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"A Case Study On The Effect Of Endometriosis On Recurent Implantation Failure In Assisted Reprodutive Technology"

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Abstract: Endometriosis has a substantial impact on recurrent implantation failure (RIF) in assisted reproductive technology (ART), causing an inflammatory and hormonally unbalanced uterine environment. This alters endometrial receptivity, limiting the likelihood of successful implantation. Chronic inflammation, altered immunological responses, and hormone imbalance are all possible mechanisms. Continued research is required to create more effective treatments, which will ultimately improve reproductive outcomes for women with endometriosis receiving ART. Endometriosis has a substantial impact on recurrent implantation failure (RIF) in assisted reproductive technology (ART), causing an inflammatory and hormonally unbalanced uterine environment. This alters endometrial receptivity, limiting the likelihood of successful implantation. Chronic inflammation, altered immunological responses, and hormone imbalance are all possible mechanism.

Key Points: Endometriosis, Assisted Reproductive Technology (ART), Recurrent implantation failure(RIF), Chocolate Cyst, Implantation, Controlled ovarian hyperstimulation(COH), In-Vitro Fertilization – Embryo Transfer (IVF-ET).

Introduction:

1. INFERTILITY.

Infertility is thought to affect approximately 15% couples of reproductive ages worldwide. Infertility is therefore defined as a disease of the male or female reproductive system defined by the failure to achieve a pregnancy after 12 or more of regular unprotected sexual intercourse (WHO, 2021).

2. FEMALE INFERTILITY

Approximately 35% of couples will experience infertility of largely female origin. The causes include ovulatory failure, fallopian, uterine or pelvic problems such as endometriosis, and advanced maternal age.

3. ENDOMETRIOSIS: A MODREN SYNDROME

Women with endometriosis may have infertility, pelvic pain, or both. Endometriosis is a frequent disorder affecting women during their reproductive years. It happens when normal uterine lining tissue, known as endometrium, connects to pelvic organs and begins to expand. This misplaced endometrial tissue creates irritation in the pelvis, which can lead to pain and infertility. During each menstrual month, the majority of the uterine lining and blood are shed via the cervix and into the vagina.

Nonetheless, the fallopian tube allows some tissue to enter the pelvis (ASRM, 2012). It's possible that endometriosis patients are just unable to get rid of these cells in their pelvis. On the vaginal surface, early endometriosis implants resemble little, flat patches or blebs. Endometriosis can grow as implants on the surface of the ovary or it can penetrate the ovary and create an endometriosis, sometimes called a "chocolate cyst," which is a blood-filled cyst (fig. 2). The blood inside chocolate cysts darkens over time to take on a rich reddish brown hue, thus the name. Adhesions, or internal scar tissue, are a side effect of endometriosis that can irritate surrounding tissue. These adhesions may encompass adjacent intestines, cover the pelvic organs entirely, or join them. Adhesions might impede the fallopian tube's ability to absorb In other situations, endometriosis may just cause infertility.

1.3.4 Treatment of pain

Women with minor symptoms may benefit from lifestyle modifications or require no therapy at all. Hormonal therapy may be recommended if discomfort interferes with family, job, or daily life. Treatments for pain in endometriosis patients include lifestyle changes, hormonal contraceptives, progesterone, GnRH analogs, and Danazol.

1.3.4.1 Surgery of pain

Surgical treatment of endometriosis is often performed when endometriosis is diagnosed. During laparoscopy, the doctor may remove adhesions, endometriosis nodules, ovarian cysts. Laparoscopy is often used to treat recurrent endometriosis when the goal is to preserve future fertility. Ovarian cystectomy is more effective than cyst drainage for pain relief and preventing recurring cysts. Hysterectomy, with removal of ovaries, is an effective approach after childbirth is completed. This surgery provides final relief from endometriosis related pain in more than 90% of women.

1.3.5 Fertility enhancing treatments

1.3.5.1 Controlled Ovarian Hyperstimulation and Intrauterine Insemination

Several studies have shown that fertility is enhanced in women with minimal or mild endometriosis by controlled ovarian hyperstimulation (COH) with intrauterine insemination (IUI). This treatment is also called superovulation with IUI.

1.3.5.2 Assisted Reproductive Technology

In general, couples diagnosed with endometriosis have success rates with ART procedures such as IVF and embryo transfer that are similar to those for couples with other causes of infertility. IVF-ET is the most effective treatment for moderate or severe endometriosis, particularly if surgery fails to restore fertility.

4. Recurrent Implantation Failure

Recurrent implantation failure is the term used to describe the failure of transferred embryos to implant after many IVF rounds. However, official criteria do not specify the overall number of embryos implanted in these IVF attempts or the number of cycles that end in failure. Because of this, different IVF centers may use different interpretations of RIF. Taking into account the typical number of embryos implanted each cycle and the present success rate of in vitro fertilization (IVF). The inability to conceive during at least three consecutive IVF rounds, in which one or two high-quality embryos implanted, is known as recurrent failure to implant. The two main players in the complex process of a successful implantation are the mother, who serves as the host, and the embryo.

2. Review of Literature:

Discovery of Endometriosis

The surgeon Thomas Callen denied for the find time the full morphological and clinical picture of endometriosis and adenomyosis (Cullen, was Jahn A Sampson who created the name endometriosis (Sampson, 1927)

2.2. Endometriosis and infertility

A reasonable body of evidence demonstrates association between endometriosis and infertility Endometriosis can reach in adhesions or distended pelvic anatomy that precludes fertility (ASRM, 2012)

2.3. Biologic mechanisms that may link endometriosis and infertility

Several mechanisms have been proposed to explain the link between endometriosis and subfertility (Schenken, 1996).

1.3.1. Distorted Pelvic Anatomy

Significant pelvic adhesions, such as those brought on by endometriosis, might hinder the collection or transport of ovum or impede the release of eggs from the ovary (Schenken et al., 1984).

2.3.2. Altered Peritoneal Function

Many studies show that women with endometriosis have more peritoneal fluid and higher concentrations of prostaglandins, proteases, and cytokines, including inflammatory cytokines like IL-1, 11-6, and TNFa, as well as antigenic cytokines like VEGF & IL-8 macrophages will produce (Pizzo et al., 2003).

2.3.3. Endocrine and Ovulatory Abnormalities

Women with endometriosis may have endocrine and ovulatory abnormalities such as luteinized unruptured follicle syndrome, luteal phase dysfunction, irregular follicular development, and premature or numerous luteinizing hormone (LH) surges.

2.345 Impaired Implantation

Certain endometriosis-affected women have been reported to have reduced endometrial expression of the cell adhesion molecule avi3 integrin during implantation (Lessey et al., 1994), although this information has not been verified. Researchers have discovered that endometriosis-affected infertile women have extremely low concentrations of an enzyme that is necessary for producing the endometrial ligand for L-selectin, a protein that coats the trophoblast on the surface of the blastocyst (Cakmak and Taylor, 2010).

2.3.6. Oocyte and Embryo Quality

Endometriosis-related infertility in women might result from altered follicles, poor egg quality and subsequent embryogenesis, or decreased endometrial receptivity. The finding that endometriosis patients' follicular fluid had different progesterone and cytokine concentrations supports this theory (Garrido et al. 2000).

2.3.7. Abnormal Uterotubal Transport

Several studies have suggested that women with endometriosis may have a decreased physiologic uterotubal transfer capacity than control individuals. Hysterosalpingoscintigraphy (HSSG) was used to detect abnormal transport (contralateral to the dominant follicle or complete transport failure) in 64% of women with endometriosis and patent fallopian tubes, compared to 32% of patients in a control group who were diagnosed with male infertility (Kissler et al., 2005).

2.5. Endometriosis and repeated failure of implantation: The etiology of endometriosis is yet unknown. According to Claire et al. (2012), its complicated and diverse function in infertility is highlighted by its considerable occurrence in the infertile population (20–30%), which influences ovarian reserve, ovulation, tubal architecture, embryo quality, implantation, and pregnancy development.

Aims & Objectives:

This study aims to analyze the basic and clinical data that points to a likely connection between endometriosis and recurrent implant failure after treatment with assisted reproductive technology. In this context, the study will also aim to determine the optimal treatment approaches that may be employed to improve the rates of future implantation and pregnancy in endometriosis patients while lowering the incidence of recurrent implantation failure (ART).

Materials & Methods

Case study of patients with endometriosis and recurrent implantation failure

The current study comprised four couples with a history of recurrent implantation failure. Endometriosis caused primary infertility in all of the female cases. Before beginning treatment, all patients completed informed permission forms and were advised to undergo ART methods (IUI/IVF/ICSI) for the treatment of RIF caused by endometriosis. The study was approved by Rayat-bahar University in Chandigarh.

4.2. History and clinical examination of patients

Before the procedure, all patients were clinically examined with serological tests, hormonal levels, semen analysis for male subjects (WHO, 2010), and couples' histories; women patients also underwent primary investigations such as transvaginal ultrasound scanning/HSG or diagnostic hysterolaparoscopy.

4.3. Treatment of the subjects with ART

The available treatment options were determined based on the patients' histories and clinical examination reports completed by the gynaecologist for each patient. Investigations were conducted on each case individually, and patients who required extra tests were advised accordingly. Patients were treated with various ART procedures and evaluated for favorable or negative pregnancy outcomes. Standard methods for IUI (Cohen, 1962), IVF (Streptoe and Edwards, 1978), and ICSI (Palermo et al., 1992) were combined with various stimulation protocols.

Case Studies

5.1. Case study - 1

5.1.1. Patient identification data.

Name: xyz Husband name: abc Age: 32 years Age: 39 years

Marital status: 3 years

5.1.2. Chief complaints and progress of the present illness:

The patient was married for 3 years and had a satisfactory marital relationship for 2 years and after that she was keen on conceiving, so she stopped using oral contraceptive pills for over a year now. About 6 months ago she started experiencing deep seated pain at the height of sexual intercourse followed by a lingering pelvic soreness for a few hours thereafter. This had intensified lately. She was desirous of securing relief from dyspareunia and keen on a conception.

5.1.3. History of the patient:

5.1.3.1. Personal history

History of using oral contraceptive pills for two years after marriage.

No known allergies. General Health: Satisfactory.

5.1.3.2. Menstrual history

Menarche at the age of 11 years.

Past menstrual cycles: 3-4/28 days. Regular, moderate flow but painful.

Past menstrual cycles on oral pills: 3/28 days. Regular, moderate flow but painless. Present menstrual cycle: 4-5/28-30 days. Regular, Moderate Flow but painful.

5.1.4. Physical Examination

5.1.4.1. General Examination: Built and nutritional status: Satisfactory

No evidence of pallor or lymphadenopathy.

No evidence of thyroid enlargement, Blood pressure normal.

5.1.4.2. Vaginal examination:

Cervix: Tubular, firm, os closed, movements cause discomfort

Uterus: Retroverted, firm to feel, mobility restricted and tender.

Fornices: Tenderness and nodularity of uterosacral ligaments.

5.1.5. Clinical Diagnosis

Primary infertility in view of History of infertility.

Regular menstrual cycles with dysmenorrhea, painful enough to require medication.

Examination revealing a retroverted uterus with restricted mobility and thickened adnexae- the clinical features suggestive of diagnosis of pelvic factors causing infertility like chronic pelvic inflammatory disease (PID) or endometriosis. The patient required further investigations.

5.1.6. Investigations

Hemoglobin: 12.0 g/dl Urine routine examination: No abnormality detected.

Stools routine: No evidence of worms or E. histolytica present.

FBS: 80 mg/dl and PPBS: 88 mg/dl. VDRL: Non-reactive.

HBsAg test: Negative. HIV screening test: Negative.

Pap smear: Negative Semen analysis (husband): Normal

5.1.7. Treatment

Oral contraceptives advised for three months and dyspareunia was controlled. Diagnostic laparoscopy: uterus normal in appearance, pelvic adhesions in pouch of Douglas lysed to free both the tubes and the ovaries. Both ovaries and right uterosacral ligaments showed evidence of endometriosis (chocolate cysts). These areas were fulgurated. Chromopertubation revealed both tubes to be patent. Patient was advised to try natural conception but did not conceive in the same cycle.2 more cycles of IUI was done but patient didn't conceive in both cycles.

In the next cycle, ultrasonographic monitoring of ovulation was undertaken as follows:

On day 2 of menstruation, transvaginal scan was done and checked for the antral follicle count which was satisfactory and as the patient age was also satisfactory and FSH was within the normal limits, the patient was started on r-hFSH 150 IU subcutaneously daily for five days and on day 5 the patient was called for rescan to look for the follicle development. The patient was started on Tab Antag 0.25 mg on day 6 along with this the patient was continued with the r-hFSH and also injection HMG 75 IU added. After 2 days i.e. on day 9 at 9 p.m., patient was given hCG injection 10,000 IU and then on day 12,9 a.m. oocyte pickup was done by the gynecologist. Ten oocytes were retrieved from the follicular fluid by the embryologist. Out of which only 5 were M II oocytes, ICSI procedure was carried out with processed husband's sperm sample. The patient was immediately started on progesterone for luteal support and folic acid. 4 of the oocytes were fertilized. On day 5, 2 blastocyst embryos were transferred successfully,

5.1.8. Result

The patient was summoned on the 15th day, and her serum (-hCG) was positive. She was transferred to a prenatal clinic for additional care. The patient was prescribed progesterone tablets to help with pregnancy and scheduled an ultrasonography scan for 8 weeks. The scan revealed a 6-7th week fetus with a heartbeat and a formed yolk sac. The clinician suggested the patient to continue taking progesterone and folic acid tablets for 3 weeks, and to have weekly hCG injections of 5000 IU to support the pregnancy. Pregnancy was continually checked. The pregnancy was successful, and the patient delivered a healthy full-term

5.2. Case study - 2

5.2.1. Patient identification data.

Name: xyz Husband name: abc
Age: 34 years Age: 37 years

living female baby weighing 3.2 kg via elective caesarean section.

Marital status: 3 years

5.2.2. Chief complaints and progress of the present illness: Patient reported having primary infertility at the age of 34 years having a married life of 5 years. She was experiencing dyspareunia and was keen on a conception. She had previously undergone 5 cycles of ovarian induction and 5 IUI cycles and was unable to conceive.

5.2.3. History of the patient

5.2.3.1. Personal history No history of using oral contraceptive pills, No known allergies. General Health: Satisfactory.

5.2.3.2. Menstrual history

Menarche at the age of 13 years.

Past menstrual cycles: 4/30 days. Regular, moderate flow but painful.

Present menstrual cycles: 4-5/30-32 days. Regular, moderate flow but painful.

5.2.4. Physical Examination

5.2.4.1. General Examination:

Built and nutritional status: Satisfactory.

Blood pressure was normal.

5.2.4.2. Vaginal examination:

Cervix: Tubular, firm, os closed, movements cause discomfort.

Uterus: Retroverted, firm to feel, mobility restricted and tunder, Fornices: Tenderness and nodularity of vaginal cul-do-c

5.2.5. Clinical Diagnosis: Primary infertility in view of

History of infertility as she had previously undergone 3 cycles of ovarian induction and one IUI and was unable to conceive. Regular menstrual cycles with dysmenorrhea, Examination revealing a retroverted uterus with restricted mobility adnexae, tenderness and nodularity of vaginal cul-de-sac-the clinical mores suggestive of diagnosis of endometriosis.

5.2.6. Investigations

The patient was treated for endometriosis with 5 cycles of gonadotropin analog Lupron depot

On the 2 day of the cycle, ultrasound scan observations showed an endometrial thickness of 6.7 mm. Prominent endometriosis were observed on both ovaries, two of 4 cm and 1 cm on the right and one with 4.8 cm on the left. Only on the right ovary 2 to 3 follicles were observed.

Estradiol level was high-1250.51 pg/ml. LH level was 3.1 IU/L

Semen analysis revealed sperm concentration of 86 million/ml, with just 17% motile and 25% sluggish, indicating just about normozoospermia.

5.2.7. Treatment

In the next cycle, in order to try IVF, on day 2 antagonist mode of stimulation was followed along with rFSH for 3 days along with HMG and monitored for follicular development by ultrasound scanning.

The initial follicular sizes were:

R.O-4 follicles at 1.0 cm LO-6 follicles below 1.0 mm and 3 follicles below 0.8 cm.

On day 9, scan report showed endometrial thickness of 10.0 mm follicular sizes were observed by scan report as follows.

R.O- 10 follicles, out of which only 1 was 1.5 cm. LO-7 follicles, all < 1.3 cm.

Therefore continued stimulation with Antag, FSH along with 1IMG.

On day 10, scan report showed endometrial thickness of 9.8 mm

The patient showed very sensitive response for the stimulation with follicular number and size as follows, indicating the risk of ovarian hyper-stimulation syndrome (OHSS).

R.O-11 follicles, out of which only 2 were >1.5 cm. LO-10 follicles, out of which 5 were >1.5 cm.

Therefore with controlled stimulation using antagonist protocol, FSH and HMG were administered, considering the risk factors, oocyte pickup was considered with the injection for hCG.

Post 34 hours of hCG administration, oocyte pickup was carried out and 15 oocytes were collected, out of which 10 oocytes were MIL.8 oocytes fertilized the next day. On day 3 after OPU, protocol in which anti-inflammatory drug and heparin was administered.

Even though the OHSS circumstances were under control on day five following OPU, the patient sensitivity component cannot be totally ruled out. As a result, the decision to transfer a single embryo was made and executed. Seven embryos that were left were preserved for later use.

R.O-8.6 cm x 6.8 cm LO-7.3 cm x 5.8 cm

Progesterone, anticoagulants, folic acid supplements were administered to support the implantation process. On day 12 post ET, following ultrasound scan observations were made Endometrial thickness-1.0 cm.

RO-Endometrium 2.5cm x 1.5 cm and 1.0 cm x 0.5 cm LO- Endometrioma2.4 cm x 2.1 cm

Since no observation in the rise of I-hCG since last menstrual cycle was observed. frozen embryo transfer (FET) was posted for the next month. On Day 4th of the next menstrual cycle, as the couple agreed to go for FET. preparation with adjuvants and supplements were started. The scan observation showed endometrial thickness of 3.3 mm.

On day 11, mock transfer was conducted and at this time endometrial thickness of 8.5 mm and FET was planned on day 18, while supplements for folic acid, progesterone and other adjuvants were given. On day 18, embryo transfer was carried out; and 3 blastocysts were transferred with case. Low molecular weight heparin, progesterone were continued.

5.2.8. Result

On day 39, B-hCG levels were checked.

Amenorrhea was observed to last till 39th day of the cycle.

B-hCG-13, 995.5

Next week, primary IVF pregnancy was confirmed.

The observations were as follows:

Sac 1: In 6th week, CRL-0.56 cm, y sac-3 mm Sac 2: In 6th week, g sac-1.3 cm.

Two weeks later,

Sac 1: in 8th week, CRL-1.8 cm, y sac-4.5 mm Sac 2: Small cyst, no fetal pole seen.

Adjuvants and supplements for folic acid, progesterone were continued

Four weeks later, USG scan observation showed intra uterine gestation of 12 week along with triple mark scan. The placenta was observed to be low lying, posterior in position. Query was raised to rule out Down's syndrome and Edward's syndrome.

Also, following tests were conducted,

Hb: 9.4 g/ml HIV and HBS Ag: Negative

TSH: 2.15 µIU/ml **RBS: 96**

Folic acid, calcium, iron and progesterone supplements were continued. On 15th week, scan resulted in observation of Placentia Previa. Pregnancy was continuously monitored. The pregnancy was successful, and the patient delivered a healthy full term alive male baby weighing 2.9 kg by caesarean section.

5.3. Case study- 3

5.3.1. Patient identification data.

Husband name: abc Name: xyz Age: 30 years Age: 36 years

Marital status: 7 years

5.3.2. Chief complaints and progress of the present illness: The patient was married for 7 years and has been on treatment for 5 years on and off. She had mild dysmenorrhea and had brown discharge for first 3 days of het menstrual period.

5.3.3. History of the patient

5.3.3.1. Personal history

No history of using oral contraceptive pills, No known allergies or addictions.

General Health: Satisfactory, 5.3.3.2. Menstrual history

Menarche at the age of 15 years.

Past menstrual cycles: 4/30 days. Regular, normal flow but painful, Present menstrual cycles: 4/30 days. Regular, normal flow but painful.

5.3.3.3. Surgical history

Hysterolaparoscopy, Adhesiolysis and left Chocolate cystectomy was done.

5.3.4. Physical Examination

5.3.4.1. General Examination:

Built and nutritional status: Satisfactory. Weight: Overweight.

No evidence of pallor or lymphadenopathy. Pulse and blood pressure normal.

PA was soft, scar healthy 5.3.4.2. Vaginal examination:

Cervix: Tubular, firm, os closed, movements cause discomfort. Uterus: Retroverted, firm to foci, mobility restricted and tender. Fornices: Tenderness and nodularity of uterosacral ligaments.

5.3.5. Clinical Diagnosis Primary infertility in view of

History of infertility.

Regular menstrual cycles with dysmenorrhea, painful enough to require medication. Examination by hysterosalpingogram (HSG) revealed that patient has moderate - severe endometriosis.

5.3.6. Investigations

Hemoglobin: 11.3 gm/dL.. RBS: 134 mg/dL.

HIV screening test: Negative. HBsAg test: Negative.

VDRL: Negative. HCV: Negative. TSH (Adult): 2.78 ulU/mL. PRL: 17.2 ng/mL.

Hysterectomy-Normal study. Semen analysis (husband): Normal

5.4.7. Treatment

Diagnostic Laparoscopy: Laparoscopy- Bilateral ovary adherent to side wall, left ovary chocolate cyst 3x 3 cm, Pouch of Douglas (POD) reformed, left tube adherent to ovary, bilateral tubes were patent, uterosacral ligament showed evidence of endometriosis. Uterus was normal in appearance.

Patient was started on superovulation using injection leupride depot 3.75 mg IM (3 doses) and on Day 9 hCG injection of 10,000 IU was administered. IVF was scheduled and oocyte pickup was done on day 12. 18 oocytes were retrieved, out of which 15 were Mll oocytes and IVF was carried out with processed husband's sperm sample. The patient was immediately started on progesterone for luizal support and folic acid, 14 oocytes got fertilized and on day 3, 2 embryos were used for embryo transfer and 5 embryos were frozen for future use. This cycle also was unsuccessful. Next month, FET was scheduled and 2 blastocysts were transferred. Progesterone supplement was given for 15 days.

5.4.8. Result

The patient was called on 15th day after FET, serum B-hCG was positive. The patient was referred to antenatal clinic for further care. The patient was advised progesterone tablets to support pregnancy and called for an ultrasonography scan at 9th week. The scan showed a 7-8th week fetus with fetal heart beat and developed yolk sac.

Patient characteristics and ovarian stimulation parameters are shown in Table.

Parameters Involved	Case 1	Case 2	Case 3		
Maternal Age	32	34	30		
Chief compliment	Dysmenorrhea Dyspareunia	Dysmenorrhea Dyspareunia	Dysmenorrhea		
Method of diagnosis	Diagnostic Hysterolaproscopy	Transvaginal ultrasound + HSG	Transvaginal ultrasound + HSG		
Diagnosis	Moderate- Sever endometriosis	Moderate- Sever endometriosis	Moderate- Sever endometriosis		
Sperm Parameters	Normozoospermia	Normozoospermia	Normozoospermia		
Stimulation Protocols used	O.I drugs(5 days) along with rhFSH 150IU + HMG 75IU	Lupron depot (5days), antagonist with rFSH (3days)	Agonist with leupride depot (3days)		
No. of failed cycles	3	6	8		

Successful	ICSI with Blastocyst transfer	FET with blastocyst transfer	FET	with	blastocyst
treatment			transfer		

Conclusion:

Millions of women worldwide suffer from endometriosis, which need medical attention. Because endometrioses can recur and cause discomfort, endometriosis may be a lifelong problem. It has the power to significantly worsen emotional suffering and impair one's quality of life. When creating an infertility treatment plan, a woman's age, the length of her infertility, her level of endometriosis, and her pelvic pain should all be taken into account.

RIF continues to be a big difficulty for physicians and embryologists even with substantial advancements in diagnosis and treatment techniques. Chromosome abnormalities and insufficient embryonic development are the main causes of RIF. New technologies like as SNP analysis and CGH arrays may make chromosomal screening more comprehensive. Some patients may be able to overcome zona stiffness with the use of aided hatching. In RIF, implantation rates and PRs may be enhanced by ideal culture conditions and blastocyst transfer.

The implantation rates have increased as a result. Better culture conditions and increased vitrification success rates for freezing embryos will help get normal, healthy embryos that can implant after transfer.

Lastly, there is ongoing debate over the decreased implantation observed in endometriosis patients. Therefore, even though many endometriosis-affected women benefit from existing medical therapies, they have drawbacks, such as unfavorable side effects in some cases and contraceptive action for those who want to become pregnant.

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Poonam Shodh Rachna