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Sir Ganga Ram Hospital,
New Delhi, INDIA

Awarded **Presidents Medal** for the Best Medical Graduate 1975.
Felicitated by **Dr. B.C Roy's prestigious award** in 1999.
Bharat Vikas Ratan Award by nations Economic Development and Growth Society 2002, **Chiktsa Ratan Award** a certificate of excellence in Medical Science International Study Circle, 2007. **Felicitated by S.N.Medical College** for outstanding contribution to the specialty in 2008

Conducting '**Fellowship in Reproductive Medicine'** for 'National board of Examinations' since 2007, and basic & advanced infertility training under aegis of FOGSI since 2008.

Member of Editorial board of '**IVF Worldwide',** peer reviewer for '**Journal of Human Reproductive Sciences'** and on advisory board for '**Journal of Fertility Science & Research**'
More than 20 chapters in OB/GYN books & more than 20 original articles in indexed journals.
Attached to Sir Ganga Ram Hospital, New Delhi since 1987. This hospital provides comprehensive infertility services under one roof as one of the most prestigious and largest center of northern India.

Infertility with Endometriosis:

diagnosis to clinical management


WHAT DO OVER
1,80,00,000
INDIAN WOMEN IN THE
REPRODUCTIVE AGE
HAVE IN COMMON?

ENDOMETRIOSIS

A disorder which is under diagnosed and inadequately treated especially in India

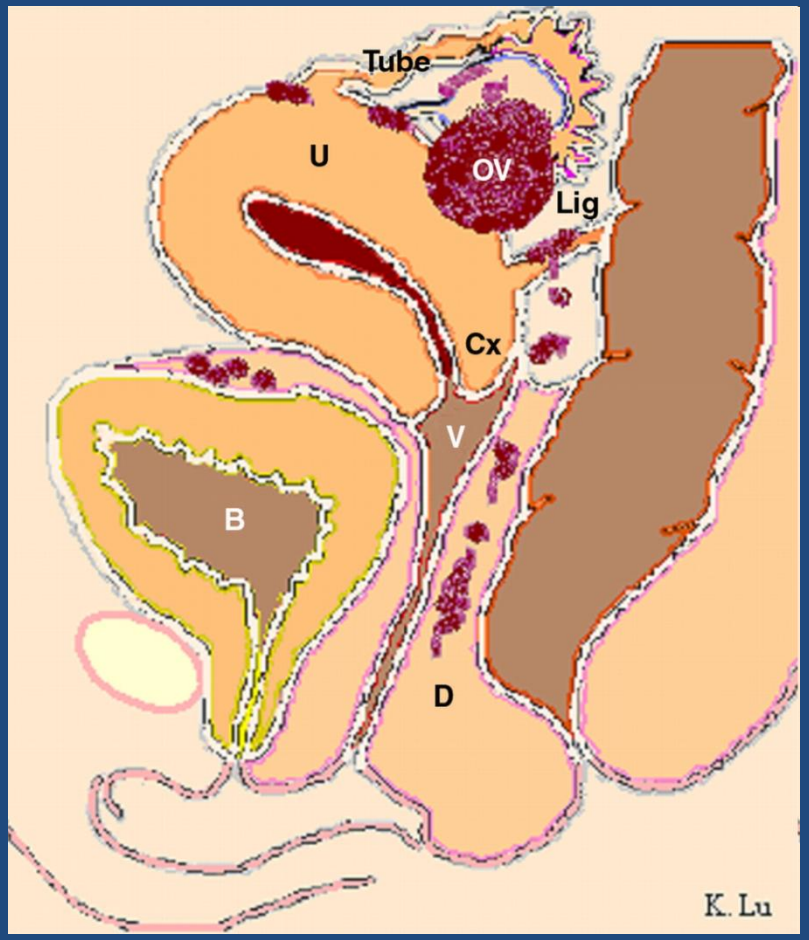
2/3rd (65%) of women present with pelvic pain

1/3rd of these women report

Endometriosis

Endometriosis is the presence of functional endometrial tissue outside the uterine cavity.

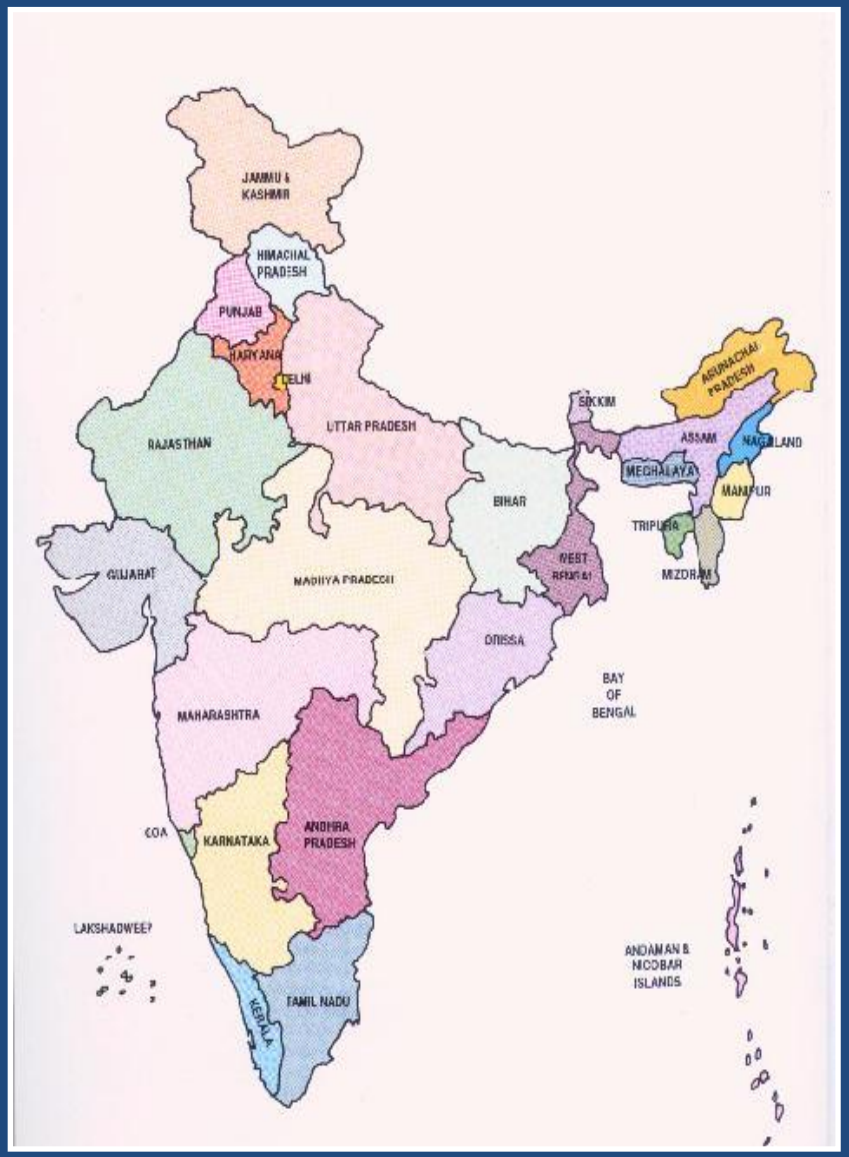
Endometriotic Sites



Prevalence

- The prevalence of endometriosis among asymptomatic women ranges from 2–22%
- In women with dysmenorrhoea, the incidence of endometriosis is 30% to 40%
- In infertile women, the rate of endometriosis is between 25% and 40%
- In women with an affected first-degree relative, there is a 10-fold increase in prevalence

Endometriosis-Disease Burden in India



- In a prospective cohort study in women having laparoscopy in kerala for infertility, reported 20.5% prevalence of endometriosis.
- 56.06% (moderate 31.06 % +severe 25%) & 43.94 had minimal to mild endometriosis

Endometriosis-Disease Burden in India (data from Delhi)

- Retrospective analysis of our data from SGRH in women undergoing laparoscopy for infertility, reports 38% prevalence of endometriosis.
- 16.4 (43.2%) had minimal to mild and 21.6 (56.8%) had moderate to severe endometriosis

Endometriosis-Disease Burden in India

- Infertility affects 1 in 6 couples in India.
- 2.1 million women report the inability to become pregnant.
- Top three causes for female infertility: tubal factor, anovulation and endometriosis,

Endometriosis why a burden? The Mystifying Disease of Modern Age

- Cause of endometriosis and its natural history are still unknown
- True prevalence, distribution in the population, or predisposing factors are still unknown
- Treatment options are limited and considerable confusion exists regarding optimal methods of therapy
- No cure for this debilitating disease
- Recurrences continue as long as women is estrogenised

Endometriosis-The Mystifying Disease of Modern Age

Many theories have been proposed as to the cause, but exact etiology is still unknown.

- Embryonic rest theory
- Coelomic metaplasia
- Retrograde menstruation

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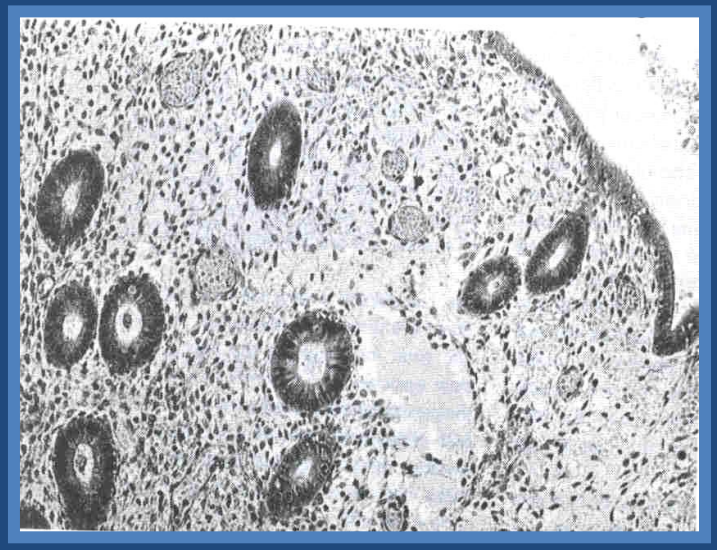
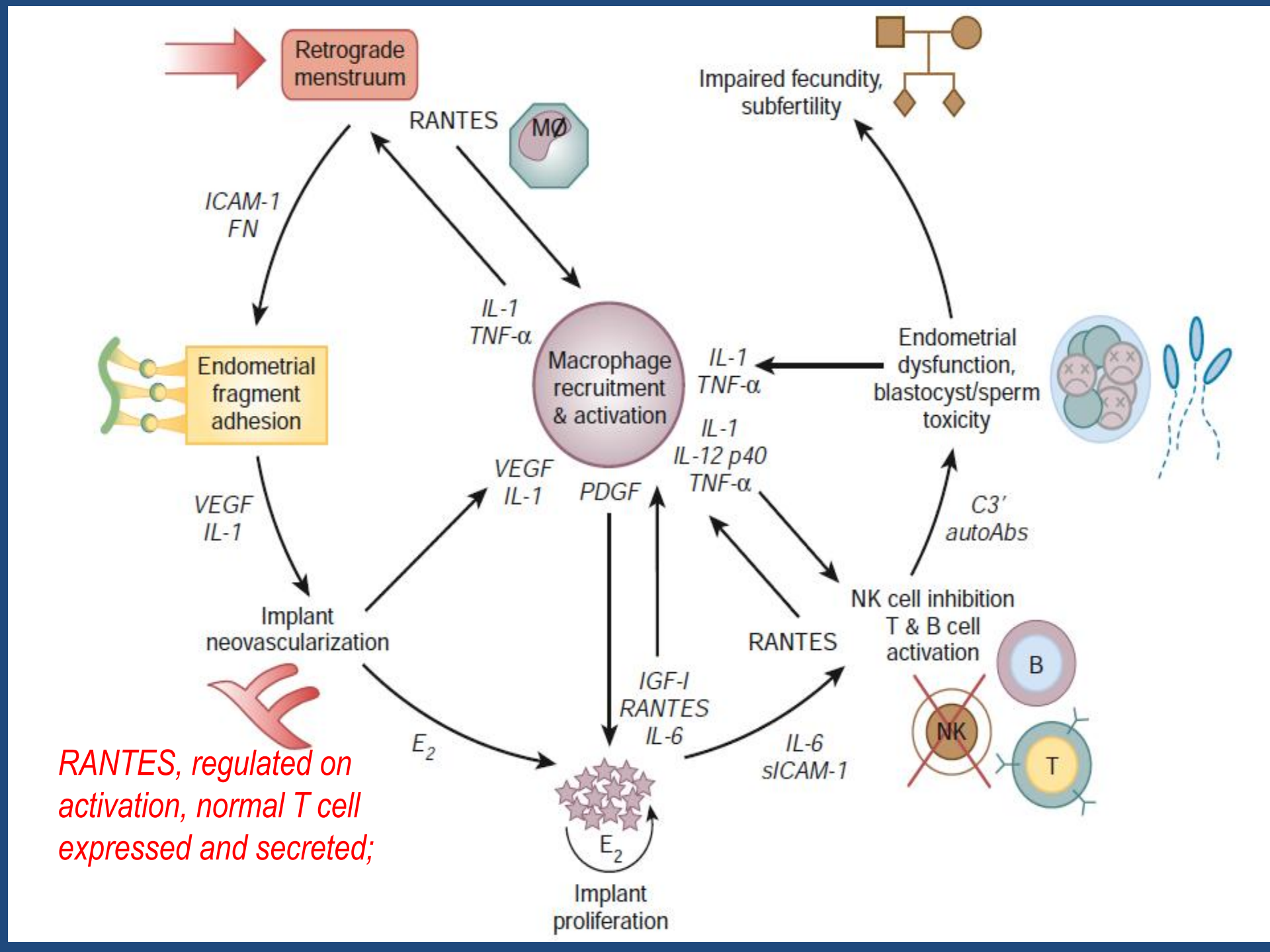




RANTES, regulated on activation, normal T cell expressed and secreted;

Managing Endometriosis with infertility :

The challenges

Early diagnosis ….. ???

Best treatment strategy for endometriosis with infertility: Medical, surgical or both combined ?

Planning surgery for Endometriosis:
role of pre or post-operative medical therapy??

ART and severe endometriosis : any interventions needed prior to ART ???

Guidelines for Diagnosis

- Ultra sound best for primary evaluation: especially in endometriotic cyst, adhesions and recto-vaginal septum involvement.
- Laparoscopy: gold standard
- Positive histology confirms diagnosis; negative histology does not exclude it
- MRI recommended in doubtful cases and in suspected extra-pelvic lesions

ESHRE guidelines: For definitive diagnosis of endometriosis visual inspection of the pelvis at laparoscopy is the gold standard investigation, unless disease is visible in the vagina or elsewhere.

Main conclusions WES 2013 for diagnosis of endometriosis

For women presenting with symptoms suggestive of endometriosis, a definitive diagnosis of most forms of endometriosis requires visual inspection of the pelvis at laparoscopy as the 'gold standard' investigation.

Classification by Revised American Fertility Society (R-AFS)

Stage1 & 2 (minimal and mild) : Peritoneal or superficial ovarian endometriotic implants with or without flimsy adhesions.

Stages 3 & 4 (moderate and severe): Deep ovarian implants and cysts, dense adhesions or complete obliteration of cul-de-sac.

- ***The degree to which infertility is present often does not co-relates with severity of the disease***
- ***The degree of pain possibly depends on depth of infiltration***

Infertility in stages 1 & 2

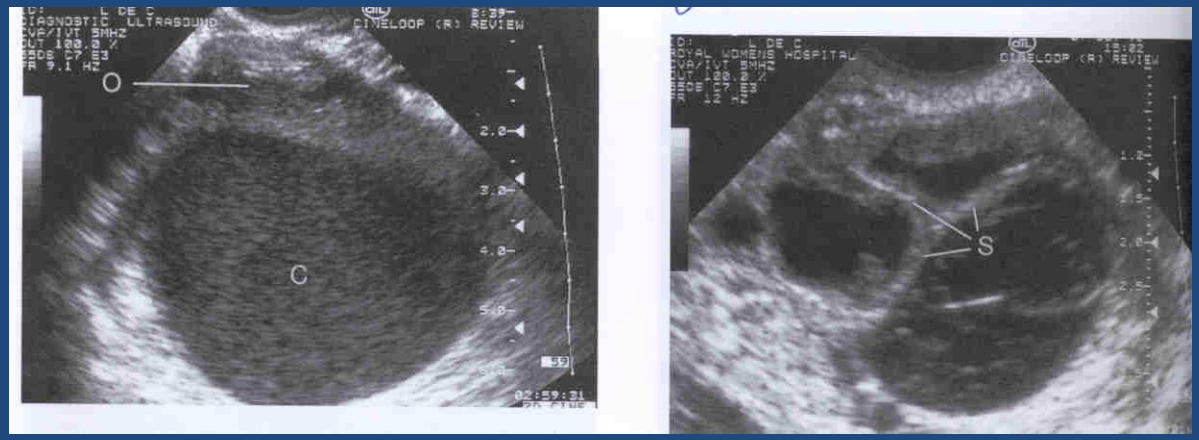
- *Increase concentration of prostaglandin* in peritoneal cavity affecting ovulation, corpus luteum function tubal peristalsis, sperm motility & uterine contractility.

- *Higher concentration of peritoneal macrophages* with increase likelihood of phagocytosis of sperms & toxic effect on embryo cleavage (mouse embryo).

- *Altered auto-immunity & deficient cellular immunity* resulting in infertility or early pregnancy loss.

Infertility in stages 3 & 4

Deep ovarian implants and cysts (endometrioma), dense adhesions or complete obliteration of cul de sac causes infertility by anatomical distortion, which interferes with tubal & ovarian function.



Management Goals

- Fertility restoration
  - medical
  - surgical
  - ART: (IUI &IVF)

Medical management

Medical management

Entire concept of medical therapy was based on the conviction that ectopic implants regress, degenerate & disappear due to unfavorable hormonal milieu

It has been seen with conviction that implants undergo simple modification in appearance with temporary & partial regression but no resorption or healing. Ectopic endometrium is still there ready to re-grow independent of type and dosage of the drug used previously.

Is medical therapy effective alone or as an adjunct to surgical therapy?

No evidence of fertility benefit from medical treatment—ovulation suppression may delay pregnancy and this is not recommended (strong).
The World Endometriosis Society Montpellier Consortium 2013

Guideline Development Group (GDG) recommends clinicians not to prescribe adjunctive hormonal treatment before surgery, as suitable evidence is lacking.
ESHRE endometriosis guideline development group 2013

Surgical management

Surgical Treatment-Gold Standard

- Peritoneal Endometriosis
  - Laparoscopy aims to
    - remove all visible areas of pelvic endometriosis
    - restore anatomy by division of adhesions
- Ovarian endometrioma
  - Two operative techniques (lap or open)
    - excision (stripping) technique
    - Incision drainage ablation of lesions in the cyst wall.

Surgical management

Surgical management of endometriosis with infertility is essentially conservative.

Laparotomy is almost replaced by laparoscopy

Surgical management

For stages 1 & 2: Laparoscopy

- Cautery, vaporization or desiccation of peritoneal implants
- Biopsy or sharp excision of lesions.
- Dividing flimsy adhesions

Surgical management

Stages 3 and 4

Mode of surgery : laparoscopic or laparotomy ?

Principles of infertility should be applied to whichever mode of surgery;

Good exposure, magnification, scrupulous hemostasis, minimal tissue handling & prevention of adhesions.

Laparoscopic surgery for advanced endometriosis can be extremely hazardous and should be under-taken only after level 3 training and adequate experience.

Drawbacks of Surgical Management

- Surgery despite its proven efficacy is challenged by high recurrence rate
  - 40–45% recurrence rate within 5 years post-operatively
  - In case of endometriomas, symptoms (pain or infertility) recur in 76% of patients
- Even after curative surgery, rates of recurrence are as great as 5–10%.

Surgery for infertility in women with endometriosis WES 2013

- Laparoscopic **removal of endometriosis** improves fertility in stage I and II endometriosis (strong)

- Laparoscopic **cystectomy** where possible for endometriomas is preferred to laparoscopic drainage and coagulation to enhance fertility (strong)

- **No role of GnRH agonist after surgery:** it will ovulation and take away what ever chance of pregnancy has increased by surgical correction no fertility benefit (strong)

Implementation of evidence-based medicine suggests

Medical treatment has little part to play in the management of endometriosis associated infertility.

The role of surgery is both rational and established in early as well as late stages of the disease.

Medical treatment as an adjunct to surgery offers no additional benefit.

ART

Current opinion on Endometriosis and ART

- For early stage disease
  - *COH with IUI* recommended in early stages and for surgically corrected endometriosis?
- For advanced stages
  - Surgery followed by *IVF* directly
  - GnRH agonist prolonged suppression followed by IVF
    - *Gynaec and obstetric investigation, 2009 (67)*
    - *Ozkan S, Ann NY academy of science 2008 april*
    - *Progress in Obs and gynae issue 18 Studd, 2008*

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 (4 fold) and the live birth rate significantly (9 fold).

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

The World Endometriosis Society Montpellier Consortium 2013

Main conclusions WES

Minimal-mild endometriosis

- In minimal-mild endometriosis, suppression of ovarian function to improve fertility is not effective, ***but ablation of endometriotic lesions plus adhesiolysis is effective*** compared to diagnostic laparoscopy alone.

Main conclusions WES 2013

- Minimal-mild endometriosis

- IUI with COS is effective in improving fertility in minimal and mild endometriosis, but the role of un-stimulated IUI cycle is uncertain (strong).

- There is no evidence to support the use of COS alone and insufficient evidence to recommend one agent over another (weak).

- Insufficient evidence of benefit of GnRH-a treatment before IUI (weak).

Main conclusions WES 2013

Moderate-severe endometriosis

- Sufficient evidence: best chance of achieving pregnancy is within the first 6 months of surgery.

- Possibly 3 to 4 cycles of COS with IUI may be tried post surgical correction.

- IVF appropriate treatment especially in coexisting causes of infertility and/or other treatments have failed, *(IVF PR lower in women with endometriosis than in those with tubal infertility)*

WES 2013 : Adjuncts to IVF in women with endometriosis

IVF to be considered to improve success rate above expectant management (strong).

Good evidence that **GnRH-a for 3–6 months** prior to IVF/ICSI increases clinical pregnancy rate (strong).

Insufficient evidence to support use of OCP prior to IVF/ICSI (weak).

No evidence that surgical removal of endometriosis pre- IVF improves success rates through IVF (weak).

Endometriotic cyst in girls or women not wanting to conceive

Medical treatment only

Oral contracetive pills:

discontinuous (stop ovulation only)

continuous: (stops ovulation & menstruation)

Progestogens or dienofirst (4th gen progestogens)

GnRh agonist 5 to 6 months only with add back and calcium supplementation

Endometriosis

DON'T'S

- No surgery for unmarried girls or women not wanting to have a child
- No role of CA 121 in deciding surgery
- Post surgery no role of GnRH agonist to clear residual disease

DO'S

- Ocp's or dienogest best options in women with pain or cyst nor desirous of pregnancy
- In Infertility - surgery best option
- IVF best option in stage 3 and 4 endometriosis with failed expectant management or IUI


CHALLENGES
ANYONE CAN HOLD THE HELM
WHEN THE SEA IS CALM.

Gold standard for diagnosis of endometriosis

- Which of the following is true

- Ultrasound
- Laparoscopy
- Histopathology

Use of depot GnRH agonist for 3 to 6 months after surgery for clearance of pelvic endomeriosis

1. Increases the chances of getting pregnant
2. Reduces the chance of getting pregnant

Which statement is true?

Leuplide depot can improve chances of pregnancy if used in the following circumstances

- Mark one as correct

1. Pre IUI
2. Pre IVF
3. After surgery
4. Before surgery

In minimal and mild endometriosis what increases the chance of pregnancy rates?

- Mark one as correct

1. IUI
2. Ovulation stimulation
3. IUI with ovulation stimulation
4. Depot GnRH agonist for 3 months and expectant treatment
5. Depot GnRH agonist for 3 months and ovulation induction

More the depth and extent of endometriosis

The degree to which infertility is present often does not co-relate with severity of the disease this statement is

- True
- false