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Current concepts of treatment of endometriosis : a review of the current literature

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CURRENT CONCEPTS OF TREATMENT OF ENDOMETRIOSIS
A REVIEW OF THE CURRENT LITERATURE

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INTRODUCTORY REMARKS

The first known mention of endometriosis in the medical literature was made by the eminent Hungarian pathologist Von Rokitansky in 1860. (2) He described the lesion as an adenoma. In 1870, Waldeyer postulated that the lesions arose from ovarian germinal epithelium. Walker, 17 years later, reported on ectopic decidual reaction of the pelvic peritoneum following intrauterine pregnancy. One year later ovarian involvement was noted by Walker who advanced the theory that the lesions originated from misplaced paramesonephric tissue. In 1895, Von Recklinghausen held that adenomyoma arose from mesonephric duct cell rests and Pick, in the following year, advocated the same etiology for ovarian endometriosis. In 1896, Iwanoff suggested that the endometrial elements of adenomyosis might develop from the peritoneal surface of the uterus and Cullen first reported involvement of the round ligament. Ries gave his report of endometrial tissue in the lymphatics in 1897 and Lockstaedt demonstrated the continuity between the normal endometrium and subserosal endometriomata in 1898. In 1903, Meyer reported on endometriosis in a laporotomy scar and 5 years later reported intestinal involvement. Cullen showed that adenomyosis can result from direct extension of the endometrium into the myometrium. In 1919, Meyer elaborated the theory of coelomic metaplasia and considered local inflammation as the inciting factor. Sampson advanced the theory of retrograde menstruation in 1921 and 1922.

Halban suggested that endometriosis results from lymphatic metastases of normal endometrium in 1924. In 1926, Novak suggested that an endocrine imbalance might cause serosal metaplasia. King, in 1931 considered the possibility that ovarian endometriosis might result from metaplasia occurring in atretic follicle and/or corpus luteum cysts. Navratil reported endometriosis of the arm in 1936 and suggested that venous metastases are possible. In 1941-1943, Gruenwald demonstrated the embryologic basis for the coelomic metaplasia theory microscopically.

It has long been known, Kistner (12) states, that there is a definitive cure for the disease, that of castration. This may be achieved surgically or by irradiation. It is also a fact that this is a self-limited disease since it is apparently dependent upon the presence of functioning ovarian tissue and, therefore, the naturally-occurring menopause causes cessation of symptoms and objective regression of the lesions.

Unfortunately, many women presenting with this disease are in their twenties or thirties and cannot wait for the menopause for relief from their symptoms. Yet, their symptoms, or the degree of involvement may not be severe enough to warrant castration with all its attendant difficulties such as osteoporosis, atrophic vaginitis and pelvic changes. Also, many women will consult their physicians with the chief complaint of infertility, either primary or secondary.

Cure by castration and/or hysterectomy has little to offer these patients.

That pregnancy causes improvement of the disease with remission of symptoms and regression of the lesions, has been common knowledge for many years. The current theory regarding this phenomenon is that pregnancy stops ovulation and that the disease is dependent upon ovulation. Another theory, which is somewhat related, is that constant progesterone and estrogen levels cause decidual reaction in the ectopic endometrium and that necrosis and fibrosis occur as a result. The one observed fact plus the theory explaining this fact have left to the search for agents to suppress ovulation or to create a pseudopregnancy. Several agents are available currently; androgens, estrogens and progestins.

The purpose of this thesis is to review the current literature in this field and to present a brief summary of treatments, observations and results.

CONSERVATIVE MEDICAL THERAPY

Basically, conservative medical therapy, consists of observation and, if necessary, the use of mild anodynes. Kistner (12) recommends this method in women with mild symptoms that may either be borne or relieved by aspirin or tranquilizing drugs. If the patient is over 35, does not desire any more children and does not have extensive involvement, then palliation by the use of hormonal agents for a period

of 6 months may be tried. If this is of no avail, then a conservative surgical approach is advocated, conserving as much tissue as possible and ovarian tissue in particular. Radical surgery should be considered last and should be supplemented with hormonal therapy if symptoms warrant it.

If the patient has an infertility problem associated with her disease then observation should be carried out for no longer than 6 months during which time a routine infertility investigation is carried out. Following this period, if pregnancy has not occurred, then definitive treatment by conservative surgical therapy and/or hormonal treatment for 6 months should be carried out. Priest (19) feels that endometriosis is a progressive disease, though many authors would not agree with him, and recommends treatment to begin immediately on diagnosis. He advocates the conservative approach.

SURGICAL THERAPY

Parsons (20) defines conservative surgery as the excision or fulguration or both of all ectopic endometrium possible. This is true of bowel involvement as well as uterosacral involvement. Preservation of the uterus and as much ovarian tissue as possible is mandatory. Presacral neurectomy may be included, but there is not substantial evidence that the pain is greatly relieved. He feels that it might provide a better blood supply to the uterus and thereby enhance fertility.

In an article by Bacon (1), in 1949, a review of the case histories of 138 women at the Free Hospital for Women, who underwent conservative (the childbearing function was anatomically preserved) surgery for pelvic endometriosis was presented. The case histories covered the period from 1905 to 1941 inclusively. The results were as follows: 68 or 49.3% were completely relieved of symptoms; 29 or 21.0% were only partially relieved of symptoms and 41 or 29.7% were classed as therapeutic failures and required radical surgery in order to effect a cure. The author does not give the length of the follow-up period, but we may assume that the statistics given above hold good for the length of time that these patients were under observation. Furthermore, 26 of these patients were not married and of the remainder 26.8% became pregnant following surgical intervention. The author polled all of the married women in this series as to whether they had attempted conception following surgery and many replied in the negative. Therefore, we may assume that the figure of 26.8% would have been considerably greater if only those patients who desired pregnancy had been included.

In 1951, Haas (7) reported on a series of 45 women treated surgically with the desire to conserve as much tissue as possible and the reproductive function in particular. Thirty five of these women were married and 14 or 40% conceived following operation. The author

did not attempt to determine if all in this group actually desired pregnancy or were using contraceptive measures to avoid it nor was the husband's fertility established. None of the patients who became pregnant have had recurrence of symptoms. Among those patients who did not conceive, two patients were reoperated because of recurrence and one patient required x-ray castration. The author failed to disclose the length of follow-up observation in his series.

Whitehouse and Bates (28) reported on a series of 57 women who were treated by conservative surgery and who had a 6 to 11 year follow-up. Forty six of these women had operations which spared the ovaries, tubes and uterus. Seventy percent had complete relief of symptoms; mild recurrence not requiring further surgery was seen in 15 percent and 15 percent required further operation because of recurrence of severe symptoms. Sixteen or 46% of 35 of the patients who attempted pergnancy conceived. Total hysterectomy was done in 5 women for severe endometriosis with evidence of recurrence. These patients had no further recurrence of the disease, subjectively or objectively. The latter suggests that perhaps oophorectomy is not necessary to prevent recurrences.

Norwood (18) reported in 1955 on a series of 54 women who had consulted him primarily for infertility. The only discernible cause of infertility in these women was endometriosis; the male factor

was demonstrated to be adequate. He reports that 51 of his 54 patients or 94.4% conceived following their operation. Thirty of these women were primarily infertile. Of the three women who failed to conceive, one was in her late thirties at operation and another was operated on only six months prior to publication.

A series of 98 cases of endometriosis treated by conservative surgery with preservation of reproductive capacity was discussed by Frederikson (3). Fifty three or 54% of these women conceived after their operation. Twenty three were less than 30 years of age; 14 were 30 to 35; 9 were 36 to 40 and 2 were over 40. The author reviewed the reports of various authors for pregnancy following conservative surgery and the precentages ran from 9% to 49% with an average of 30%.

Parsons (20) feels that the indications for surgical approach are greater when ovarian masses are palpable than when nodules can be palpated only on the pelvic floor or on the uterosacral ligaments. His reasons for this statement are as follows: 1. The adnexal masses might not be endometriosis. 2. The disease is more apt to be progressive with ovarian involvement. 3. The gradual expansion of the cyst will further replace normal ovarian tissue. He feels that little is to be gained by operation when only the pelvic floor is involved. One exception to this is the patient with severe dyspareunia who of necessity avoids intercourse. He feels that the necessity for radical

surgery following a conservative approach is no greater than 10 to 15% although one takes a calculated risk when ovarian tissue is left in the face of known endometriosis. Many workers feel that an endometriotic pelvis is an extremely dangerous one when approached for a second time. Many prefer x-ray castration rather than oophorectomy. Kistner (13) feels that this is inadvisable because of the increased incidence of carcinoma of the ovaries, uterus, or cervix following such treatment.

ANDROGEN THERAPY

In 1940, Wilson (30) reported the results of testosterone therapy of a case of endometriosis involving the rectovaginal septum. The patient was treated for 13 months with monthly doses of 300-600 mg. for a total dosage of 4800 mg. during this period. Menses were suppressed during this period and the patient gained complete remission of symptoms. The rectovaginal endometrioma decreased markedly in size and the uterine endometrium became atrophic. Therapy was stopped because of masculinization and pelvic pain and increase in tumor size returned shortly.

Preston and Campbell (21) reported in 1953, a series of 187 cases treated with methyl testosterone during the previous nine years. In most instances, the diagnosis had been made on a clinical basis alone. In only 16 instances were histological diagnoses made. These

authors used testosterone propionate for periods of 4 to 6 months. No patient received over 300 mg./month and the only symptoms of androgenicity were hirsutism of the face in 3.2% and acne in 1.1%. They reported complete relief from symptoms in 76%, partial relief in 17.6% and no relief in 10.2%. Of further interest, was that 48 women conceived during treatment. Arrest of symptoms lasted from 6 to 12 months following withdrawal of the drug. Apparently, these women continued to menstruate throughout therapy.

Scott and Wharton (25) treated Rhesus monkeys with endometriosis with pure crystalline testosterone for periods of 6 to 27 months. During this time, periodic biopsies of the ectopic endometrium were observed. All of the animals had normal ovarian function during the experiment. No evidence of any atrophy or fibrosis of the lesions was noted. No decidual formation was noted. All of the biopsies had a nonsecretory proliferative pattern with evidence of both old and recent hemorrhage. These authors conclude that this drug is of little value in treatment of external endometriosis in monkeys.

ESTROGEN THERAPY

Karnaky (10) reported on a series of 37 cases of endometriosis treated by diethylstilbestrol for periods of 3 to 6 months. Diagnosis of endometriosis was made on a clinical basis only in 27 of the women and by histological means in the remainder. The author used the

following dosage schedule: 0.5 mg is given per orum for 3 nights and every fourth night the dose is increased by 1.0 mg until 5.0 mg are being taken daily. This dosage is continued until spotting or bleeding occurs and then 10 mg is given every 15 minutes until the bleeding stops. The patient is then maintained on 10 mg daily until bleeding occurs again at which time she is given 15 mg every 15 minutes until the bleeding stops and is then maintained on 15 mg as before. All subsequent breakthrough bleeding is handled in this fashion. The purpose of this treatment is to keep the patient amenorrheic for 3 to 6 months. The author states that estrogens must be increased every 2 to 6 weeks because the patient becomes accustomed to a dosage schedule and breakthrough bleeding will occur. The author achieved 100% remission of symptoms in all patients during the course of therapy. Five of the patients became pregnant subsequent to therapy. He states that none of the patients with severe dysmenorrhea have been completely relieved of discomfort at menses but, the symptoms were not severe enough to require anything more than aspirin for relief. In 3 patients who showed extensive pelvic involvement a exploratory laporotomy, no definitive surgery was done other than the taking of a biopsy. Five months of stilbestrol treatment enabled the pelvic organs to be freely moveable on bimanual examination and these women have been free of pelvic pain for periods of 1 to 9 years.

Gray and Barnes (5), in 1952, reported on a case of endometriosis in a 21 year old nullipara with extensive pelvic involvement. They started the patient on 1 mg per day of stilbestrol and increased the dose by 1 mg each week until 5 mg was the daily dose. This dose was increased in 5 mg increments until a dose of 25 mg per day was reached at which time excessive vaginal bleeding developed. Doses of up to 110 mg daily were of no avail and after 10 days of profuse bleeding the drug was stopped, the patient transfused and a uterine curettement was done. The endometrium obtained showed a marked degree of hyperplasia. Therapy was reinstituted as before and by 5-1/2 weeks the patient was again bleeding excessively and this was again refractory to increased doses of stilbestrol. The bleeding continued until 17 days after the drug was withdrawn. The patient's symptoms recurred immediately and a total abdominal hysterectomy and bilateral oophorectomy was done. At biopsy, both the uterine and ectopic endometrium showed marked cystic hyperplasia without any evidence of atrophy. The patient had excellent relief of symptoms following the operation.

Hurxthal and Smith (9) reported on a series of 25 patients reated with micronized stilbestrol. They used doses of 5 to 50 mg daily. They state that symptoms were completely relieved in 4 cases, markedly decreased in 12 patients and only slightly decreased in the remainder. None of the patients had any dyspareunia while undergoing treatment. These authors feel that the drug inhibits the anterior

lobe of the pituitary causing ovarian atrophy. They feel that the use of estrogens is of limited value because of the unpleasant side effects and that the improvement seen is far more subjective than objective.

Haskins and Woolf (8) reported on a series of 15 patients treated with stilbestrol and observed for 7 to 46 months after therapy. They treated their patients as follows: 1 mg on the first day of the menses which was increased by 1 mg every three days until the dose was 5 mg daily. The dose was then increased by 6.25 mg increments every three days until the dosage was 100 mg daily and this was the maintenance dose for 90 days. The dose was then decreased by 6.25 mg daily until the last dose was given. These authors used micronized stilbestrol as recommended by Karnaky since it is thought to insure more even absorption. All patients in this series were amenorrheic during treatment. No serious vaginal bleeding occured. The patients uniformly experienced relief of their symptoms almost from the onset of treatment. No definite decrease in the size of the lesions could be felt but they became softer and there was less induration of contiguous structures. The lesions did decrease markedly in tenderness to palpation. Curettage failed to reveal any endometrial atrophy. The average length of treatment was 190 days. The patients were symptom free on an average of 20 months including the period of therapy. Re-

currences had developed in only 4 patients at the time of publication, and these were seen at an average of 18 months. The authors feel that this therapy is of definite value although the improvement in the patient is primarily subjective.

Scott and Wharton (23) reported on the effectiveness of stilbestrol in treatment of endometriosis in Rhesus monkeys. These animals were treated for periods of 3-1/2 to 24 months. Cyclic menstruation occured throughout therapy and biopsy revealed evidence of old and recent hemorrhage in the areas of ectopic endometrium suggesting that ectopic endometrium is subject to breakthrough bleeding as is the normal endometrium. Cystic hyperplasia was noted in both the ectopic and uterine endometrium. From these findings the authors concluded that estrogens were of little benefit to these animals.

PROGESTATIONAL AGENTS

In 1958, Kistner (11) reported on 12 patients who were treated with a combination of progestational agents and estrogen. These patients were treated for periods of 2-1/2 to 4 months with considerable improvement. This led the author to conclude that progestational agents in combination with estrogens are of value in the treatment of endometriosis. He postulated that these drugs, when given continuously, create a pseudopregnancy and that the ectopic endometrium

responds in a fashion similar to that seen in a normal pregnancy.

Since that time, the same author has published many articles concerning his experience in treatment of endometriosis with these agents. To date, there are over 200 patients in his series. The bulk of his experience has been with the 19-norsteroid, norethynodrel (Enovid) but he has also used other progestins. The following is a brief summary of his experience with these agents.

Delalutin (17-alpha-hydroxyprogesterone caproate)

This drug was administered parenterally in doses of 62.5 mg weekly with 5.0 mg of diethylstilbestrol. The dosage was increased every 2 weeks so that by the end of 12 weeks the patient was receiving 500 mg weekly. The dosage of the estrogen was increased weekly so that the patient was receiving 60 mg daily by 12 weeks. The author also used Deluteval (Delalutin and estradiol valerate, 250 mg and 5 mg/cc respectively). The latter is the same preparation that Thomas (27) used on 28 patients. They were given bi-weekly injections of one ml. He treated these women for 4 to 10 months with excellent results. Kistner feels that Delalutin has less androgenic potential than the other progestins since no signs of androgenicity were observed in any of the patients treated by this drug. Also, he feels that there are advantages to the use of this drug because it can be administered parenterally and, therefore, greater constancy of absorption is afforded.

Enovid (17-alpha-ethynyl-17-hydroxy-5-10-estren-3-one with 1.5% ethynyl estradiol 3-methyl ether)

Kistner (13, 14, 15, 16) has treated the majority of the patients in his series with this drug. Enovid contains 9.85 mg of the progestational agent, norethynodrel, and 0.15 mg of the estrogen per 10 mg tablet. The author has used the following dosage schedule: 10 mg daily for 2 weeks with 10 mg increments every 2 weeks until the maintenance dose of 30 to 40 mg daily is attained. Subsequently, (16) the author states that a maintenance dose of 20 mg daily is adequate and that higher doses contribute nothing more to a successful outcome. The highest incidence of recurrence has been in those women treated less than 6 months. Therefore, the author recommends treatment of no less than 6 months and for 9 to 12 months in those patients with extensive involvement. Norethynodrel, though a 19-norsteroid, has a slight estrogenic effect and this in combination with the small amount of estrogen present in Enovid tends to cause nausea and mastalgia. These side effects usually do not persist past the first 2 to 3 weeks of treatment and they are rarely severe enough to warrant discontinuance of the drug. The author feels that an initial dose of 5 mg rather than 10 mg diminishes both the frequency and the severity of these symptoms. The author also feels that this progestin is less androgenic than other progestational agents which have the double bond in the 4-5 position as does testosterone. No overt signs of masculinization have been noted in his series.

Provera (6-alpha methyl-17-alpha hydroxyprogesterone acetate)

This drug is administered every 2 weeks by the parenteral route. The dose is a constant one, 100 mg every 2 weeks and the patient is also given 0.05 mg of ethynyl estradiol daily. The latter may be increased in 0.05 mg increments every 2 to 3 weeks if desired or one may wait until breakthrough bleeding occurs before increasing the dose. Breakthrough bleeding and nausea have been minimal with this drug and the former is easily controlled by increasing the dose of the estrogen. This regimen is similar to that employed by Greenblatt and Barfield (6) who reported 75% improvement in their series.

Norlutin (17-alpha-ethynyl-19-nortestosterone)

This drug is essentially the same as norethynodrel except for a greater androgenic potential as revealed by both animal experiments and clinical observations. Neither nausea nor mastalgia have been reported by those using this drug, but sodium retention and edema have been on a par with Enovid. The lack of estrogen probably accounts for the absence of nausea and mastalgia. Breakthrough bleeding is a much greater problem with this drug, again because of the absence of estrogen. Acne, hirsutism and increased libido are not uncommon with this drug. The author used the following dosage schedule. 20 to 50 mg per orum daily for 7 to 9 months. An

acetic ester, Norlutate, has been prepared and it is thought to have twice the potency of the parent compound. This drug has been used with good effect in doses of 10 to 20 mg daily. No mention was made of any increase in androgenic potential. It is of interest to note a report by Scott and Wharton (26) on the use of norethindrone, Norlutin, in the treatment of endometriotic monkeys. They were unable to find any beneficial effect on the lesions from the use of this drug. A similar finding was noted in the same paper in monkeys treated with progesterone. They did note, however, that the lesins were more readily identifiable after treatment and that the adhesions were dissected much more readily. They suggest that the use of progesterone for a 4 or 5 week period prior to surgery would make the surgeon's task easier.

In summary, Kistner reports 75 to 85% clinical improvement regardless of the progestin used. He feels that any of these agents can satisfactorily maintain a pseudo pregnancy and that the drug of choice is the one which the patient tolerates best. These drugs may be used interchangeably; for example, if the patient is unable to tolerate Enovid because of uncontrollable nausea, Norlutin may be substituted. Conversely, if the patient develops hirsutism or excessive breakthrough bleeding while on Norlutin, then Enovid may be used.

Other authors have reported on their experiences in the treatment of this disease with progestational agents and have had a degree of success comparable to that of Kistner.

Riva et al (22) reported on a series of 123 women treated with Enovid. Eighty one of their patients were re-evaluated by culdoscopy after an average of 6.3 months of continuous therapy. Complete regression of the lesions was seen in 79.5%. They felt that these results were not dependent on the age of the patient or the extent of involvement.

Williams (29) treated a series of 22 patients with Enovid. These patients had all undergone surgical treatment with the aim of conservation of as much tissue as possible. He reported 95% improvement.

Lebherz and Fobes (17) had a series of 112 patients that were treated with Enovid and Norlutin. The latter drug was discontinued because it was felt to cause more acne, fluid retention and break-through bleeding. These authors reported 77.6% improvement.

Andrews et al (31) reported similar results on a series of patients treated with Enovid. They did repeated curettements on their patients and noted decidual reaction in all specimens. Biopsy of the ectopic endometrium in 5 patients showed a decidual response and 3 of the specimens showed necrosis and macrophage activity.

Goldzieher (4) discussed the changes noted in the uterine endometrium in patients on continuous 19-norsteroid therapy. For the first few days the effect is similar to that seen with progesterone but the glands fail to progress past the 16 or 17 day stage of the normal menstrual cycle and they regress to the 5-day stage. Pseudodecidual changes begin to appear after 12 days. After 20 days the stroma resembles that of an early pregnancy while the glands continue to regress. After 2 months a decidual response is present with minimal vascular growth and hypoplastic glands. Later, focal decidual necrosis develops and after 6 months the endometrium degenerates to a pattern of atrophic glands and sparse stroma made up of fibroblast-like cells.

SUMMARY

The ideal treatment of endometriosis, as stated by Kistner, is pregnancy. Remission of symptoms ensues almost immediately and persists for considerable lengths of time after delivery. Unfortunately, this ideal treatment is not ordinarily feasible since many of the patients are infertile and many others have no desire to remain pregnant for half of their adult lives.

Androgen therapy has proven to be of limited value because of masculinizing side effects. Dosages of less than androgenic levels do not suppress ovulation and the patients continue to menstruate throughout the course of treatment. Most of the side effects of androgen therapy disappear on withdrawal of the drug but hirsutism or baldness are usually irreversible. It is of interest to note the high incidence of conceptions occurring in women while taking the drug. One wonders if the drug has a direct effect on the lesions or whether the increase in libido that is so often seen is the cause.

Estrogens offer considerable subjective improvement while the patient is undergoing treatment, but many of the patients experience recurrence within a short while after cessation of therapy. Also, the side effects are often very annoying, particularly the nausea

and breakthrough bleeding. Some women experience severe withdrawal bleeding which is probably secondary to the cystic hyperplasia of the uterine endometrium that is commonly seen. There is little objective improvement in these patients other than softening of the lesions and decreased tenderness on palpation.

The progestational agents appear to have the most beneficial long-term effects without significant side effects. It is apparent that these agents have an immediate salutary effect in most instances, both subjectively and objectively. Experience with these drugs is too limited as yet and longer follow-up studies are required before any definite statements can be made concerning curative effects. There appears to be little to choose from among these agents, and side effects are the determining factor in their selection.

A surfical approach is of value in many instances and, as mentioned before, radical surgery offers a definite cure to the patient. Another advantage of the surgical approach is that a histological diagnosis may be made and the exact extent of involvement may be determined. Many authors advocate routine use of culdoscopic examinations with biopsy as part of the work-up of patients with endometriosis. Statistically, this approach has yielded the best results in management of the infertile endometriotic patient.

In summary, there are now available to the clinician several therapeutic approaches to the patient which are conservative in nature, thereby preserving the reproductive function. The use of radical surgery is now generally condemned except as the last resort. The progestins have proven to be the most effective hormonal agent and it is hoped that continuous use of these drugs with longer follow-up studies of the patient will cause them to be universally accepted as the treatment of choice for endometriosis.

CONCLUSIONS

1. A brief review of the salient features of the history of endometriosis has been presented.

2. The non-surgical, non-hormonal approach to the patient with only minor symptoms has been discussed.

3. A review of some of the current thinking on the surgical management has been presented.

4. Reports of the experiences of several workers in the use of testosterone in the treatment of endometriosis have been presented. The use of androgens has been of some value but its use is limited by the tendency to masculinization on prolonged use.

5. The results of the use of estrogens in the treatment of endometriosis have been reviewed. The use of estrogens are of greater value but they do not appear to cause much objective improvement in the disease and they are prone to cause nausea, mastalgia and breakthrough bleeding. withdrawal bleeding can be severe.

6. The results of the use of progestational agents in the treatment of endometriosis have been reviewed. The progestational agents have yielded the best results to date, 75 to 85% improvement. Their use, either alone or in conjunction with conservative surgery is the best therapy available today short of pregnancy.

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