where success rates are unaffected by the presence of endometriosis and are comparable to outcomes following oocyte donation for other indications. However, it is possible that poor quality embryos with a decreased ability to implant, and alterations in the endometrium, which result in a hostile endometrial environment, are both contributing factors in endometriosis-related infertility.

There is conflicting data with the use of integrins as biochemical markers of uterine receptivity, but aberrant expression of integrins may alter endometrial receptivity.[31-34] Whether changes in the expression of some integrin genes occur before the development of endometriosis, or as a result of endometriosis, remains to be elucidated. While the exact mechanism by which the integrin genes are regulated is unknown, cytokines, growth factors and sex steroids, the levels of which are altered in endometriosis, may modulate their expression.[35]

It has been seen that there is a direct association of endometriosis with any functional change in many immuno-logical components in the peritoneal fluid. For example, there is an increased level of macrophages in peritoneal fluid, which secrete cytokines and growth factors, in response to endometriosis-associated inflam-mation.[36] Cytokines are involved during endothelial cell implantation, the proliferation and formation of endometriotic lesions, and play a critical role in decreased immunological surveillance, recognition and destruction of ectopic endometrial cells. Increased cytokine production is one of the similarities endometriosis shares with autoimmune diseases such as rheumatoid arthritis and Crohn's disease.[37] It is generally accepted that women with endometriosis have autoimmunity to endometrial and ovarian targets.[38] When autoantibodies are directed against an ectopic endometrium, they may also affect normal uterine endometrium and lead to early implantation failure and increased early pregnancy loss.

CONCLUSION

According to the best available evidence, endometriosis compromises fertility by several different mechanisms. Advanced stages of the disease compromise the monthly fecundity rate even further. Different ART available are able to bypass most of the endometriosis-related mechanisms of infertility in order to achieve a pregnancy, except for oocyte/embryo quality. In vitro fertilization would seem to be an effective treatment for many of the mechanical alterations in reproductive events that are associated with endometriosis-related infertility. Ovarian hyperstimulation and luteal phase support may correct some effects of endometriosis on ovulation and the endocrine environment. Decreased fertilization, implantation and pregnancy rates in women with endometriosis may be a reflection of reduced oocyte quality, which leads to a reduction in embryo quality and the ability of these embryos to implant in an altered endometrial environment. Endometrial receptivity does not seem to be affected, as results from egg donation are not diminished in endometriosis patients. When considering surgery prior to ART, it is crucial to consider patient symptoms as well as the potential benefit of this surgical procedure, as ovarian reserve may be compromised after surgery; however, careful technique does not compromise ovarian reserve. In cases

where the ovarian function may be seriously compromised, egg banking may be offered.

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CHAPTER

Implantation in Endometriosis

INTRODUCTION

The final step in establishment of pregnancy is called implantation. In this process the fertilized egg gets firmly attached to the uterine wall, which generally occurs 6–7 days after conception. Even after a lot of technological advancement, this process is still enigma for the researchers. Despite rapid advances in the field of in vitro fertilization (IVF) since the first success in 1978,[1] the success rate of IVF has stagnated around 25–30%,[2] mainly limited due to our failure to improve implantation rates. As per known process of implantation till now, human embryo implantation is a three-stage process (apposition, adhesion, and invasion) which also involve synchronized crosstalk between receptive endometrium and functional blastocyst.[3] This is an ovarian steroid-dependent phenomenon which can only take place during a ready-reception period of endometrium which is called the window of implantation.[4] The implantation window is characterized by changes to the endometrium cells, which aid in the absorption of the uterine fluid. It is a self-limited period of endometrial receptivity spanning between day 20 and day 24 of the menstrual cycle. The process of implantation is a complex process and it involves a complex sequence of signaling events, consisting of the acquisition of adhesion ligands together with the loss of inhibitory components, which are crucial to the establishment of pregnancy.

MECHANISM OF IMPLANTATION

Implantation is the process by which a foreign blastocyst is accepted by the maternal endometrium. It is complex and requires interplay of many systems. The process of apposition, adhesion, and invasion is arranged by sequential appearance and disappearance of molecules in the endometrial epithelium and stroma controlled by steroid hormonal signaling and manifested histologically by changes in the appearance of epithelium and stroma in various stages. This process gets started only when the blastocyst directly comes into the contact of endometrium. The key to the process is the establishment of controlled aggression orchestrated by a family of chemokines, adhesion molecules and T cells, uterine natural killer (NK) cells and T regulatory (T_{reg}) cells.

The endometrium has enhanced proliferation during the first part of mensuration due to increased levels of estrogen. After the ovulation process, the progesterone which is secreted by luteinized follicles leads to differentiation of endometrial cells. The prostaglandins help in the fine-tuning of window of implantation timing which is very crucial.[5] This in turn, induces a variety of molecules playing a pivotal role in implantation. These mediators include a large variety of inter-related molecules including adhesion molecules, growth factors cytokines and lipids.[5]

The readiness of the endometrial receptivity starts with the acquisition of adhesion ligands and with the loss of inhibitory molecules that may act as a barrier to the attaching of embryo.[6] In around two-thirds of the cases, inadequate uterine receptivity is responsible for implantation failures, and out this one-third of the failures are due to embryo itself.[7]

The main step in the process of implantation is decidualization, when there are extensive changes in the endometrium in terms of morphology, expression, and secretion pattern. All this happens to make the implanting blastocyst to gain access to the maternal system that majorly done by different actions of steroid hormones. Initial studies of the implantation process shows characteristic microvillar protrusions on the luminal surface of the endometrium—pinopods, during the window of implantation.[8,9] These are the hallmark of endometrial receptivity. Blastocyst attachment occurs at the site of pinopod expression.[10]

Interleukin

The successful implantation occurs only after there is the establishment of a two-way dialogue between the embryo and the endometrium through a host of molecules, which needs more research. Chemokine gradient in the uterus guides the implanting blastocyst to the most appropriate site.[11] Cytokines especially interleukin-6 (IL-6) family are the important molecules which have major role in implantation, these also include leukemia inhibitory factor (LIF), IL-11 and IL-6 all of which have intracellular signaling through gp130. The LIF and IL-6 are pro-inflammatory cytokines, which act on the stromal

cells and control the migration of macrophages and T cells into the endometrium[12] while IL-11 is an anti-inflammatory one, which controls trophoblast invasion.[13] The LIF and IL-6 receptors are also present on the embryo, which indicate a role in the cross-talk.[14]

Another important group is the IL-1 family, which consists of two agonists IL-1a and IL-1b, two receptors IL-1R1 and IL-1R2, an accessory protein IL-1RAcP and a naturally occurring antagonist IL-1RA and IL-18. IL-1 stimulates LIF production, upregulates integrin β3 and aids in decidualization. IL-1 is also produced by the blastocyst, and it also expresses its receptors.[15,16] IL-18 is a proinflammatory cytokine produced by the stromal as well as epithelial cells which has an important role in decidualization. IL-18 induces Th1 response but in the absence of IL-12, it affects type 2 helper T cell (Th2) response.[17]

Leptin

Leptin is another molecule playing a crucial role by modulating the action of cytokines, upregulating integrin β3[18] and regulating the action of molecules involved in tissue remodeling like matrix metalloproteases (MMPs).[19] Leptin receptors are also found in early blastocyst.[20] The insulin-like growth factor (IGF)/IGF-binding protein (IGFBP) system also has an important role in implantation. IGF-2 is secreted by trophoblast, which helps in invasion while IGFBP-1 expressed by endometrium controls the invasion. An imbalance between two may impair implantation.[21,22]

Other Molecules

In the peri-implantation period increased glycodelin levels help in suppression of the maternal immune system to the fetal allograft.[23] Osteopontin is also upregulated in the secretory phase under the influence of IL-1, TNFα, TGFβ, and IFNγ, which helps in cell–cell attachment and communication.[24]

Adhesion Molecules

Selectins and Integrins

Another type of molecules which are involved in apposition and adhesion are selectins. Out of which, L-selectins act on both the endometrium and the blastocyst indicating a role in communication.[25] Integrins, especially integrin avβ3, are another class of molecules proposed to play an important role in adhesion being expressed on both endometrium and blastocyst.[26]

MUC-1

The MUC-1 is another class of molecules, which aids in implantation by global upregulation and selective downregulation at most suitable implantation site during the implantation window.[27]

Cadherins

Cadherins are a class of molecules, which have a role in adhesion junction formation. E-cadherin is especially implicated in guiding the invasion of implanting embryo by forming a permeability barrier in the endometrium. Both endometrium and embryo express this molecule.[28]

Immune Cells, Complement Factors and Major Histocompatibility Complex

Natural Killer Cells

Uterine NK cells, which are phenotypically similar to peripheral CD56+ T cells, play an important role in decidualization by elaboration of IFNγ and TNFα. They also aid in implantation through their interaction with blastocyst HLA-G molecules preventing immune rejection and at the same time controlling trophoblastic invasion by a complex interplay of pro- and anti-inflammatory cytokines.[29,30] They also play an important role in vascularization of the endometrium by elaboration of VEGF.[31]

Macrophages

Macrophages are present in high density in the peri-implantation endometrium. Many roles of these macrophages has been proposed, e.g. elaboration of cytokines to maintain a proper cytokine environment, clearing up apoptotic material resulting from apoptosis of trophoblast throughout pregnancy.[32,33]

Dendritic Cells

Besides uterine NK cells and macrophages, dendritic cells (DCs) also form an important population of cells in endometrium. They are the sentinels of the immune system activating it as and when provoked. However, they can also induce immune tolerance. Immature DCs differentiate into CD83+ DCs around the time of implantation mediated by cytokines and facilitate Th2 response.[34,35] NK and DCs are in close relation in the endometrium and help in each other's differentiation and maturation and also regulate each other's action through negative feedback loop.[36]

T cells

T cells are the type of lymphocyte that plays a central role in cell-mediated immunity. And here in implantation also play an important role. The shift of balance of Th1–Th2 in pregnancy as previously postulated is now known to be not as clear-cut. Th1 response is required in peri-implantation period. In fact Th1 by elaboration of cytokines helps to shift the balance toward Th2. Elaboration of IL-11 to IL-18 is so complex that their classification into Th1/Th2 seems to be an over simplification.[37] T_{reg} cells are an important mediator in the implantation. They are derived from peripheral CD4+ cells and help in controlling maternal immune response to embryo by modulating T cell activity.[38]

The embryo which enters the endometrial cavity searches for a suitable site for implantation and also responds by expressing receptors for the cytokines, adhesion molecules, e.g. LIF, α5 integrin, etc. and secretes certain factors like human chorionic gonadotropin, corticotropin-releasing hormone (CRH), carcinoembryonic antigen 1, etc., which in turn modulate the uterine environment further facilitating implantation. The expression of complementary molecules and their receptors on the blastocyst and endometrium provides insights into the ways by which both participate in the two-way dialogue (Fig. 11.1). Implantation is a simpler act of aggression of embryo and an act of invitation by endometriosis.

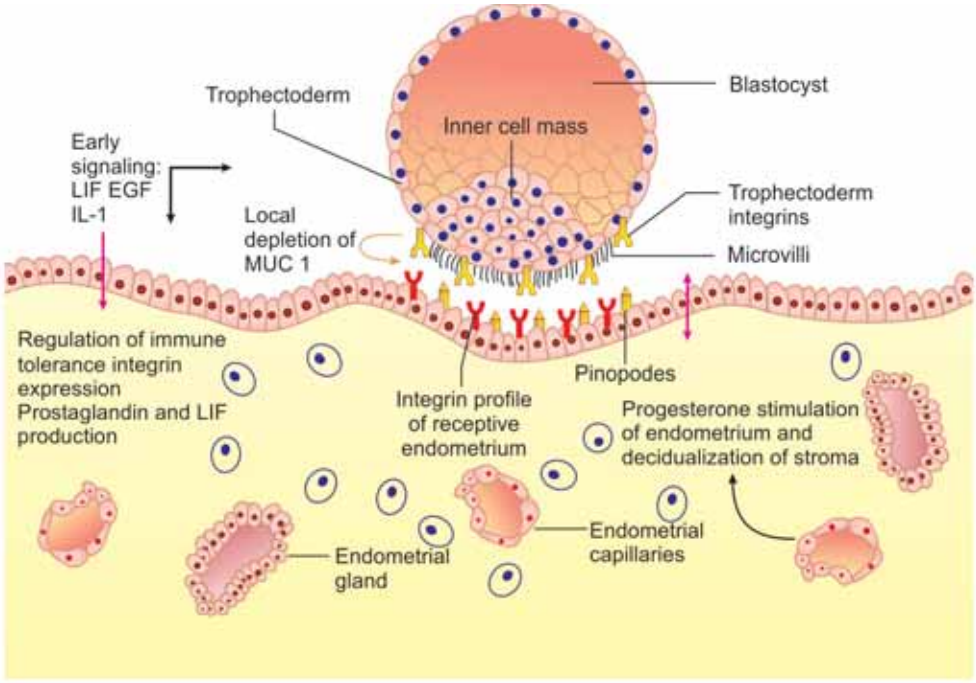

Figure 11.1: Embryo-endometrium dialogue.

PATHOGENESIS OF DEFECTIVE IMPLANTATION

Endometriosis and Infertility

It is now a well-known fact that endometriosis has been associated with infertility; but, the exact mechanism by which it causes is still unclear and needs more research. Endometriosis is encountered in 35–50% couples seeking infertility treatment.[39] The fecundity rate in women with endometriosis is reduced to 2–10%[40,41] compared to 15–20% in normal couples.

The invention of IVF has increased the possibility to investigate the effect of endometriosis at various stages of reproduction. Even with assisted reproductive techniques, the success rates in cases with endometriosis are lower than other causes of infertility.[42] Although there is well-known relationship between endometriosis and infertility, there is difficulty in proving any causal association due to the multiple mechanisms that might be involved.

The inflammatory effects of the disease process affects both oocyte production and ovulation in the ovary,[43] and in advanced cases, there may be impaired gamete transport due to distortion of the pelvic anatomy. Earlier studies emphasized on the adverse effects of hostile peritoneal environment prevailing in endometriosis, which proves toxic to the growing oocyte and impairs its developmental potential to varying extent reflected in impaired fertilization and cleavage rates. Then there have been theories about the inflammatory environment affecting the sperm quality reflected in poor fertilization rates.[44] Controversies abound, but the recent studies have refuted any effect of the disease on oocyte quality per se.[45] Poorer ovarian response may be due to reduced ovarian reserve due to repeated surgeries leading to loss of cortex[46] or impaired blood supply, and hence impaired delivery of gonadotropins to the growing follicles.[47]

Implantation and Infertility

Recent studies focusing on the molecular defects have unraveled newer secrets. Cells migrate from ectopic endometrial implants to the eutopic endometrium.[48] Wnt7a expression is essential to estrogen mediated uterine growth and implantation by signaling between epithelium and stroma.[49-51] Aberrant activation of Wnt pathway disturbs endometrial development during implantation window.[52] The increased expression of Wnt7a outside of the gland in endometriosis likely disrupts the normal epithelial and stromal polarity required for normal fertility (Table 11.1).

Failure of down-regulation of progesterone receptors during the window of implantation[53] is associated with reduced *HOXA*-10 and -11 genes expression[54,55] that lead to decreased avβ3 integrin expression,[56] which is critical to attachment of the blastocyst. Concurrent with this endometrial CRH and urocortin peptides involved in endometrial decidualization is downregulated in endometriosis. There is also an altered expression of activin A, which increases MMP activity helping in neovascularization and trophoblastic invasion.[57] Membrane bound IL-1RAcP expression is unaltered in endometriosis while soluble IL-1RAcP is decreased in patients of endometriosis which is critical in binding to IL-1 to reduce its activity[58] critical to implantation.

The progesterone action is mostly mediated by methylation and demethylation of specific promoter regions of the genes for proteins and cytokines, which mark endometrial receptivity. Endometriosis is associated with the aberrant expression of these genes, which in turn may be due to relative progesterone resistance state. Thus, many authors have postulated that the defects seen in this disease is basically an epigenetic phenomenon.[59]

TABLE 11.1: Summary of changes in the implantation window.

Normal endometrium (Upregulated)	*Eutopic endometrium in endometriosis*
• αvβ3 integrin	Upregulated
• Selectins	• Uterine NK cells (CD16)
• Soluble ICAM	• Cadherins
• MUC-1	• MUC-1
• LIF	• Glycodelin
• IL-6	• Osteopontin
• Soluble IL-1RAcP	• LIF
• Uterine NK (CD56) cells	
• Osteopontin	Downregulated
• Glycodelin	• αvβ3 integrin
• Leptin	• Soluble ICAM
• IGFBP-1	• Soluble IL-1RAcP
• E-cadherin	• T_{reg} cells
• Dendritic cells CD83+	• Dendritic cells CD83+
• Macrophages	• Macrophages

(ICAM, intercellular cell adhesion molecule; LIF, leukemia inhibitory factor; MUC-1, mucin 1, cell surface associated)

Earlier it was believed that there is a shift in Th1 to Th2 type immunity during window of implantation leading to successful establishment of pregnancy, which now seems to be oversimplification of the mechanisms involved. Uterine NK cells play a pivotal role in implantation by controlling maternal immune response to fetal allograft as well as trophoblast invasion and modulating endometrial neovascularization.[60] T_{reg} cells is another population of T cells, which appear around window of implantation essential for establishment of allotolerance by controlling autoreactive T cells.[60] DCs facilitate Th2 response. Close association of DCs and uterine NK cells stimulate each other maturation and maintain a negative feedback loop on each other activity.[36]

In endometriosis, there is a significant decrease in the DC population in the basal as well as the functional layer of the endometrium.[61] Along with this, there is no increase in the macrophage population in the endometrium of endometriosis which is normally seen during the window of implantation, and may be associated with altered immune cell environment.[62]

T_{reg} population is decreased in eutopic endometrium while it is increased in ectopic sites which leads to recruitment of NK cells crucial in the implantation process from eutopic to ectopic sites and hence the disruption of the entire process.[63]

MANAGEMENT OF ENDOMETRIOSIS

The rate of pregnancy in endometriosis being similar to or reduced as compared to other causes of infertility is still under discussion.[64,65] IVF success rates are diminished compared to other causes of infertility but IVF likely maximizes cycle fecundity for those with endometriosis. However, Society for Assisted Reproductive Technology (SART) has emphasizes similar outcomes compared to other infertile population in its latest review.[66] However, there are a few therapies, which have been well established in management of endometriosis patients.

Surgical Therapy

Surgery has a definite role to play in this disease at all stages. Possible effects may be due to correction of anatomical distortion, removal of implants and endometrioma and resulting decreased inflammation, which has an effect on all aspects of fertility. Even in earlier stages of the disease, surgery has significant benefit over no intervention in terms of pregnancy rates.[67]

Medical Therapy of Endometriosis

Medical therapy as such is discouraged in patients with endometriosis who are trying to conceive as all therapies revolve around suppression of ovulation.[68] However, in the setting of IVF, gonadotropin-releasing hormone (GnRH) agonist therapy prior to IVF has proven to improve success rates.[69,70] Proposed mechanisms are by means of increased oocyte retrieval, higher implantation rates and reduced preclinical abortions[71] by suppressing the vicious cycle of inflammatory and immune processes. Similar to the GnRH agonist therapy, 4–6 weeks of continuous oral contraceptive pill therapy results in improved outcomes.[72]

ADVANCE TECHNIQUES NEEDING RESEARCH

A number of novel medical therapies are being currently examined for benefits in endometriosis related infertility. As research is throwing light on the various molecular mechanisms, the focus of treatment is gradually shifting from ablation or suppression of the disease foci to complete eradication of the disease by attacking the underlying process leading to persistence of the disease. Some of areas of focus are:

Stem Cell Therapy

Bone-derived stem cells can give rise to endometrial cells. Damaged endometrium can be replaced with stem cells. This is especially appealing given the epigenetic damage to the endometrium in women with endometriosis; epigenetic alterations are persistent, and at present, there are no known therapy to reverse this damage. Replacement of endometrium with a stem cell based therapy may be optimal way to restore normal endometrial function and implantation in women with endometriosis.[73]

Immunoconjugates (ICON)

They are meant to specifically target aberrantly expressed tissue factors on endometriotic endothelium and prompt regression of the disease probably by devascularization.[67] It has the potential to destroy preexisting implants in a non-toxic, non-hormonal manner, which could potentially improve fertility rates.

Aromatase Inhibitors

Aromatase is found in eutopic endometrium, where it is normally absent, which may impact estradiol levels and implantation. In fact, use of aromatase inhibitors has been shown to improve implantation in preliminary trials.[74]

Genetic Engineering

The underlying cause of all defects in endometriosis is gradually being traced to aberrant expression of genes due to abnormal hyper/hypomethylation of promoter or repressor regions without causing any change in the actual genetic makeup. Some of the genes involved are HOXA-10, progesterone receptor, E-cadherins, estrogen receptor and steroidogenic factor-1.[56,75] Potential future treatments could involve targeting these altered molecular pathways and correcting abnormal methylation.

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12

CHAPTER

Endometriosis and Leiomyoma

INTRODUCTION

Uterine leiomyomata or fibroids are the benign tumors ascending from monoclonal production of an altered myocyte, originating in the smooth muscle of the uterus. These leiomyomata's are unusually common with a predictable cumulative incidence, by the age of 50 years, of over 80% in black women and nearly 70% in Caucasian women.[1,2] Reason for the occurrence of uterine fibroids is unclear. While fibroids might be asymptomatic, numbers of females have regenerative troubles, metrorrhagia, menorrhagia, pelvic torment and weight, and urinary symptoms. They are the most widely recognized sign for hysterectomy in the United States. Leiomyomata are available in 5–10% of infertile patients.[3] Women with fibroids face a 10% threat of obstetrical difficulties, such as preterm labor or early pregnancy loss.[4] Myomectomy may enhance fertility and pregnancy results for some of the patients.[5,6]

INTERCONNECTION OF LEIOMYOMA WITH ENDOMETRIOSIS

Research studies have specified a substantial association between uterine fibroids and endometriosis. The purpose for this association still remains to be studied. A research study in 2016 assessed the rate of coexistence of endometriosis in women with symptomatic leiomyoma. In this 244 patients were treated at a tertiary medical care and were evaluated for symptomatic leiomyoma. 208 patients underwent laparoscopic or laparoscopic-assisted myomectomy or hysterectomy. The remaining 36 patients underwent medical therapy and were excluded from the study. Of the 208 patients with the giving chief fear of symptomatic leiomyoma and who underwent surgical therapy, 181 had concomitant diagnoses of leiomyoma and endometriosis, whereas 27 had leiomyoma. Of the 27 patients, 9 also had adenomyosis. Thus, the primary consequence measured was the coexistence of histology-proven endometriosis in women with symptomatic leiomyoma.[7] In a study in 2010, medical records of 131 patients who underwent laparoscopic myomectomy or hysterectomy were studied. Of the 131 patients, 113 were diagnosed with endometriosis and fibroids, while 18 were diagnosed with fibroids alone. Patients with fibroids were on average 4.0 years older than those with endometriosis and fibroids (41 vs. 45). Patients with both diagnoses were also more likely to present with pelvic pain and nulliparity than those with fibroids alone.[8] Another study in 2011 demonstrated that symptomatic endometriosis frequently gives the impression together with symptomatic fibroids, and that both of the circumstances have negative effects on female fertility independent of each other.[9]

An association between fibroids and endometriosis is not at all shocking, as both the circumstances are steroid-hormone reliant and act correspondingly under the effect of estrogen.[9-11] Ovarian and exogenous estrogen are the hormones in the body to which both these conditions (fibroids and endometriosis) have shown response. Moreover, both these conditions are known to show intrinsic estrogen production, as demonstrated by some cases of persistent disease subsequent to menopause and under exposure to gonadotropin releasing hormone agonist (GnRH-a) therapy.[12-15] There is an imbalance in the levels of aromatase and 17b-hydroxysteroid dehydrogenase (17b-HSD) in both these conditions which could be easily analyzed with molecular and biochemical studies. [1]

Aberrant aromatase activity and 17b-HSD type 2 deficiency have been established in endometriosis.[16,17] 17b-HSD type 2 in normal endometrium transforms the biologically active form, estradiol to inactive estrone.[16] In the case of leiomyomata, the contrary appears to be true. Owing to the improved activity of 17b-HSD type 1, inactive form estrone is transformed to active form of estradiol.[13] Increased levels of the estradiol occurs in both the conditions. Aromatase is easily detectable in the endometrosis while normal endometrial tissues when taken from patients with absence of uterine disease, does not reveal aromatase activity.[16] Steroid precursors are converted into estradiol and estrone by aromatase. Aromatase activity is also present in 90% of uterine leiomyomata and is not detectable in disease-free myometrium.[16]

Fibroids can be easily detected by imaging techniques, thus it becomes the primary reason for surgical intervention in the symptomatic patients. Patients, enduring surgery for symptomatic leiomyomata are at maximum threat for coexisting endometriosis, have a tendency to be younger, nulliparous, and with pain inconsistent to the size of their fibroids.[1] Infertility has been the major risk factor for the occurrence of these two conditions. It is extensively documented that women with

infertility issues have a greater occurrence of endometriosis and are more probable to have advanced-stage disease when associated with fertile women.[18] Additionally, treatment of endometriosis by laparoscopic methods have been shown to intensify the fecundity.[19,20] The effects of myomectomy on fecundity are not yet understood, management must be adapted for the affected patient.[21] Recent studies indicate that uterine fibroids might disturb uterine peristalsis, unfavorably distressing fertility, and that myomectomy might improve pregnancy outcomes.[6]

MANAGEMENT

The foremost concern for patients suffering with symptomatic fibroids ought to be recognizing the endometriosis that may also be present and should be concomitantly treated. Moreover, every situation might act as a reservoir for intrinsic estrogen and aromatase activity, possibly contributing to the reappearance of one or the other, if both are not systematically treated at the same time. It is reasonable that medical treatment for one might have coinciding benefits for the other, provided the hormonal similarities between leiomyoma and endometriosis and without a doubt, this is true. Both these conditions (leiomyoma and endometriosis) might respond to GnRH-a therapy, and aromatase inhibitors representing noteworthy promise in the management of both.[15,16] Treatment for both are inadequate by risk of osteopenia, and careful consideration should be given to the duration of treatment as well as use of the add-back therapy.[15,22,23]

When surgical methods of management are considered, the surgeon must deliberate the likelihood of co-occurrence of endometriosis.[1] The reverse case is also right. While carrying out diagnostic laparoscopy for pelvic pain, hysteroscopy should also be considered, as approximately 30% of patients with endometriosis will also have abnormalities on hysteroscopy.[24] In symptomatic patients, treatment by laparotomy or hysteroscopy will cause suboptimal treatment of endometriosis. Laparoscopy treatment offers superior visualization and access for biopsy in endometriosis than laparotomy.[1,25,26] Because of the substantial overlap in the symptoms united by both conditions and trouble in preoperative diagnosis, it might not be probable to regulate which is responsible for the patients' problems.[1,27] Consequently, all patients undergoing surgical management method for fibroids should meet the expense of a thorough and systematic assessment of the abdominal and pelvic cavities with thorough treatment of endometriosis. Recurrence of symptoms might occur when the patient fails to comply with the management methods.

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13

CHAPTER

Drug Therapy: Fibroid Versus Endometriosis

INTRODUCTION

Main aim of drug therapy in fibroid uterus is to get rid of correct anemia, unadorned pain, decreased size of fibroid preceding to myomectomy and to evade hysterectomy. Management of endometriosis with drug therapy provides suppression of active symptomatic disease such as pre-operative therapy in unadorned recurring endometriosis to assist surgical excision, as postoperative therapy if excision is not complete or in the management of recurrent disease and for anticipation of disease advancement when conception must be hindered. Drugs used in medical management of fibroid are given in Table 13.1.[1-7]

GONADOTROPIN RELEASING HORMONE AGONIST

A hypogonadotrophic-hypogonadism state is achieved by gonadotropin releasing hormone (GnRH) agonists by downregulation of the pituitary gland.

Indications of Use

These agonists helps to decrease the total uterine volume by 35% and fibroid volume by 30% when they are used for a period of 6 months in regular dosing schedule. Uterine size decreases in the first 3 months. If the GnRH is discontinued, menses return in 4–8 weeks' time and the uterus comes back to the pretreatment levels in 4-6 months.

Contraindication

- Pregnancy and breastfeeding.

Adverse Drug Reaction

- Headache
- Hot flushes
- Night sweats
- Loss of libido
- Osteoporosis
- Breast atrophy
- Depression
- Dry vagina

Drug Interactions

- Antidiabetic agents
- Mifepristone

TABLE 13.1: Drug therapy for management of fibroid and endometriosis[8-14]

Class	*Drug(s)*
Gonadotrophin releasing hormone agonists	Leuprolide, goserelin, buserelin, nafarelin, and triptarelin
Anti-gonadotropic agents	Danazol and gestrinone
GnRH antagonist	Cetrorelix and ganirelix
Progestins	Medroxyprogesterone acetate, Dienogest, dydrogesterone, and depot medroxyprogesterone acetate
Selective progesterone receptor modulators	Asoprisnil and ulipristal
Selective estrogen receptor modulators	Raloxifene
Non-steroidal anti-inflammatory drugs	Mefenamic acid, ibuprofen, diclofenac sodium
Combined contraceptives	Ethinyl estradiol plus levonorgestrel Contraceptive transdermal patch or vaginal ring
Aromatase inhibitors	Letrazole and anastrozole
Intrauterine progesterone	LNG -IUS
Antifibrinolytics	Tranexamic acid
Progesterone antagonist	Mifepristone
Newer drugs	Cabergoline and pirfenidone

(LNG–IUS, levonorgestrel-releasing intrauterine system; GnRH, gonadotropin releasing hormone agonists)

Monitoring

Monitoring is done by bone densitometry former to repeat course of treatment.

Dosage

The daily dose of GnRH agonist can be controlled by observing estradiol levels. Their side effects can be diminished by accumulation of small dose of progestin or estrogen-progestin in add-back regimens. Dosing schedule has been discussed in Table 13.2.

TABLE 13.2: Dosing schedule of GnRH agonist in fibroid and endometriosis.

GnRH	*Dosage*	*Preparations*
Nafarelin	200 µg intranasal twice daily	Synarel
Leuprolide	3.75 mg IM monthly 11.5 mg IM every 3 months	Lupron
Goserelin	3.6 mg SC monthly	Zoladex

(GnRH, gonadotropin releasing hormone agonists; IM, intramuscularly; SC, subcutaneously)

Nafarelin

Pharmacology: Nafarelin is a potent agonistic analog of GnRH. It helps in desensitizing response to endogenous GnRH, which in turn decreases secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) and consequently causing reduced ovarian and testicular hormone production. Its half-life is 3 hours, 80% protein bound with enzymatic hydrolysis and excreted in urine and feces. Its preliminary outcome occurs at 1 month and peak effect at 12 weeks on endometriotic implants.
Contraindications: There are some conditions in which the use of this medication is contraindicated such as pregnancy, lactation, undiagnosed and abnormal vaginal bleeding, and hypersensitivity, etc.
Indications of use: The medication is likely used for the management of endometriosis and fibroids.
Adverse drug reaction: Withdrawal bleeding.
Dosage: For the treatment of endometriosis, start the intake of medicine on day 2–4 of menstrual cycle with initial dose of 1 spray twice daily maximum of µg intranasally per day.

Leuprolide

Leuprolide is easily accessible in the form of depot injec-tions which is used in the treatment of endometriosis including respite in pain and decline of the size. It is also used for the management of anemia caused due to fibroids.

Goserelin

Goserelin is easily accessible in the form of implantable cylinder placed subcutaneously. This medication gets metabolized in liver and is excreted in the form of urine. Implants with Goserelin 3.6 mg is administered subcutaneously every 28 days. Add back therapy is given to preclude vasomotor symptoms.

ANTIGONADOTROPIC AGENTS

Antigonadotropic agents show their action by suppressing the hypothalamic-pituitary-ovarian axis thereby preven-ting the mid-cycle FSH and LH surge and inhibiting steroidogenesis in the corpus luteum. They also suppress endometriosis at a local level.

Danazol

Pharmacology

Danazol is a derivative of the synthetic steroid ethisterone, a modi-fied testosterone. Danazol has antigonadotropic and anti-estrogenic activities. Danazol acts as an anterior pituitary suppressant by inhibiting the pituitary output of gonadotropins. It possesses some androgenic properties. Danazol suppresses the pituitary-ovarian axis possibly by hindering the production of pituitary gonadotropins. Dana-zol depresses the preovulatory surge in output of follicle-stimulating hormone (FSH) and luteinizing hormone (LH), thereby reducing ovarian estrogen production.

Danazol acts by meddling with autocrine and paracrine functions. It reduces the number of endometrial growth factor receptor, which has a potential role in preservation of ectopic endometrial tissue. It also inhibits the production of interlukin 1-β and tumor necrosis factor. Peak levels are reached in 2 hours; it gets extensively metabolized in the liver to 2-hydroxymethyl ethisterone. Half-life is 24 hours. It is highly concentrated in liver, adrenals and kidney. Its complete clearance is done by liver in 8 hours and is excreted in feces and urine.

Contraindication

- Pregnancy
- Breastfeeding
- Porphyria
- Undiagnosed abnormal genital bleeding
- Hypersensitivity
- Liver, renal, and cardiac disease, etc.

Indications of Use

- Endometriosis
- Fibroid (reducing fibroid size slightly and minimizing blood loss or even producing amenorrhea).

Adverse Drug Reaction

- Weight gain
- Acne
- Hirsutism
- Edema
- Hair loss
- Deepening of voice
- Flushing.

Drug Interaction

- Warfarin
- Carbamazepine
- Statins
- Cyclosporine.

Dosage

- Endometriosis:
  - Mild: 200–400 mg/day orally twice daily
  - Moderate-to-severe: 800 mg/day orally twice daily.

Dose should be titrated downward to a dose adequate enough to preserve amenorrhea. Therapy is sustained for 6 months or can be persistent up to 9 months.

- Fibroid: 200–400 mg/day orally for 3 months.

Monitoring

Danazol is monitored by liver function test and kidney function test at 4 weeks interval, signs, and symptoms of intracranial tension (papilledema, headache, nausea, and vomiting), lipo-proteins and androgenic changes.

Preparation

- Gonablok, gynazole: 50, 100, 200 mg capsules
- Endozol, gynadom: 100 and 200 mg tablets.

Safety during Pregnancy

Pregnancy category X, breastfeeding is contraindicated.

Gestrinone

Gestrinone, also identified as ethylnorgestrienone, is a synthetic steroid of the 19-nortestosterone group with androgenic, antiestrogenic, antiprogestogenic, and anti-gonadotrophic activities.

Pharmacology

Gestrinone shows its action by acting centrally and peripherally to rise up the level of free testosterone and decrease sex hormone binding globulin (androgenic effect), reducing the serum estradiol values to initial follicular phase levels (antiestrogenic effect), decrease, mean LH levels, and eradicate the FSH and LH surge (antigonadotrophic effect). It also causes cellular inacti-vation of endometriotic implants. Amenorrhea occurs in 50–100% of women and resumption of menses after 33 days of discontinuation. Half-life is 28 hours.

Indications of Use

- Endometriosis
- Fibroid uterus
- Benign breast disease.

Adverse Drug Reaction

- Acne
- Nausea
- Seborrhea
- Breast hypotrophy
- Muscle cramps
- Weight gain
- Oily hair and skin.

Contraindications

- Pregnancy (causing masculinization of female fetus)
- Renal, hepatic, cardiac, metabolic, and vascular dis-orders.

Drug Interaction

- Antiepileptic drugs
- Rifampicin.

Dosage

For the proper dosing schedule, 1.25-2.5 mg orally is taken twice weekly, starting on the first day of cycle with second dose 3 days later. Repeat on the same days of the week and preferably at the same time for about 6 months.

Marketed Preparations

- Dimetrios
- Dimetros
- Florizel—2.5 mg

Safety during Pregnancy

Contraindicated in pregnancy. Pregnancy category X.

GnRH ANTAGONISTS

Cetrorelix and Ganirelix

Pharmacology

Both the GnRH antagonists cause abrupt suppression of endogenous GnRH and are deliberated for medical treatment previous to surgery in case of fibroid and endo-metriosis. The drugs are rapildy absorbed subcutaneously with extreme plasma concentrations occurring 1–2 hours after administration.

Indications of Use

Ganirelix brings about 29% decrease in fibroid volume in 3 weeks.

Contraindications

- Hypersensitivity
- GnRH analog
- Pregnancy and lactation
- Severe renal impairment.

Dosage

- In case of endometriosis: 3 mg subcutaneously, once a week for 8 weeks.
- In case of fibroid: 3 mg subcutaneously, every 4 days for 2–4 weeks prior to surgery. Treatment is commenced on first day of periods.

Adverse Drug Reaction

- Headache
- Mood swings
- Hot flushes
- Vaginal dryness
- Spotting.

Marketed Preparations

Marketed preparations for GnRH antagonists have been specified in Table 13.3.

Safety during Pregnancy

Contraindicated in pregnancy and lactation.

PROGESTINS

Pharmacology

All the progestational agents show their action by decidualization and atrophy of the endometrium. These effects are intervened directly by cellular hormonal receptors and are revealed to comprise fluctuations in estrogen metabolism in

TABLE 13.3: Marketed preparations for GnRH antagonists.

GnRH antagonists	*Marketed preparations*	*Dosage*
Cetorelix	Cetrotide, cetace, ovuralix	0.25 mg injection for subcutaneous use
Ganirelix	Orgalutran	250 µg/0.5 mL for subcutaneous injection

the endometrial tissue. Use of this category of drugs depends on high-dose hormones which prevents ovulatory function and induce amenorrhea. Progestins are also known to have suppressive outcome on the expression of endometrial matrix metalloproteinases which contributes to the pathogenesis of endometriosis.

Contraindications

Depot medroxyprogesterone acetate is contraindicated in infertile women as it causes profound amenorrhea and anovulation and the time mandatory for ovulation to recommence after discontinuation varies.

Indications of Use

- Endometriosis to reduce pelvic pain
- Reducing uterine bleeding by 30–70% in cases of fibroid uterus
- As progestin only contraceptives
- Progestin implants, injections or pills may be used.

Adverse Drug Reaction

- Nausea
- Weight gain
- Fluid retention
- Breakthrough bleeding
- Depression
- Mood disorders.

Dosage

The progestins used to decrease bleeding from fibroids and lessen pelvic pain in endometriosis are briefly described in Table 13.4.

SELECTIVE PROGESTERONE RECEPTOR MODULATORS

Selective progesterone receptor modulator (SPRM) is a new class of progesterone receptor modulators that acts on progesterone receptors. These modulators have emerged as a valuable management option for hormone dependent circumstances like uterine fibroids, which have a major impact on women's quality of life. They modulators utilize tissue selective progesterone agonist, antagonist or mixed agonist-antagonist effects on various tissues including the endometrium.

Asoprisnil

Pharmacology

Asoprisnil is an orally active SPRM used in controlling the symptomatic uterine leiomyomata, as it suppresses both the duration and intensity of menstrual bleeding in a dose-dependent method. Asoprisnil establishes a high degree of receptor and tissue selectivity, with high-binding affinity for PR, moderate affinity for glucocorticoid receptor (GR), low affinity for androgen receptor (AR), and no binding affinity for estrogen or mineralocorticoid receptors. Use of this drug causes statistically significant decrease in frequency and intensity of uterine bleeding and decreases fibroid size by 35–40%.

TABLE 13.4: Dosages for progestins for use in fibroid and endometriosis.

Progestin	*Dosage*
Lynestrenol	10 mg daily orally
Depot medroxyprogesterone acetate	150 mg IM every 3 months
Dienogest	2 mg once daily
Medroxyprogesterone acetate	30 mg orally daily, max 100 mg daily

Indications of use

- Fibroids
- Endometriosis.

Adverse Drug Reaction

- Breast pain
- Bloating
- Night sweats
- Aymptomatic ovarian cysts
- Flatulence
- Hot flushes.

Dosage

Asoprisnil is to be taken 5–25 mg orally on daily basis.

Ulipristal Acetate

Pharmacology

Ulipristal is a selective progesterone receptor modulator used for the management of uterine fibroids (Fibristal). It is a derivative of 19-norprogesterone having both antago-nistic and partial agonist activity at the progesterone receptor. Ulipristal binds to glucocorticoid receptor, and has lower glucocorticoid activity and better binding affinity.[15-17]

Indications of Use

- Fibroid uterus.

Contraindications

- Uterine, cervical, and ovary and breast cancers
- Genital bleeding of unknown etiology
- Severe liver disorders.

Dosage

Ulipristal acetate is to be given 5 mg orally daily for only 3 months.

Adverse Drug Reaction

- Headache
- Nausea
- Abdominal pain.

Drug Interactions

- Antifungals
- Barbiturates
- Digoxin
- Hormonal contraceptives.

Monitoring

Evaluate if persistent vaginal bleeding.

Marketed Preparation

- Fibristal 5 mg tablet

Safety during Pregnancy

- Pregnancy category X.

Food Drug Administration Approval

It has been licensed in Europe for use in medical treatment of fibroids since 2012.

SELECTIVE ESTROGEN RECEPTOR MODULATORS

Raloxifene

Pharmacology

It acts as partial estrogen agonist in bone and cardiovascular system (CVS) while acts as antagonist in endome-trium and breast. It has long half-life so single dose is administered. It decreases size of fibroid but has no effect on uterine bleeding. Its role in endometriosis is unclear.

Contraindications

- Active or past history of venous thromboembolism
- Coronary artery disease.

Dosage

Raloxifene is given 60 mg orally per day.

Adverse Drug Reaction

- Vaginal bleeding
- Leg cramps
- Hot flushes
- Increased risk of Deep vein thrombosis (DVT)
- Pulmonary embolism.

Drug Interaction

- Warfarin
- Lidocaine
- Cholestyramine
- Diazepam
- Hormone replacement therapy.

Monitoring

- Bone mineral density
- Lipid profile
- Endometrial sampling if indicated due to abnormal uterine bleeding.

Marketed Preparations

- Ralotab
- Rolafen
- Ralista
- Gynista—60 mg tablets.

Safety during pregnancy

Not safe in pregnancy.

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

Endometriosis is a gynecological form that normally affects women of childbearing age causing painful symptom such as pelvic and lower abdominal pain, pain during or after sexual intercourse, painful periods and infertility. Nonsteroidal anti-inflammatory drugs (NSAIDs) are most commonly used as first-line treatment for women with endometriosis because they have few side effects, and many are available over the counter. These drugs block the synthesis of the prostaglandins, which contribute to pain and inflammation in endometriosis. Most commonly used NSAIDs include mefenamic acid, ibuprofen and diclofenac sodium. Many research studies have reported that NSAIDs are not at all effective for the management of menorrhagia in women with fibroids.

COMBINED CONTRACEPTIVES

Combined contraceptives are the contraceptive pills available in combination form which acts by suppressing the action of ovary. These contraceptives show their action by changing the levels of estrogen and progesterone in the body causing low enough estrogen level thereby controlling the growth of fibroid. Thus, pseudodecidualization of endometrium occurs and brings about atrophic changes in the endometriotic implants. At first, a trial of continuous or cyclic combined oral contraceptives should be given for a period of about 3 months. If the patient's pain is dismissed, this treatment is sustained for about 6–12 months. Subsequent pregnancy rates are 40–50% upon discontinuation of the contraceptive pill.

Dosage

- Ethinyl estradiol 0.03 mg in combination with levonorgestrel 0.15 mg daily taken either in cyclical or continuous manner
- Contraceptive vaginal ring—releases on average 0.120 mg of etonogestrel and 15 μg of ethinyl estradiol per day
- Transdermal patch Ortho Evra—releases 150 μg of norelgestromin and 20 μg of ethinyl estradiol into the blood per day.

AROMATASE INHIBITORS

Letrozole and Anastrozole

Pharmacology

These aromatase inhibitors help to block the aromatase activity in extra-ovarian sites suppressing the conversion of androstenedione and testosterone to estrogen. This process causes suppression of endometriosis at a local level. Letrozole is rapidly absorbed with 100% bioavailability and causes decrease in E2 levels while the bioavailability for anastrozole is 85%.

Indications of use

- Fibroid
- Endometriosis.

Contraindication

- Pregnancy.

Dosage

- Letrozole is given 5 mg orally daily for 3 months.
- Anastrozole 1 mg is given daily for 3 months orally and is effective in dropping the volume of fibroids by an average of 9.32% and control of symptoms without changes in levels of FSH and estradiol.

Adverse Drug Reaction

- Diarrhea
- Hot flushes
- Nausea
- Dyspepsia
- Thinning of hair.

Drug Interaction

- Tamoxifen

Marketed Preparations

Aromatase inhibitors are easily available in the market in tablet forms (Table 13.5).

Safety during Pregnancy

Contraindicated in pregnancy.

INTRAUTERINE PROGESTERONE

Levonorgestrel-Releasing Intrauterine System (LNG-IUS)

Indications of Use

- Menorrhagia associated with fibroids when the size of uterine is not larger than 12 weeks with normal cavity.
- Endometriosis with substantial development in severity, frequency of pain and menstrual symptoms is seen. Endometriosis related pain caused by peritoneal and rectovaginal endometriosis and risk of recurrence of dysmenorrhea after conservative surgery is decre-ased.

Contraindications

- Liver disorders
- Pelvic inflammatory disease
- Suspected uterine or cervical cancer.

Drug Interaction

- Warfarin
- Steroids
- Insulin.

Adverse Drug Reaction

- Headache
- Breast tenderness
- Acne
- Irregular bleeding.

Monitoring

Check for proper placement of intrauterine device (IUD).

Dosage

It releases 20 µg per day of levonorgestrel.

Marketed Preparation

- Mirena.

Safety during Pregnancy

Mirena is to be removed if woman becomes pregnant.

TABLE 13.5: Marketed formulations for aromatase inhibitors.

Aromatase inhibitors	*Dosage*	*Brand*	*Formulation*
Letrozole	2.5 mg	Letroz, Letoval	Tablet
Anastrozole	1 mg	Altraz, Armotraz	Tablet

ANTIFIBRINOLYTICS

Tranexamic Acid

Pharmacology

Tranexamic acid is an antifibrinolytic that competitively inhibits the activation of plasminogen to plasmin. It is a synthetic derivative of lysine. Absorption of tranexamic acid after oral administration in humans represents approximately 30–50% of the ingested dose and bioavailability is not affected by food intake.

Indications of Use

First-line nonhormonal therapy for menorrhagia associated with uterine fibroids and dysfunctional uterine bleeding.

Contraindications

Disseminated intravascular coagulation from upper, genitourinary bleeding tract, e.g. kidney and ureters.

Dosage

- For menorrhagia: 10–15 mg/kg of body weight or 500 mg orally 2–3 times a day for up to 5 days during monthly menstruation for menorrhagia
- In severe bleeding: 500–1000 mg slow IV 2–3 times a day can be given.

Adverse Drug Reaction

- Nausea
- Diarrhea
- Thromboembolic events
- Disturbed color vision
- Allergic reactions.

Drug Interaction

- Antifibrinolytic agents
- Fibrinogen concentrates
- Hormonal contraceptives
- Tretinoin.

Monitoring

No specific laboratory test is required. Observe the symp-toms of severe allergic reactions and any changes in vision.

Marketed Preparations

Antifibrinolytics are easily available in the market in various dosage forms (Table 13.6).

Safety during Pregnancy

Pregnancy category B.

PROGESTERONE ANTAGONISTS

Mifepristone

Mifepristone is a progestational and glucocorticoid hormone antagonist. Inhibition of progesterone induces bleeding during the luteal phase and in early pregnancy by releasing endogenous prostaglandins from the endo-metrium or decidua. It is a 19-norsteroid derivative with potent antiprogestational and significant anti-glucocorticoid and anti-androgenic activity.[18-21]

Pharmacology

Mifepristone has a noncompetitive antiestrogen action. It helps in blocking the endometrial tissue to grow in response to estrogen, thereby used in the treatment of endometriosis and fibroid. It is orally active but only 25% is bioavailable. It is largely metabolized in liver and excreted in bile.

Indications of Use

It is used for treatment of fibroid associated menorrhagia and to reduce the size of fibroids. Around 48% decrease in mean uterine volume is noted after 6 months.

Contraindications

- Hemorrhagic disorders
- Inherited porphyria
- Adrenal failure
- Long-term corticosteroid therapy.

Adverse effects

- Endometrial hyperplasia
- Elevated liver enzymes
- Hot flushes.

Drug Interactions

- CYP3A4 inhibitors (erythromycin, and ketoconazole)
- Inducers (rifampin and anticonvulsants).

TABLE 13.6: Marketed formulations for antifibrinolytics.

Antifibrinolytics preparations	*Formulation*
Pause	500 mg and 1 g tablets 500 mg injection per 5 mL vial
Texid	500 mg tablets 500 mg injections
Tranarest	250 mg tablets 500 mg tablets

Dosage

- In fibroid uterus: 2.5–50 mg orally daily for 3 months
- In endometriosis: 25–50 mg orally daily for 3 months.

Marketed Preparations

- Mifegest
- Mifeprin
- Mifty
- Colestone: 200 mg tablets.

Safety during pregnancy and lactation

Pregnancy category X. No data on excretion of mifepristone in breast milk.

NEWER DRUGS

Cabergoline

Cabergoline, an ergot derivative (lysergic acid derivative), is a long-acting dopamine agonist and prolactin inhi-bitor. It is used for the management of leiomyoma uteri. Cabergoline possesses potent agonist activity on dopamine D2 receptors. This drug has inhibitory effect on GnRH secretion because of the dopaminergic effect.[22] Various research studies have evaluated cabergoline as a therapeutic option for uterine leiomyomas. The rational for such an approach lies in its effect as an inhibitory agent on GnRH release. A study conducted in Iran favored the use of cabergoline as a medical treatment for uterine leiomyomas, in which a volume reduction of about 50% with 6 weeks of use was reported. These findings clearly assess the potential use of carbergoline in the treatment of uterine leiomyomas.[23]

Pirfenidone

Pirfenidone is orally active small molecule drugs that might hinder the collagen synthesis, downregulate the production of multiple cytokines and block the action of fibroblast proliferation and stimulation in reaction to cytokines. It is a new drug which that blocks the growth of existing fibroids and may stop formation of new fibroids. Exact mechanism of action of this new drug is not known yet. But, however it affects the production of collagen, a major component of fibroid and may have effect on cell growth factor. However, it not available and studies are under way to establish its safety and efficacy. Pirfenidone is an effective inhibitor of myometrial and leiomyoma cell proliferation in vitro and decreases the messenger RNA intensities of collagen types I and III in a dose-dependent manner. This compound might substantiate to be an effective nonsteroidal therapy for treatment of uterine leiomyomas.[24]

CONCLUSION

Endometriosis and uterine fibroids (also recognized as uterine leiomyomas) are the serious medical conditions distressing large numbers of women worldwide. Many women are asymptomatic but those with symptoms have need of medical intervention to get rid of chronic pain and dysmenorrhea and to address infertility. Drug delivery has played a role in reducing some of the symptoms associated with endometriosis and uterine fibroids.

TABLE 13.7: Summary of drugs used in medical management of fibroid and endometriosis.

Drug class	*Mode of action*	*Effect*	*Adverse/Side effects*
GnRH agonists	Suppression of ovarian steroidogenesis production—delayed pituitary downregulation	Fibroid size and symptom reduction up to 50% within 3–6 months	Hot flashes, vaginal dryness, and headaches. Prolonged use associated with reduced bone mineral density
GnRH antagonists	Suppression of ovarian steroidogenesis production—immediate pituitary downregulation	Reduction in fibroid size 25–40% and symptom improvement within 3 weeks	Hot flashes, vaginal dryness, and headaches. Prolonged use associated with reduced bone mineral density
Progestins	Endometrial stabilization/atrophy and variable effects on leiomyomas	Mixed results—both fibroid shrinkage and enlargement have been shown; may induce amenorrhea	Use judiciously—progesterone may promote fibroid growth (increased mitotic activity)
Mixed progesterone receptor antagonist/ agonists	Local progesterone mediated effects on leiomyomas and endometrium	Decreased menstrual bleeding (up to 80%) and fibroid size reduction up to 36% within 12 weeks, may induce amenorrhea	Maintains follicular phase estrogen levels, no adverse endometrial effects-causes nonphysiologic secretory changes (clinical relevance unknown)
Mixed estrogen receptor antagonist/ agonists	Estrogen antagonist effects on fibroid and endometrium	Inconsistent results—trend to decreased fibroid size in small heterogeneous studies	Leg cramps and hot flashes. Increased risk of thromboembolic events
Androgens	Combination hormonal and vascular effects (androgenic, progestogenic, antiprogestogenic, and antiestrogenic actions)	24% fibroid size reduction in 4 months, may improve bleeding symptoms	Weight gain, edema, acne, oily skin, hirsutism, voice changes, headaches, hot flashes, altered libido, decreased breast size, and muscle cramps
Oral contraceptives	Endometrial stabilization and variable effects on leiomyomas	May improve uterine bleeding, but no significant decrease in fibroid size	Use judiciously—both estrogen and progesterone may promote fibroid growth (increased mitotic activity)
Aromatase inhibitors	Reduces estrogen synthesis and effects	Fibroid size reduced 60–70% within 1–2 months in a case report	Hypoestrogenic side effects; further studies needed
Antiprogestins	Antiprogesterone effect—reduces action and number of progesterone receptors in fibroids and myometrium	Improved symptoms in 60–75%, may induce amenorrhea, reduction in fibroid volume 25–50% within 3 months	Hot flashes, elevated hepatic enzymes, and endometrial hyperplasia
Antifibrotics	Interfere with growth factors, leiomyoma cell proliferation, and extracellular matrix/ collagen production	Interfere with fibroid growth	Long-term effects not known, further studies needed

(GnRH, gonadotropin releasing hormone agonists)

TABLE 13.8: Outcomes of medical therapy in fibroid.

Drug type	*Product*	*Effect on fibroid size*	*Effect on abnormal uterine bleeding*	*Effect on fertility*
Nonhormonal	NSAIDs and tranexamic acid	No effect on fibroid size	Decrease by 30%	No effect
Hormonal	Combined oral contraceptive	No data	Decrease 20–30%	Contraceptive
	GnRH analog (3–6 months duration of therapy)	Decrease 30%	Decrease >80%	Contraceptive
	Oral progestins	Decrease 30%	Decrease >60%	Contraceptive
	Long-acting reversible contraceptive (e.g. Depoprovera, Implanon)	Decrease uterine volume by 35%	Breakthrough bleeding	Contraceptive
	Levonorgestrel intrauterine device (Mirena)	Decrease 20–30%	Decrease 40%, No systemic side effects	Contraceptive

(NSAIDs, Nonsteroidal anti-inflammatory drugs; GnRH, gonadotropin releasing hormone agonists)

The mechanism of action, effects on fibroid or endometriosis, and adverse effects of all the drugs used in management of fibroid endometriosis is summarized in Table 13.7. Summary of therapeutic effects of these drugs on fibroid is given in Table 13.8.

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