# ENDOMETRIOSIS IN INFERTILITY

by

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## SUMMARY

**Incidence of endometriosis associated with infertility in the present series is 18.7 per cent. This figure is more or less similar to those reported by authors from western countries. Routine use of laparoscope in the infertility work up has helped the diagnosis of many asymptomatic early endometriosis leading to unexplained infertility. Apart from anatomical distortion of pelvic organs caused by moderate to severe grades of endometriosis, early endometriosis may also lead to infertility – the factors responsible being defective ovulation and altered tubal motility. Result of treatment has been encouraging in early cases with medical management and 35 per cent pregnancy has been achieved in the present series following treatment with low dose Danazol. In moderate to severe grades of the disease, results in terms of conception were slightly better after combined conservative surgical and hormonal than after conservative surgical treatment alone.**

### *Introduction*

Endometriosis in relation to infertility has recently created renewed interest. This is because : (1) Incidence seems to have apparently increased following introduction of diagnostic laparoscope in infertility work up. (2) Some of the cases of unexplained infertility have been explained by the presence of asymptomatic minimal endometrial implants in the pelvis. (3) Results of medical management with Danazol a new drug which induces pseudomenopause and not pseudopregnancy has been claimed to be superior either alone or in combination with conservative surgical approach for stages of endometriosis so far as relief of symptoms and restoration of fertility are concerned.

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### *Objective Of The Present Study*

It is generally believed that endometriosis is a rare disease in Indian women. This may be true for the general population but so far as infertile women are concerned the incidence of endometriosis needs evaluation. The objectives of the present study, therefore, are to evaluate the incidence of endometriosis in our infertility clinic, the relationship between asymptomatic minor endometrial implants and unexplained infertility

and the comparative results achieved by conservative surgery and medical management specially with Danazol in different stages of the disease.

*Incidence*

Incidence of endometriosis has been determined on laparoscopic or laparotomy findings. Impression of endometriosis on clinical evaluation and those presenting with records of operation for endometriosis by other surgeons have not been included in the present study. From January 1983 to March, 1985 — 936 laparoscopic examinations were performed as a part of investigation of female infertility. One hundred fifty-seven cases of endometriosis were recorded giving an incidence of 18.7 per cent. This incidence of endometriosis in infertility is more or less parallel to those reported by Cohen (1976) as 23 per cent and Jones and Rock (1977) as 25 per cent in their series. Apart from infertility, the incidence of endometriosis in India does not seem to be as high as in western countries. Williams and Pratt (1977) have reported 50 per cent endometriosis in gynaecological laparotomies while Schneider (1983) reports 18.7 per cent in 2000 consecutive laparotomies performed in a recent 5-year period. But in recent camp laparoscopic sterilisation performed by team of gynaecologists of N.R.S. Medical College, Calcutta, no case of endometriosis was recorded in 4336 women sterilised from December 1983 to September 1984. Obviously this figure comprised a cross section of general population of Indian rural women with high parity.

*Grading of endometriosis in relation to age :*

Grading of endometriosis has been done based on the classification suggested by Acosta *et al* (1973).

It is observed from Table-I that in our study the highest number of cases belonged to moderate grade and these were most frequently observed in women of age group 26 to 35 years.

It appears that voluntary or involuntary childlessness and consequently the effect of long and uninterrupted continuous menstrual years may be primarily responsible for the genesis of this specific disease (Chakravarty and Mukherjee 1982). The same view has also been expressed by Kistner *et al* (1977). Genetic (Simpson *et al* 1980) and immunological factors (Weed and Arquemboug, 1980) have recently been involved in the etiopathogenesis of the disease because endometriosis is occasionally found in parous women and on the other hand all nulliparous women do not suffer from endometriosis.

It is reasonable to expect infertility in moderate and severe grades of endometriosis with extensive tubal and ovarian distortion but infertility with minimal endometriosis (mild) has created curiosity and several explanations have been suggested. Explanations include (a) defective ovulation, (b) defect in ovum pick-up, (c) defect in migration of ovum, sperm and fertilised egg.

Defective ovulation may be due to associated hyperprolactinaemia (Abe *et al* 1983). Treatment with bromocriptine rather than specific therapy for endometriosis helps to

TABLE I

| Age in years | No. of cases | Mild | Moderate | Severe |
|---|---|---|---|---|
| Less than 25 | 33 | 17 | 10 | 6 |
| 26-35 | 105 | 33 | 60 | 12 |
| 36 and above | 19 | 6 | 5 | 8 |

restore fertility in these cases. Non-ovulation may also be due to reduced number of LH receptors in the follicles (Kauppila *et al* 1983), may be an auto immune phenomenon (Schneider, 1983) or due to ovarian cortical destruction (Jones and Rock 1977). The fascinating 'Delilah' theory suggests that the endometrial implant seduces the ovum and keeps it away from the fallopian tubes. Defective ovum pick-up and failure of migration of fertilised ovum through the fallopian tube could be the result of altered tubal mobility brought about by excess prostaglandin secreted by ectopic endometrial implants (Meldrum *et al* 1977). Weed and Arquem Bourg (1980) pointed the possibility of autoimmune response characterised by peritoneal irritation and fibrosis leading to impaired tubal motility and infertility.

*Management*

There are three modalities of management of endometriosis associated with infertility (a) Hormonal, (b) Conservative surgical, (c) Combined i.e. hormonal treatment preceding or following conservative surgical approach.

*Medical Management*

Mild and few moderate grades of endometriosis were primarily treated with hormones. Specific hormones used in treatment of endometriosis in the present study consisted of combination of oestrogen and progesterone, progesterone alone, Danazol and in selected cases methyl testosterone and bromocriptine. Even for small sized ovarian endometriomas laporoscopic aspiration, flushing of the cyst cavity and pelvis followed by hormone therapy was the primary treatment of choice.

Evolution of hormonal management for pelvic endometriosis dates back to late 1950s. Induction of a state of pseudopregnancy by oestrogen and progestogens singly or in combination did not gain much popularity due to undesirable side effects. In the present series, pregnancy rate was 22.2 per cent following either combination or single progesterone therapy.

In late 1960s hormonally induced amenorrhoea of pseudomenopause became another approach to the treatment of endometriosis. Danazol, an isoxazol derivative of 17 ethynyl testosterone has been found to be an useful drug for the treatment of endometriosis by inducing pseudomenopause rather than pseudopregnancy.

The recommended dose of Danazol is 600 to 800 mgm per day. The dosage, however, can be adjusted on the basis of extent of the disease and weight of the patient. In our series, for early and moderate endometriosis, the dosage varied on an average between 100 to 200 mgm per day for a period of 3 to 6 months. The results were encouraging with pregnancy rate of 35 per cent. On rare occasion the dose was increased upto 400 mgm per day. Treatment with low dose danazol has also been recommended by Samaras, Gambrell and Greenblatt (1983).

Out of 40 women treated primarily with Danazol, 22 (with unexplained infertility) had asymptomatic minimal pelvic endometriosis. Following three months therapy with low dose Danazol, 9 out of 22 conceived immediately after withdrawal of the drug. Five others who conceived following Danazol had mild or moderate grades of endometriosis and duration of treatment varied between six months to nine months.

Methyl testosterone in daily dose of 5 mgm for 6 to 9 months was tried by Katayama *et al* (1976) who reported pregnancy rate of 19 per cent. Because of possible side effects this therapy has not been generally acceptable. In the present series, Methyl Testosterone 2.5 mg. daily used cyclically or continuously for 3-6 months resulted in conception and term delivery in 1 out of 4 cases.

Though paradoxical but it may be possible that bromocriptine may prevent progression of endometriosis. In 7 women in the present series, prolactin level was elevated and 1 responded with conception following bromocriptine therapy.

The hormonal management with results in terms of pregnancy is detailed in Table-II.

TABLE II
*Medical Treatment*

| Nature of drugs used | No. of cases | Conception | Percentage |
|---|---|---|---|
| Combination of oestrogen and progestogen or only medroxyprogesterone | 18 | 4 | 22.2 |
| Methyl testosterone | 4 | 1 | 25.0 |
| Bromocriptine | 7 | 2 | 28.3 |
| Danazol | 40 | 14 | 35.0 |
| Total | 69 | 21 | 30.4 |

*Conservative surgical approach* :

In advanced endometriosis with gross ovarian enlargement and with distortion of tubal or ovarian anatomy, conservative surgical approach was undertaken. Surgical treatment was also given priority to women with advanced age even with minimal anatomical distortion of either tube or ovary or both.

The extent and type of surgery is to be decided after laparotomy. If one ovary is severely destroyed by the disease, especially if the corresponding fallopian tube is compromised, and the contralateral adnexa are free from endometriosis, unilateral salpingo-oophorectomy is the treatment of choice. Rajan *et al* (1984) reported the same procedure under similar circumstances. In our series, out of 18 such procedures adopted, 3 pregnancies have resulted so far. The density of pelvic adhesion in some cases of severe endometriosis in the age group 25 to 35 years left us no choice but to abandon adhesionolysis. In these cases, the ovaries after partial resection were fixed to the fundus of the adherent uterus with the possible hope of laparoscopic oocyte recovery for in vitro fertilisation in future.

The overall success rate in terms of pregnancy following conservative surgical approach varies between 32 per cent (Garcia and David 1977) to 87 percent (Ranney 1970). Rajan *et al* (1984) reported pregnancy rate by similar approach as 42 per cent. In the present series, the pregnancy rate by surgical approach was low; only 22 per cent. This is perhaps because most of the cases treated surgically in the present series had variable grades of tubal distortion in addition to ovarian endometrioma. Weed and Holland (1977) noted 10 per cent reduction in pregnancy rate with ovarian involvement.

*Combined therapy*

Apart from few cases of moderate endometriosis, where we were happy with restoration of pelvic anatomy without leaving much raw areas behind, in a substantial number of women in the present series, surgical procedure was supplemented by hormonal therapy in the immediate post operative period. This approach is contrary to the current opinion (Hammond and Haney, 1978; Buttram, 1979; Rock *et al* 1981; Rajan *et al* 1984) which advocates that

TABLE III
*Primary Surgical Procedure*

| Nature of surgery | No. of cases | Conception | Percentage |
|---|---|---|---|
| Resection of chocolate cyst | 20 | 4 | 20.0 |
| Adhesionolysis | 12 | 3 | 25.0 |
| Unilateral adnexectomy and lysis of adhesion on other side | 18 | 4 | 22.2 |
| Total | 50 | 11 | 22.0 |

hormone therapy should be withheld following conservative surgical treatment, because chance of pregnancy increases within six months to one year following surgery. But in the present study, there were too many cases of severe endometriosis with dense pelvic adhesion and complete removal of all endometriotic foci with conservative surgical approach was impossible. Therefore in many women surgical procedure had to be followed by either Danazol or combination of oestrogen and progestogens. Dmowski (1981) advocates hormonal treatment (Danazol) following conservative surgical approach. He believes that invariably some residual implants are left behind following conservative surgical approach and the possibility of post operative adhesions cannot be entirely eliminated even with currently used microsurgical technique.

TABLE IV
*Combined Surgical and Medical Treatment*

| Treatment modality | No. of cases | Conception | Percentage |
|---|---|---|---|
| Combined | 38 | 9 | 28.9 |

*Results*

The overall results in our series with three modalities of treatment are summerised in Table-V.

TABLE V

| Treatment modality | No. of cases | No. conceived | P.C. | Term delivery | Abortion | On going |
|---|---|---|---|---|---|---|
| Hormonal | 69 | 21 | 30.4 | 18 | 1 | 2 |
| Conservative surgical | 50 | 11 | 22.0 | 10 | — | 1 |
| Combined | 38 | 9 | 23.7 | 6 | 2 | 1 |
| Total | 157 | 41 | 26.1 | 34 | 3 | 4 |

TABLE VI

| | No. of cases | Conception | Percentage |
|---|---|---|---|
| Total in the series | 157 | 41 | 26.1 |
| Fibroid | 41 | 3 | 7.3 |
| Seminal defect | 20 | 1 | 5.0 |
| Corrected pregnancy rate for endometriosis | 96 | 37 | 38.5 |

*Corrected Pregnancy rate*

Out of 157 cases of endometriosis reported in this series, there were 61, who had defects other than endometriosis to account for infertility. Forty-one had fibroid and 20 husbands had seminal defects. Four of these 61 women conceived. Hence the corrected pregnancy rate will be 37 out of 96 cases i.e. 38.5 per cent.

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