Endometriosis

A Review

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• **Endometriosis, the cause of which is unknown, is on the increase. Treatment is surgical—conservative in the childbearing years. Hormonal therapy is sometimes palliative for a time, and the disease may regress during pregnancy. Endometriosis of the bowel should be borne in mind in the differential diagnosis of partial obstruction.**

The literature contains reports of 14 cases of ovarian carcinoma arising from endometriosis.

THAT THERE IS GREAT INTEREST in endometriosis is well borne out by the accumulated literature on the subject since Sampson's[51] paper on perforating hemorrhagic cysts of the ovary appeared in 1921. A condition which seemed rare as a gynecological entity in the twenties is today one of the most common causes of pelvic invalidism in this country, either as a single pathological condition or in association with other pelvic diseases such as fibroids, chronic inflammatory disease, ovarian neoplasms and adenomyosis. It may occur rarely in a teen-aged girl but is most prevalent in the third and fourth decades of life. The process is one occurring during the menstrual life of woman but has been found after the menopause in association with other pelvic disease such as granulosa cell tumors, fundal adenocarcinomas and myomas.

The diagnosis of endometriosis is on the increase. This is shown by the statistical reports of numerous investigators on proven microscopic studies of the pelvic tissues removed at laparotomy. Still, many cases with gross characteristic changes are diagnosed at the operating table but the diagnosis is not substantiated by the pathologist at later study. Many times the specimen looks different after standing, and the smaller lesions cannot be recognized in the laboratory unless definitely marked at the time of removal.

The medical profession is also more alert to the pelvic symptoms and changes associated with endometriosis. This has led to a more critical survey of the history of this condition and to closer observation and examination of patients both pelvically and rectally. Nevertheless, if there is also some other pelvic pathologic condition to confuse the issue, the presence of endometriosis may remain obscured until direct observation is made at the operating table.

The incidence in various classifications of patients has been reported by a number of observers, and it is obvious from these studies that endometriosis is a disease of white women in the higher economic brackets. This fact led Meigs[32] to postulate that the reason endometriosis is more common in patients observed in private practices is that young women in this stratum marry later in life and have fewer pregnancies than do those who are observed in clinics. He expressed belief that infrequent interruptions of menstrual cycles due to present day contraception and late marriages may well account for this greater number of cases of endometriosis. Infection does not seem to increase the incidence, as it is uncommon in the negro race.[18,44] Blinik and Merendino[3] noted endometriosis in 0.11 per cent of 4,477 cases in which laparotomy was done in the Harlem Hospital. It is also rarely encountered in South America, as cited by Greenhill[18] from the observations of Correa de Costa in 1946, who noted 32 cases of endometriosis in 2,285 laparotomies, an incidence of 1.44 per cent. Data from various investigators may be compared in Table 1.

The cause of endometriosis is still unsolved although a great amount of clinical and experimental work has been reported in the literature to clarify understanding of this moot question. Sampson's[54] theory of tubal regurgitation of menstrual fluid with implantation and seeding of viable menstrual endometrium is yet to be proven. To be sure, endometrium has been transplanted in various animals and organs, but no one has proven that shed menstrual endometrium is capable of transplanting itself nor that this tissue is viable. Specimens of endometrium removed by curette at the time of menstruation and then implanted have grown, but this is in all probability impertinent, for undoubtedly the specimen obtained by this means is endometrium of the basal layer, which is known to be prolific. Tissue cultures have shown that endometrium taken at the time of menstruation is less viable than that taken during the proliferative phase. Desquamated or dislodged mucosa has been seen in the lymphatic and venous spaces, but whether this tissue is capable of implantation and growth is problematic. Keettel and

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TABLE 1.—*Incidence of Endometriosis as Reported by Various Investigators*

Reported by	Year of Report		Number of Laparotomies	Cases of Endometriosis	Incidence (Per Cent)
Sampson	1925		332	98	29.5
Fallas and Rosenblum	1940		15,975	....	1.62
Meigs	1941	Private practice	400	144	36.0
		Clinic	400	33	8.3
Holmes	1942		307	80	26.0
Haydon	1934		620	52	8.4
	1940		713	94	13.1
Correa de Costa	1946		2,285	33	1.44
Scott and Te Linde	1950		516	....	15.9

Stein[28] reported successful tissue culture of cast-off menstrual endometrium with the addition of penicillin and streptomycin for bacteriostasis. Te Linde and Scott[48] and Allen, Peterson, and Campbell[1] produced experimental endometriosis in monkeys by various operative procedures. Te Linde and Scott believed their work substantiates Sampson's theory, but this has been challenged by Novak and others who favor the Iwanoff-Meyer theory of coelomic metaplasia as the cause of endometriosis. Allen, Peterson, and Campbell[1] conjectured from their experimental work that if menstrual discharge does bring about endometriosis, there must be an irritating substance as an etiologic factor that passes through the myometrium and mucosa. Their experiments in monkeys with the transected cervix implanted extraperitoneally suggested heteroplasia rather than transplantation, and this view supports the coelomic metaplasia theory. Scott and Te Linde[48] took venous blood from a monkey's vein at the time of menstruation and injected it intraperitoneally in four animals without bringing about endometriosis. This suggests very strongly that venous blood lacks some component substance that is capable of causing coelomic metaplasia and resulting endometriosis.

The coelomic metaplasia theory in simple form merely is that the müllerian duct is derived from the embryonic coelomic epithelium and mesenchyme, and forms most of the female genital tract, including the endometrium. Other adult tissues derived from coelomic epithelium may retain the potentiality of forming tissue which is indistinguishable from endometrium. Just what stimulates this differentiation of tissues, whether hormones or what not, is still a mystery. It is felt by most investigators that this theory explains most adequately the greatest distribution of endometriosis, coupled with an embryologic basis, as explained by Gruenwald.

Another theory known as the "metastatic spread" theory was offered by Halban and Sampson and was championed by Javert.[24] This really deals with a mode of spread rather than the cause of endometriosis. It explains very well the involvement of lymphatic nodes in the pelvis, the groin and along the channels to the round ligaments, and venous channels through the vertebral circulation to distant points of involvement, such as the arms and legs. But whether these findings within lymph nodes are due to metastasis of endometrial cells or are due to metaplasia of the lymphatic endothelium and stromal cells is not known. Nor is it known if the endometrial tissue within these lymphatic spaces or venous spaces is capable of propagation. It is generally felt that no single explanation seems to fit all situations, but that one theory may be applicable in some cases and another theory in others.

TABLE 2.—*Fertility in Patients with Endometriosis as Reported by Various Investigators*

Reported by	No. Cases	Per Cent Fertile
Counseller	131	32.1
Payne	238	40.0
Haydon	168	53.0
Keene and Kimbrough	118	40.9
Jenkinson and Brown	39	34.0

The symptoms of endometriosis vary in frequency and intensity, although in this regard some of the reported variation may depend upon the observers evaluation. Some patients with extensive involvement in the pelvis may have little in the way of pelvic discomfort or pain, while others with small lesions along the uterosacrals and in the cul de sac may complain bitterly of dyspareunia and pressure on the rectum with pain extending to the back and radiating down the legs. The classical symptoms of progressive dysmenorrhea, menorrhagia, metrorrhagia, dyspareunia and infertility may all be present or lacking in an individual case. At times menorrhagia is a prominent symptom, particularly if associated with other pelvic pathologic conditions such as fibroids, endometrial hyperplasia or polyps. On the other hand, with minimal lesions it may be entirely absent as a symptom. Infertility is relative and frequently is the factor that causes the patient to consult a physician. Reynolds and Macomber expressed belief that the normal fertility rate in marriage is about 88 per cent. In patients with endometriosis, the percentages of fertility noted by various investigators are shown in Table 2.

Because pregnancy is frequent enough following

conservative operation, when it is possible in endometriosis, the surgeon must always bear in mind the importance of preserving the childbearing function. The treatment should be individualized to suit the case under consideration, for it is impossible to make rules to fit all cases. If the disease is not too extensive, conservative operation should be employed to preserve the possibility of future pregnancy, with the patient's full understanding that further operation may be necessary in the future.

In the majority of cases, as was pointed out by Sampson,[54] the tubes may be patent (both tubes were patent in 284 of 293 cases of endometriosis). The ovaries may be extensively involved but the endometrial cysts may be dissected out and some ovarian tissue conserved. Smaller areas of endometriosis may be resected or destroyed by cautery unless they involve the muscle layer of the bowel, particularly in the rectovaginal septum. If, however, one explores a patient of any age and there is found extensive involvement with implants involving the sigmoid, rectum or ileum, it may really be conservative to be radical and remove both ovaries, both tubes and the entire uterus. If that is done, the residual small endometriomas in the bowel wall will regress and the bowel will return to normal function, unless too much scarring has occurred. In that event resection may become necessary. The ovaries should never be removed and the uterus left in situ. Total hysterectomy should be practiced if it is at all possible without adding too much risk to the patient's survival. With extensive involvement in the cul de sac and rectovaginal septum, great care must be exercised not to injure the rectum; this entails staying in good cervical tissue in the dissection and leaving endometriosis on the bowel wall. Many observers have set 45 years as the age limit for conservative operation if the patient desires to have a family; and they carry out radical operation if the patient is beyond this age. One must still keep in mind that the treatment of endometriosis is surgical and therefore destructive in principle. Since ovarian function is essential in the metabolism of bone and skin of woman, this tissue should be conserved whenever and for as long as possible.

Physicians must keep the possibility of endometriosis in mind and include it in differential diagnosis if the more unusual lesions of the intestinal tract are to be recognized. Recurrent abdominal pains and symptoms of partial obstruction appearing during the premenstrual phase must arouse suspicion of bowel endometriosis. The sigmoid and rectum are more frequently involved than the small bowel. The lesion encroaches on the bowel lumen from without and a mass may be palpated on rectal examination. The patient may have pain on defecation, particularly during menstruation, and there may be a slight amount of rectal bleeding at this time if the lesion has eroded the bowel mucosa. Proctoscopic examination may show the mucous membrane to be intact and x-ray examination may be of great aid in such cases by showing an extrinsic lesion with normal appearing mucosal pattern. The crux of the situation is that the lesion may be confused with carcinoma of the rectum or sigmoid and a colostomy performed for a benign tumor. This should not occur if one keeps the possibility in mind. Examination of a frozen section before definitive operation is done may save the day. Proper bowel preparation is imperative if there is a possibility that resection of the large bowel will be carried out. However, as was stated before, the bowel lesions will recede with total ablation of the ovaries, so resection is rarely necessary.

Obstruction of the ileum by endometriosis presents a less characteristic picture than that of the large bowel. Vomiting is a frequent symptom, diarrhea is infrequent and constipation is rare. X-ray films may demonstrate obstruction of the small bowel. It may be confused with appendicitis and certainly will be missed in the differential diagnosis unless endometriosis is constantly kept in mind and the symptomatology is correlated with the menstrual cycle. A pelvic and combined rectal-pelvic examination may aid greatly in the diagnosis, if endometriomas are palpable in the cul de sac or along the uterosacral ligaments.

Endometriosis is probably much more often associated with pregnancy than one would be led to believe from the current literature. Many women become pregnant with minimal lesions and the diagnosis is not made during the prenatal examination, delivery, or puerperium because the course has been normal and nothing has brought the condition to the attending physician's attention. The most common site is in the cul de sac, the rectal shelf or along the uterosacral ligaments. The lesions usually increase in size and are firm until about the fourth month; then they begin to soften and recede, so that at times it is difficult to know such a process is present unless it had been previously noted.

In 1944 Scott[42] searched the literature for cases of endometriosis complicated by pregnancy. He found reports of 11, involving the posterior cul de sac or rectovaginal septum. The ovaries were involved next most frequently. There were four such cases and he added reports of two more, in one of which the patient had a ruptured ovarian endometrioma, caused by tearing of adhesions by the enlarging uterus. In the second case the patient, in early pregnancy, had a right ovarian cyst the size of a grapefruit. At operation there was found also a small chocolate cyst on the left ovary, which could be resected. There were adhesions between the right

ovary and broad ligament, and in the region of the lower segment and sigmoid colon. This area was stained with old chocolate material, although no leaking area could be demonstrated. The postoperative course was uneventful and antinatal progress was normal. Spontaneous labor occurred in the thirty-fifth week and a boy weighing 2,390 gm. was delivered. The blood pressure and urine were normal but the placenta showed a small area of separation.

Scott also noted reports of cases in less common sites associated with pregnancy—two cases of cervical endometriosis, one case in the anterior cul de sac, one case in the inguinal canal associated with endometriosis of the appendix, and one case of endometriosis of the ileum with rupture of the viscus and generalized peritonitis. He emphasized that the medical profession should be cognizant of the potential problems that can arise in pregnancy with endometriosis, although most cases terminate in an uneventful manner.

Following are reports of two additional cases in which pregnancy was complicated by endometriosis.

CASE 1. The patient, a housewife, became pregnant for the first time after nine years of marriage. The last menstrual period had been January 11, and the estimated date of confinement was October 18. Catamenia had begun at age 13 and periods had been regular with dysmenorrhea and backache the first day. The prenatal course and results of physical examination and laboratory studies were all normal until September 27, when the patient complained of pain in the left lower quadrant of the abdomen, radiating to the flank and down the left leg. There was no regularity to the pain but it was constant and sharp in character. The patient was hospitalized for observation. Upon physical examination, increased tone and generalized tenderness over the uterus were noted. Fetal heart tones were normal. Shortly after entering the hospital the patient had some painless vaginal bleeding for the first time. A diagnosis of premature separation of the placenta with concealed hemorrhage was made and cesarean section was carried out. A boy weighing 7 pounds 4 ounces was delivered.

The placenta was separated by an old clot of approximately 350 to 500 cc. The uterus was mottled and did not contract well despite massage, intravenous administration of ergotrate, injection of pituitrin into the muscle and hot packs. The uterine wound was closed in layers and the bladder flap of peritoneum was about to be sutured in place when it was decided to remove the uterus because of uterine apoplexy (Couvelaire uterus). On the left ovary was an endometrioma that had torn prior to operation and was leaking thick old chocolate material which had stained the posterior leaf of the broad ligament and rectosigmoid. The right ovary was plastered down to the right broad ligament by an extensive endometriotic process and the cul de sac was obliterated by an endometrioma. A right salpingo-oophorectomy, subtotal hysterectomy and resection of the left ovary were accomplished. The postoperative course was uneventful. The patient was examined regularly thereafter, and nine years later the patient complained for the first time of a feeling of pressure in the lower abdomen and rectum, radiating into the low back. Androgen therapy relieved the symptoms.

CASE 2. A white housewife, 26 years of age who had been married four and a half years without becoming pregnant sought examination for determination of fertility. Catamenia had begun at age 14. Periods lasted four days and were 24 to 25 days apart. Bleeding was scant. The patient had backache but not dysmenorrhea. Third degree retroposition of the uterus and slightly tender small nodules in the cul de sac were noted upon pelvic examination. The nodules were believed to be endometriotic. In the succeeding four months the nodules in the cul de sac increased in size and became more tender. The patient complained of dyspareunia. Laparotomy, right oophorectomy, a Coffey suspension and appendectomy were carried out. The cul de sac was obliterated by endometriosis, a firm adhesive process.

Some three months after operation the patient became pregnant. Slight vaginal bleeding in the third month of pregnancy was controlled by bed rest and administration of stilbestrol. Otherwise the prenatal course and results of physical examinations and laboratory studies were all normal.

Two weeks before the estimated date of confinement the patient complained of left lower abdominal discomfort and pain radiating into the rectum and inner aspect of the left thigh. The pains were not regular. On the way into the hospital the patient had a severe vaginal hemorrhage. Conditions noted at examination were compatible with premature separation of the placenta. The baby was well engaged, fetal heart sounds were satisfactory and they were heard in the left lower quadrant of the abdomen.

Cesarean section was carried out. When the peritoneal cavity was opened, some free blood was encountered and there was blood staining of the uterine serosa. A 6 pound 6 ounce girl was delivered. Upon exploration of the pelvis after the cesarean section, a small left ovary with decidual reaction was noted. The tubes appeared normal, and apparently the endometrioma in the cul de sac had been changed by decidual reaction and had become bisected by the development of the lower uterine segment so that the serosa of the lower uterine segment, the cul de sac and the rectum had the shaggy appearance of the separation of two slices of bread and butter. The serosa exuded free blood, which undoubtedly accounted for the blood in the peritoneal cavity and the bizarre symptoms, not pertinent to the onset of labor, complained of by the patient.

Three and a half years later the patient became pregnant again and after a normal prenatal course a normal term boy was delivered by cesarean section. Upon exploration of the cul de sac at that

time some old thickening was noted, but no definite endometrioma.

The medical profession is cognizant of improvement during pregnancy in patients with endometriosis, but neither the nature nor the cause of this change is understood. Maybe the second of the two cases reported, and others like it, will help toward a clearer understanding of how nature manages to improve the lesions.

Some investigators have noted similarity of the change that endometriosis undergoes during pregnancy to the change that takes place when large doses of estrogenic hormones are employed. Karnaky,[26] Hurxthal,[23] and Cooke[6] reported cases in which dramatic change was noted during estrogenic therapy. The treatment must be carried out for a period of three to nine months or more and, unfortunately, endometriosis returns after a variable length of time. There are very definite side effects with this mode of treatment, such as hemorrhage, psychosis, increased pigmentation, edema of the vulva and other manifestations of water imbalance. Since only a short period of relief is obtained, some investigators have expressed preference for use of the male hormone. Even with androgens, however, there are undesirable effects that must be watched for, such as water imbalance, hirsutism and voice changes. These effects are usually avoided by small doses, 300 mg. or less a month, but even so the possibility of side effects should be explained before therapy, lest the patient suffer psychic embarrassment.

Still, surgical operation in some form is the treatment of endometriosis. It should be conservative when possible, but the probability that further operation may be necessary in the future should not be minimized. It is important to avoid castration as long as possible because of the undesirable postmenopausal changes in skin and bone. At times x-ray therapy to the remaining ovarian tissue after conservative operation may be necessary, particularly in the presence of bowel involvement. X-ray should never be used without surgical proof of existing endometriosis—certainly not on clinical suspicion alone. Presacral sympathectomy and ovarian neurectomy in association with conservative operation have been advised by numerous investigators, but as time moves along there are fewer ardent advocates for these procedures.

Another facet that must be touched upon is the possibility of malignant disease arising from endometriosis. It is taught in medical schools and mentioned in textbooks that here is a lesion which invades its neighboring structures like a malignant growth but rarely takes on the potentiality of a carcinoma. Novak,[35] Scott,[43] Sampson[53] and others have questioned the histologic derivation of certain carcinomas of the ovary as arising from endometriosis. The condition is rare, to be sure, but undoubtedly a possibility. It is difficult to prove, because usually when an ovarian carcinoma comes to one's attention it is so extensive that it would be folly to hazard a guess as to origin. Sampson[53] postulated very rigid criteria for such a diagnosis: The coexistence of benign and malignant tissue in the same ovary which have the same histologic relationship to each other as in endometrial carcinoma of the uterine corpus; the carcinoma must be seen to arise in this tissue and not to be invading it from some other source. Additional evidence includes the finding of tissue resembling endometrial stroma surrounding characteristic glands with old hemorrhage.

Scott[43] in 1953 found reports of 12 cases in the literature, and Postloff and Rodenberg[37] in 1955 found 13 cases of carcinoma of the ovary that fulfilled Sampson's conditions for proving endometrial origin. They added one case of adenoacanthoma, bringing the number to five reported cases to arise from endometriosis, in which it was possible to demonstrate both benign and malignant lesions in the same tissue. Fourteen cases out of the total number of cases of endometriosis is certainly a very few, but it is probable that if all cases were reported the incidence would be greater.

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