



Director

**Center of IVF and Human Reproduction
Sir Ganga Ram Hospital, New Delhi,
INDIA**

Recipient of 'President's Medal' for the best medical graduate in 1975.

Felicitated on Doctors day by Dr. B.C Roy's award in 1999 for outstanding contribution towards medicine and field of specialty.

Awarded 'Nations Vikas Ratan Award' in 2002 , 'Chikitsa Ratan Award' in 2007 by the International Study Circle and Felicitated by parent institution for 'outstanding contribution towards field of specialty' in 2006.

Appointed by the National Diplomate Board as teacher for awarding Fellowship in Reproductive Medicine to post graduates, and by FOGSI for basic as well as advanced infertility training in 2007.

She is the immediate past President of Indian Fertility Society.

Her field of interest is management of all cases related to infertility with special focus on reproductive endocrinology, endoscopic surgery, open microsurgery & macrosurgery for infertility and ART.

She has been in the team of doctors responsible for the first IVF baby born in 1991 and the first frozen oocyte baby born in january 2009 of Northern India.



IVF AND ENDOMETRIOSIS

Dr.Abha Majumdar

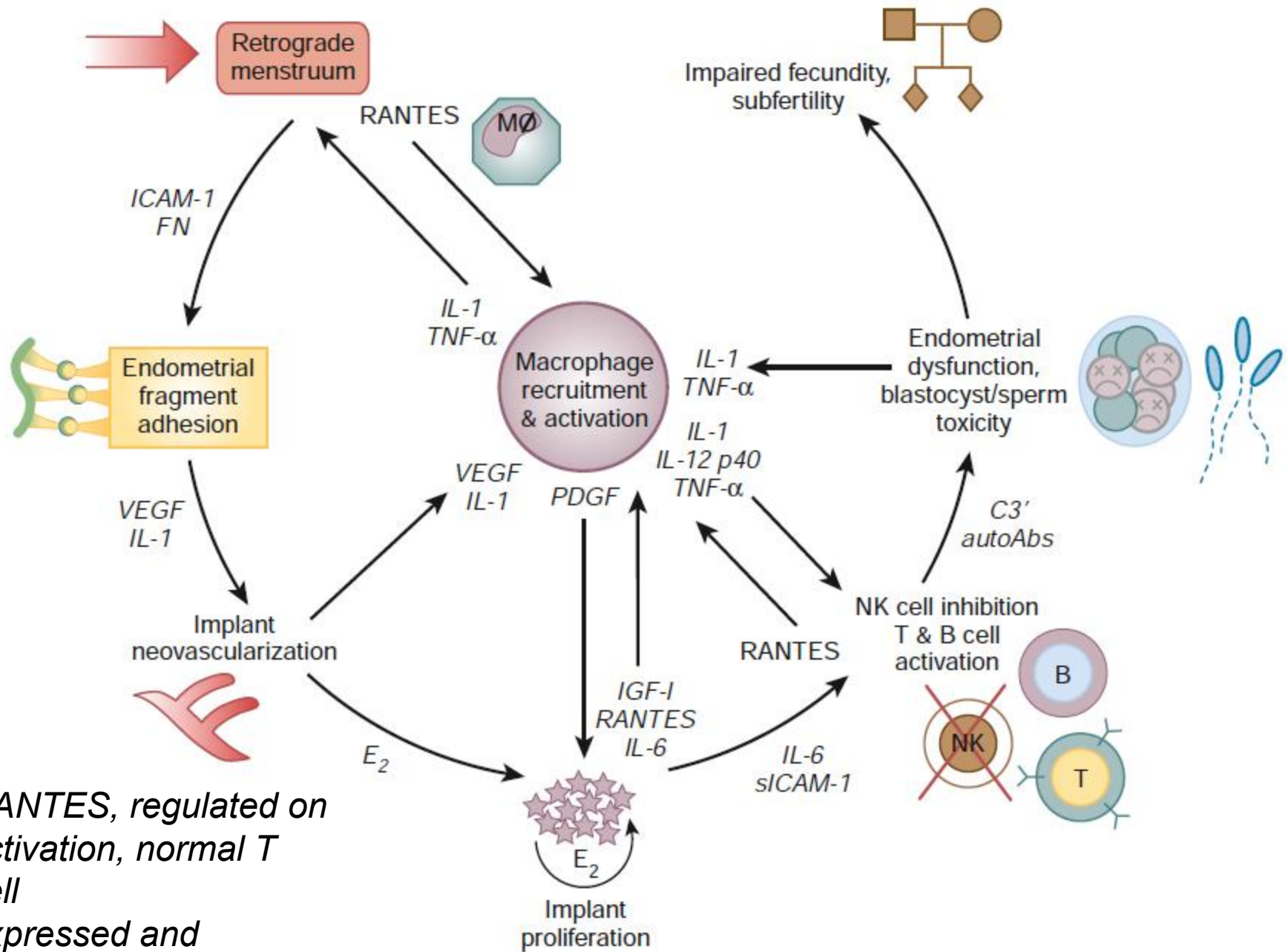
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IMPAIRED FERTILITY WITH ENDOMETRIOSIS



RANTES, regulated on activation, normal T cell expressed and secreted;

MECHANISM OF INFERTILITY

○ Mechanical interference:

- Pelvic adhesions
- Altered tubal motility
- Distorted tubo-ovarian relation
- Impaired oocyte pick-up

○ Alterations in peritoneal fluid:

- Increased concentration of prostaglandins, macrophages, cytokines
- Increased phagocytosis of gametes



MECHANISM OF INFERTILITY

- Abnormal systemic immune response- cell-mediated gamete injury, auto-antibodies
- Hormonal or ovulatory dysfunction- defective folliculogenesis, LUFS.
- Fertilization and implantation failures
 - Sperm-oocyte interaction, sperm motility, sperm binding
 - Decreased rate of cleavage, blastocyst development and hatching.
 - Defects in uterine receptivity: expression of glycodeclin lost



WHEN TO DECIDE FOR IVF IN CASES OF ENDOMETRIOSIS

- IVF first choice in
 - Stage 3 and 4 endometriosis with severe distortion of tubes or adhesive disease
 - Woman's age is >38
 - Couples with combined male factor
 - Recurrent endometrioma with repeated surgeries
 - Poor ovarian reserve
- Stage 1 and 2 endometriosis with failed COH with IUI more than 5 to 6 times (unexplained infertility)



Cycle specific and cumulative fecundity COH + IUI VS IVF with endometriosis

1 cycle IVF-ET offers better probability of conception than 4 cycles of COH & IUI. This is regardless of the woman's age & or stage of the disease.

W.Paul et al, Fertil Steril; 78 (4) Oct. 2002.



WHAT DO WE NEED TO KNOW?

- Effect of endometriosis on the procedure of IVF
- Effect of endometriosis on ovarian reserve
- Effect of endometriosis on oocyte thus embryo quality
- Effect of endometriosis on uterine receptivity thus implantation rate
- Effect of endometriosis on IVF outcome



EFFECT OF ENDOMETRIOSIS ON IVF PROCEDURE

- Recruitment of follicles may be difficult
- Enlargement of endometrioma during stimulation
- Difficulty in approaching adherent ovaries
- Penetration of endometrioma to reach follicles
- Inadvertent aspiration of endometrioma
- Abscess formation after aspiration or embryo transfer



Endometrioma mediated damage to ovarian reserve

Reduced number of follicles in histopathology sections of ovarian cortex adjacent to endometrioma suggest that the disease per se may damage the surrounding ovarian tissue.

Maneschi et al 1993

Endometriosis surgery mediated damage

- ❑ Surgery related local inflammation
- ❑ Adverse changes in ovarian artery blood flow following ovarian stripping
- ❑ Electro-surgical coagulation during hemostasis (*La Torre et al., 1998*)

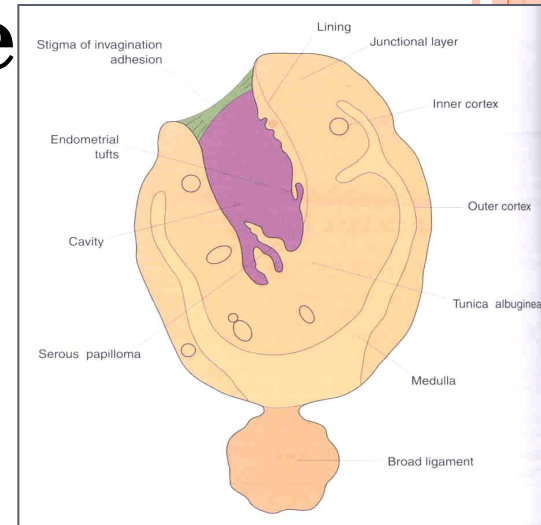


Surgery mediated damage

Accidental removal of consistent amount of ovarian tissue during cystectomy

- Presence of healthy ovarian tissue adjacent to cyst wall in 14 of 26 endometrioma (54%)
- Presence of healthy ovarian tissue adjacent to cyst wall in 1 of 16 non endometriotic benign cyst (6%)

Muzi et al 2002; Hachisuga et al 2002



Endometrioma may arise from invagination of ovarian cortex

Quality of embryos derived from women with endometriosis compared to embryos from tubal infertility in an IVF cycle

- ❑ At 48 hours no difference in no. of blastomeres and fertilization rates
- ❑ After 72 hours significant decrease in number of blastomeres
- ❑ Increase in percentage number of arrested embryos at 72 hours

Pellicer et al ,1995 Hum Reprod. 10 (supple. 2)



METANALYSIS OF 8 RELEVANT STUDIES

**~900 cycles in 700 women with endometriosis and
>2500 cycles in >1700 women without endometriosis**

- Statistically significant impairment of pregnancy rate (28.6 versus 34.2%)
- Statistically significant impairment of implantation rate (13.6 versus 17.6%)
- No difference in oocyte retrieved (9.5 versus 9.7 per cycle) or fertilization rate (56.6% versus 59.3%)
- Summary of meta-analysis:
 - Implantation was significantly impaired in women with endometriosis
 - Quality of embryos replaced was poor indicating poor oocytes



EFFECT OF ENDOMETRIOSIS ON UTERINE RECEPTIVITY AND IMPLANTATION

Oocyte donation model in women with endometriosis (*retrospective study*)

3 groups of donor oocyte recipients

- POF (n=54)
- Low responders to ovarian stimulation (n=77)
- Women with endometriosis and low response (n=11)

No difference in pregnancy and implantation rate in the 3 groups.

(Simon et al., Hum. Reprod. 9 725-729)



EFFECT OF ENDOMETRIOSIS ON UTERINE RECEPTIVITY AND IMPLANTATION

Oocyte donation model in women with endometriosis
prospective study

- Group 1: donor recipient without endometriosis n=44
- Group 2: donors with endometriosis donated oocytes to recipients without endometriosis n=14
- Group 3: donors without endometriosis donated oocytes to recipient with endometriosis n=16

Results

- Impairment of pregnancy rate per transfer in group 2 (28.6% versus 61.4% and 60.0% in group 1 & 3) & lower implantation rate in group 2 compared to group 1 and 3

Pellicer et al., 1994 Progress in Endometriosis 177 to 183



EMBRYO OR ENDOMETRIUM: THE DEBATE CONTINUES.....

Contradictory reports regarding pregnancy rates in women with endometriosis but in studies reporting lower PR factors are:

- Lower ovarian reserve
- Poorer quality oocytes and altered follicular micro-environment leading to poor embryo quality and development
- Endometrial implantation factors possibly also involved
- In oocyte donation programs good embryos could by-pass an affected endometrium



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TREATMENT OF ENDOMETRIOSIS

ESHRE guideline for the diagnosis and treatment of endometriosis, 2007


The guideline has been produced by the ESHRE Special Interest Group for Endometriosis and Endometriosis Guideline Development Group, and the original, concise, version was published in [Human Reproduction 2005;20\(10\):2698-2704](#)

The aim of this guideline is to provide clinicians with up-to-date information about the diagnosis and treatment of endometriosis, based upon the best available evidence. This guideline, which is reviewed annually, was last updated on 30 June 2007

[Human Reproduction 2005;20\(10\):2698-2704](#)



MAIN CONCLUSIONS

- Definitive diagnosis of endometriosis: ***visual inspection by laparoscopy*** 'gold standard'
 - Minimal-mild endometriosis: ovarian suppression to improve fertility not effective; ***ablation of endometriotic lesions plus adhesiolysis is effective*** vs diagnostic laparoscopy alone
 - Insufficient evidence : surgical excision of moderate-severe endometriosis enhances pregnancy rates
 - IVF : especially if coexisting causes of infertility and/or other treatments have failed. IVF PR lower in women with endometriosis than with tubal infertility"
- 

Treatment of endometriosis: A review

For infertile patients, medical therapy has a limited role.
The two current treatment options include:

Surgery

or

In Vitro Fertilization (IVF).

According to the review, it seems that correct management of infertile women with endometriosis is a combination of surgery and IVF in women who did not obtain post-surgery pregnancy spontaneously.

Scarselli G, Rizzello F, Cammilli F, Ginocchini L, Coccia ME. *Minerva Ginecol.*
2005 Feb;57(1):55-78.

Surgery may improve endometriosis related sub- fertility

Littman et al; Fertil Steril 2005;84(6) Researchers Stanford University

Role of laparoscopic treatment of endometriosis in patients with failed **IVF cycles**

29 patients with prior IVF failures underwent laparoscopic treatment of endometriosis

22 (76%) conceived, including 15 non-IVF pregnancies and 7 IVF pregnancies

Research shows laparoscopic evaluation and surgical technique may give the patient a greater rate of success."



TREATMENT OPTIONS PRE-IVF WITH ENDOMETRIOMA

- ❖ Surgery (cyst excision or drainage & fulguration)
- ❖ Expectant management
- ❖ Ultrasound guided aspiration
- ❖ Medical treatment



FACTORS TO BE CONSIDERED BEFORE UNDERTAKING SURGERY PRE-IVF

- ❖ Bilaterality of endometrioma
- ❖ Dimension of the cyst
- ❖ Number of previous interventions
- ❖ Ovarian reserve
- ❖ Age of the woman
- ❖ Presence or absence of pain
- ❖ Duration of infertility
- ❖ Possibility of occult malignancy



RISKS OF SURGERY BEFORE IVF

Meta-analysis by Chapron et al., 2002;
Patients selected for surgery generally have
advanced disease & multiple previous surgeries

- Major complications 1.4%

- Minor complications 7.5%

- Higher economic costs
(\$1735 Philips et al., 2000)



Ovarian surgery resulted in longer stimulation, higher FSH requirement, lower oocyte number but fertilization, pregnancy and implantation rates did not differ between the groups.

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Gurgan et al; Turkey ESHRE 2005



RISK OF EXPECTANT MANAGEMENT

- ❑ Difficulties in oocyte retrieval
 - ❑ follicles beyond endometrioma.
 - ❑ ovary displaced to un-comfortable position,
 - ❑ Contamination of follicular fluid with endometrioma & its effect on oocyte quality; controversial report.
- ❑ Risk of rupture of endometrioma & acute abdomen

Dicker et al., 1993

- ❑ Risk of developing pelvic abscess. *Padilla et al 1993; Yaron et al., 1994; Younis et al., 1997; Matsunaga et al 2003.*

- ❑ Missing an occult early stage malignancy (0.9%)


Mostoufizadeh & Scully 1980; Stern et al 2001.

- ❑ Progression of endometriosis on ov stimulation; debatable



There is a lack of randomized trials aimed to establish benefits of surgical treatment. Authors have tried to draw preliminary conclusions using retrospective studies which provided us with the following evidence

At present insights from non- randomized studies suggests that surgery for endometrioma does not benefit asymptomatic women preparing to undergo IVF-ET.



Ultrasound guided aspiration pre-IVF

Better fertilization rate and better PR with aspiration as compared to surgery or no treatment

Dicker et al.,1991; Suganuma et al 2002;

Similar no of oocytes, fertilization rate, implantation rate and PR with aspiration versus no treatment

Pabuccu et al.,2004.

Potential benefits of adjuvant intra cystic sclerotherapy is being investigated.

Promising results with injection of 5% tetracycline with cyst aspiration reported. *Fisch & Sher, 2004*



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GNRH AGONIST PRE IVF

Action of GnRH agonist

- ❑ Classical action H-P-O axis:
 - ✱ Inhibition of synthesis, storage and release of FSH & LH
- ❑ Direct action on endometrial cells: inhibition of growth and proliferation by regulation of apoptotic and angiogenic mechanisms.
 - ✱ Increase in expression of the pro-apoptotic proteins Bax & FasL and decrease of the anti-apoptotic protein Bcl-2.
 - ✱ Reduced production of VEGF-A and IL-1beta in eutopic endometrial cell cultures



Other novel mechanisms of action

- ❑ Suppression of ovulation: reduction in exposure of endometriotic implants to midkine a growth factor in follicular fluid involved in the proliferation of endometriotic cells
- ❑ Inhibition of menstruation: reduced exposure to thrombin and its protease activated receptor; factor in cell inflammation
- ❑ Inhibition of uterine contractions: blocks mechanical stress



Long term GnRH agonist pretreatment compared to gonadotropin alone

- Long term GnRH agonist suppresses endometriosis lesions and improves IVF outcome for patients with endometriosis
 - *Olivennes F. Fertil steril. 1995; Oehninger S. HR 1989*
- Better clinical pregnancy rates after 6 months of agonist therapy compared to Gonadotropin alone
 - *Dicker et al FS 199; Rickes et al FS 2002*



Meta analysis ESHRE 2005 H Sallam [1], JA Garcia-Velasco [2], A Arici [3] Alexandria, Egypt

The administration of GnRH agonists for a period of 3–6 months prior to IVF or ICSI in patients with endometriosis increases the clinical pregnancy rate and the live birth rate significantly.

Cochrane data base systemic review 2006 Sallam HN

Long term down regulation for 60 to 90 days before IVF for women with endometriosis better than long protocol

3 RCTs with 165 women

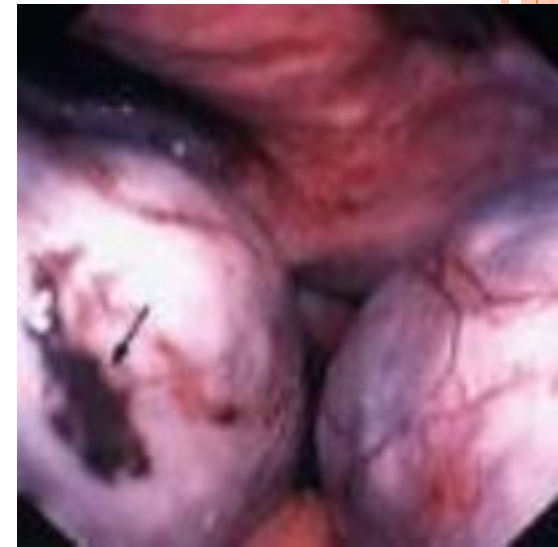
Live Birth Rate/ woman OR 9.19

Clinical Pregnancy Rate: OR 4.28



Endometriosis is associated with highest live birth rate per cycle in IVF programs when compared to other causes of infertility, mainly with tubal infertility as control group.

The center for disease control and prevention 2002 report



Controversial reports using meta-analysis methodologies with severity of endometriosis

Barnhart et al: OR for PR 0.56(95% CI=0.44-0.70)

☐ PR with severe endometriosis was significantly lower than those with mild disease.

Azem et al.,1999; Al-Azemi et al.,2000; Norstendt et al 2001; Geber et al.,2002; Aboulghar et al.,2003; Pabuccu et al.,2004.

☐ No difference in PR with severity of disease

Bukulmez et al., 2001; Canis et al., 2001; Donnez et al.,2001;; Hichman,2002; Marconi et al., 2002.



Current opinion on treatment

- For early stage disease
 - COH with IUI recommended in early stages and for surgically corrected endometriosis
 - For advanced stages
 - Surgery is the first line management
 - IVF is the second line therapy
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- Gynec and Obstetric investigation, 2009 (67)
 - Ozkan S, Ann NY academy of science 2008 April
 - Progress in Obs and gynae issue 18 Studd, 2008



Thank you

